

# Bağırsak Mikrobiyomu Sağlık ve Hastalıklara Etkisi



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Çeviri Editörü  
Prof. Dr. Tarkan KARAKAN

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# Bağırsak Mikrobiyomu ve Mikrobiyomun Sağlık ve Hastalıklara Etkisi İnsan ve Hayvanın Mikrobiyal Dünyaya ve Ekolojik Dengeye Katkısı

**Zajeba Tabashsum, Zabdiel Alvarado-Martinez, Ashely Houser, Joselyn Padilla, Nishi Shah, and Alana Young**

## 1. Giriş

300 yıldan daha uzun bir süre önce Antonie van Leeuwenhoek, insan plaklarında morfolojik olarak çeşitli mikropları gözlemlemiştir ve bu çevrede olduğu kadar hayvan ve insan vücudunda da var olan karmaşık bir mikrobiyotanın keşfedilmesine yol açmıştır (Lane2015). Böylece, mikropların bu dünyanın bir parçası olduğunun anlaşılması başlamıştır ve o zamandan beri mikropların yaşamın her alanında önemli roller oynadığı fikri daha belirgin hale gelmiştir. Mikrobiyom, sistemde bulunan tüm mikropların toplamı olan faydalı, nötr ve zararlı mikropların toplamıdır. Çeşitli mikroplar; insanlar, bitkiler, hayvanlar, toprak, su kütleleri ve atmosfer gibi farklı ortamların bir parçası olarak bulunabilirler, bu da bir konağın mikrobiyomunun sağlığını ve dengesini şekillendirmenin ve korumanın son derece önemli olduğunu kanıtlamaktadır, bu nedenle mikrobiyom konusu son zamanlarda daha fazla çalışmanın konusu haline gelmiştir (McFall-Ngai ve ark. 2013). Mikrobiyomun metabolizma, bağırsak homeostazı ve bağışıklık gelişimi gibi insan sağlığı ve hastalığının çeşitli bölümleriyle yakından ilişkili olduğu bildirilmiştir (Tasnim ve ark. 2017). Her bireyin mikrobiyomu benzersizdir, ancak genel sağlığı sürdürmek için tutarlı ve çeşitli bir bağırsak mikrobiyotasına sahip olmak gerekir. Bağırsak mikrobiyotası, fizyolojik ve metabolik süreçlere yardımcı olan metabolitlerin üretilmesinden sorumludur ve aynı zamanda komensallere karşı bağışıklığı korurken, patojenlere karşı koruyucu bağışıklığın gelişmesine yol açan lokal ve sistemik bağışıklık tepkilerini ayarlamaktadır (Tasnim ve ark. 2017). Öte yandan, bağırsak mikrobiyotasının dengesizliği (disbiyoz) genel sağlığı sürdüren önemli faaliyetleri bozabilir ve gastrointestinal, kardiyovasküler, otoimmün ve metabolik bozukluklar gibi hastalıklarla ilişkili olabilir (Jandhyala 2015). Bu olgu ışığında, bağırsak mikrobiyomu hayati bir organ olarak kabul edilir ve mikrobiyal ekosistem içindeki dengenin bozulması ciddi kronik hastalıklara ve gelecekte sağlık sonuçlarına yol açabilir.

Kendi içlerinde de çok çeşitli bir bakteriyofaj topluluğunu içeren, bakteriler, arkeleler, mantarlar ve virüslerden oluşan istikrarlı ve geniş kapsamlı bir bağırsak mikrobi-

yönlendiren faktörleri izlemek çok karmaşık hale gelebilir (Gyles 2016). Daha doğru modeller geliştirmek için, daha çok konakçının ilişkisine ve filogenilerin belirli mikrobiyal toplulukların büyümesini nasıl yönlendirdiğine odaklanan, evrimsel ve ekolojik çalışmalar yapmak gerekir (Gyles 2016).

Gelecekteki “(Bütüncül) tek sağlık” araştırması; bulaş potansiyelini azaltmak için diyetlerin probiyotiklerle desteklenmesine ek olarak; yaşam ortamındaki çevresel mikropları değiştirerek ya da evcil ve refakatçi hayvanların diyetlerini değiştirerek; hayvanlar, insanlar ve çevre arasında patojenik mikropların yayılmasını azaltmanın yollarına odaklanacaktır. (Gyles 2016).

## 7. Sonuç

Mikrobiyal ekosistem birçok farklı mikroptan oluşur, ancak en yaygın ve ana bileşenler bakteri, mantar ve virüslerdir. Bu mikroplar, hayvan bedeninin, farklı organlar arasında özel olarak belirli oyuklarda -nişlerde yaşayan sayısız filum ve türün de yaşadığı birçok farklı ekosistemde kendilerine bir alan oluşturur. Su ve hava gibi birçok faydalı mikrop içeren diğer çevresel bileşenlerde olduğu gibi, bitkiler de bu mikroplara barınak sağlar, fakat mikrop içeren bu çevresel bileşenler, aynı zamanda patojenik mikropların yeni bir konakçıyla kolayca temasa geçebileceği kanallar da olabilir. Son olarak, mikroplar ayrıca yüksek tuzlu sular, kaplıcalar ve hidrotermal menfezler gibi olağandışı kaynaklardan da gelebilir. Tüm bu kaynaklar birlikte, mikrobiyom olarak adlandırılan mikrobiyal ekosistemin bir parçasını oluşturan, birçoğu birbirleriyle ve çevreleriyle etkileşime girebilen ve daha önce karşılaştığımız gibi, genellikle bir hayvan konakçısı olabilen, özel bir mikrop yelpazesi sağlayacaktır. Bağırsakların en zengin ve en çeşitli mikrobiyal ekosistemlerden birini oluşturduğunu öğrendiğimiz için, insanlar da mikrobiyom konusunda bir istisna değildir.

## Kaynaklar

- Akiyama, K., Matsuzaki, K., & Hayashi, H. (2005). Plant sesquiterpenes induce hyphal branching in arbuscular mycorrhizal fungi. *Nature*, 435, 824–827.
- Al-Dhabi, N. A., Esmail, G. A., Duraipandiyar, V., Valan Arasu, M., & Salem-Bekhit, M. M. (2015). Isolation, identification and screening of antimicrobial thermophilic *Streptomyces* sp. Al-Dhabi-1 isolated from Tharban hot spring, Saudi Arabia. *Extremophiles*, 20, 79–90.
- Arce-Rodríguez, A., Puente-Sánchez, F., Avendaño, R., Libby, E., Rojas, L., Cambronero, J. C., Pieper, D. H., Timmis, K. N., & Chavarría, M. (2016). Pristine but metal-rich Río Sucio (Dirty River) is dominated by *Gallionella* and other iron-sulfur oxidizing microbes. *Extremophiles*, 21, 235–243.
- Bahrndorff, S., Alemu, T., Alemneh, T., & Nielsen, J. L. (2016). The microbiome of animals: Implications for conservation biology. *International Journal of Genomics*, 2016, 1–7.
- Belser, J. A., Wadford, D. A., Pappas, C., Gustin, K. M., Maines, T. R., Pearce, M. B., Zeng, H., Swayne, D. E., Pantin-Jackwood, M., Katz, J. M., & Tumpey, T. M. (2010). Pathogenesis

- of pandemic influenza a (H1N1) and triple-reassortant swine influenza a (H1) viruses in mice. *Journal of Virology*, 84, 4194–4203.
- Bhattacharya, A., Goyal, N., & Gupta, A. (2007). Degradation of azo dye methyl red by alkaliphilic, halotolerant *Nesterenkonia lacusekhoensis* EMLA3: Application in alkaline and salt-rich dyeing effluent treatment. *Extremophiles*, 21, 479–490.
- Brandt, L. J. (2012). Fecal transplantation for the treatment of *Clostridium difficile* infection. *Gastroenterología y Hepatología*, 8(3), 191–194.
- Cabral, J. P. (2010). Water microbiology. Bacterial pathogens and water. *IJERPH*, 7, 3657–3703.
- Chandler, J. A., Lang, J. M., Bhatnagar, S., Eisen, J. A., & Kopp, A. (2011). Bacterial communities of diverse *Drosophila* species: Ecological context of a host-microbe model system. *PLoS Genetics*, 7, e1002272.
- Cheung, M. Y., Liang, S., & Lee, J. (2013). Toxin-producing cyanobacteria in freshwater: A review of the problems, impact on drinking water safety, and efforts for protecting public health. *Journal of Microbiology*, 51, 1–10.
- Cho, I., & Blaser, M. J. (2012). The human microbiome: At the interface of health and disease. *Nature Reviews. Genetics*, 13(4), 260–270.
- Clements, K. D. (1997). Fermentations and gastrointestinal microorganisms in fishes. In R. I. Machie & B. A. White (Eds.), *Gastrointestinal microbiology*. Boston: Chapman & Hall Microbiology Series. Springer. Editorial. (2011). Microbiology by numbers. *Nature Reviews. Microbiology*, 9, 628.
- Ejtahed, H. S., Hasani-Ranjbar, S., & Larjani, B. (2017). Human microbiome as an approach to personalized medicine. *Alternative Therapies in Health and Medicine*, 23, 8–9.
- Elliott, M. L. (2011). First report of Fusarium wilt caused by *Fusarium oxysporum* f. sp. palmarum on Canary Island date palm in Florida. *Plant Disease*, 95(3), 356–356.
- Fenselau, S., Balbo, I., & Bonas, U. (1992). Determinants of pathogenicity in *Xanthomonas campestris* pv. vesicatoria are related to proteins involved in secretion in bacterial pathogens of animals. *Molecular Plant-Microbe Interactions*, 5, 390–396.
- Fernandez, C. (2019). *No guts, no glory: How microbiome research is changing medicine*. Labio Tech. <https://labiotech.eu/features/gut-microbiome-research/>. Accessed 17 June 2019.
- Forster, S. C., Kumar, N., Anonye, B. O., Almeida, A., Viciani, E., Stares, M. D., Dunn, M., Mkan-dawire, T. T., Zhu, A., Shao, Y., Pike, L. J., Louie, T., Browne, H. P., Mitchell, A. L., Neville, B. A., Finn, R. D., & Lawley, T. D. (2019). A human gut bacterial genome and culture collection for improved metagenomic analyses. *Nature Biotechnology*, 37, 186–192.
- Gowtham, H. G., Murali, M., Singh, S. B., Lakshmeesha, T. R., Murthy, K. N., Amruthesh, K. N., & Niranjana, S. R. (2018). Plant growth promoting rhizobacteria- *Bacillus amylolique-faciens* improves plant growth and induces resistance in chilli against anthracnose disease. *Biological Control*, 126, 209–217.
- Gritz, E. C., & Bhandari, V. (2015). The human neonatal gut microbiome: A brief review. *Frontiers in Pediatrics*, 3, 17–27.
- Gyles, C. (2016). One medicine, one health, one world. *Canadian Veterinary Journal*, 49(11), 1063–1065.
- Hasan, N., & Yang, H. (2019). Factors affecting the composition of the gut microbiota, and its modulation. *PeerJ*, 7, e7502.
- Holtenius, K., & Bjornhag, C. (1985). The colonic separation mechanism in the guinea-pig (*Cavia porcellus*) and the chinchilla (*Chinchilla laniger*). *Comparative Biochemistry and Physiology. A, Comparative Physiology*, 82, 537–542.
- IOM (Institute of Medicine). (2009). *Microbial evolution and co-adaptation: a tribute to the life and scientific legacies of Joshua Lederberg*. Washington, DC: The National Academies Press.
- Jandhyala, S. M. (2015). Role of the normal gut microbiota. *World Journal of Gastroenterology*, 21(29), 8787–8803.
- Jatzlauk, G., Bartel, S., Heine, H., Schloter, M., & Krauss-Etschmann, S. (2017). Influences of

- environmental bacteria and their metabolites on allergies, asthma, and host microbiota. *Allergy*, 72(12), 1859–1867.
- Khan, A. G. (2005). Role of soil microbes in the rhizospheres of plants growing on trace metal contaminated soils in phytoremediation. *Journal of Trace Elements in Medicine and Biology*, 18, 355–364.
- Kho, Z., & Lal, S. (2018). The human gut microbiome – a potential controller of wellness and disease. *Frontiers in Microbiology*, 9, 1835.
- Kostic, A. D., Howitt, M. R., & Garrett, W. S. (2013). Exploring host-microbiota interactions in animal models and humans. *Genes & Development*, 27, 701–718.
- Koeth, R. A., Wang, Z., Levison, B. S., Buffa, J. A., Org, E., Sheehy, B. T., Britt, E. B., Fu, X., Wu, Y., Li, L., Smith, J. D., DiDonato, J. A., Chen, J., Li, H., Wu, G. D., Lewis, J. D., Warrier, M., Brown, J. M., Krauss, R. M., Tang, W. H. W., Bushman, F. D., Lusi, A. J., Hazen, S. L. (2013) Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nature Medicine* 19(5), 576–585.
- Lane, N. (2015). The unseen world: reflections on Leeuwenhoek (1677) “Concerning little animals.” *Philosophical Transactions of the Royal Society of London. Series B, Biological sciences*, 370, 1666.
- Ley, R. E. (2008). Evolution of mammals and their gut microbes. *Science*, 320(5883), 1647–1651.
- Ley, R. E., Bäckhed, F., Turnbaugh, P., Lozupone, C. A., Knight, R. D., & Gordon, J. I. (2005). Obesity alters gut microbial ecology. *Proceedings of the National Academy of Sciences of the United States of America*, 102, 11070.
- Ley, R. E., Peterson, D. A., & Gordon, J. I. (2006). Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell*, 124(4), 837–848.
- Lozupone, C. A., Stombaugh, J. I., Gordon, J. I., Jansson, J. K., & Knight, R. (2012). Diversity, stability and resilience of the human gut microbiota. *Nature*, 489, 220–230.
- Lu, S., Liu, X., Liu, C., Wang, X., & Cheng, G. (2019). Review of ammonia-oxidizing bacteria and archaea in freshwater ponds. *Reviews in Environmental Science and Biotechnology*, 18, 1.
- McFall-Ngai, M., Hadfield, M. G., Bosch, T. C. G., Carey, H. V., Domazet-Lošo, T., Douglas, E., Dubilier, N., Eberl, G., Fukami, T., Gilbert, S. F., Hentschel, U., King, N., Kjelleberg, S., Knoll, A. H., Kremer, N., Mazmanian, S. K., Metcalf, J. L., Neelson, K., Pierce, N. E., Rawls, J. F., Reid, A., Ruby, E. G., Rumpho, M., Sanders, J. G., Tautz, D., & Wernegreen, J. J. (2013). Animals in a bacterial world, a new imperative for the life sciences. *Proceedings of the National Academy of Sciences*, 110(9), 3229–3236.
- McNear, D. H., Jr. (2013). The rhizosphere – roots, soil and everything in between. *Nature Education Knowledge*, 4(3), 1.
- Muyzer, G., Teske, A., Wirsén, C. O., & Jannasch, H. W. (1995). Phylogenetic relationships of *Thiomicrospira* species and their identification in deep-sea hydrothermal vent samples by denaturing gradient gel electrophoresis of 16S rDNA fragments. *Archives of Microbiology*, 164, 165–172.
- Oren, A. (2009). Microbial diversity. In *Encyclopedia of life sciences*. Chichester: Wiley.
- Prussin, A. J., II, & Marr, L. C. (2015). Sources of airborne microorganisms in the built environment. *Microbiome*, 3, 78.
- Raina, J.-B., Eme, L., Pollock, E. J., Spang, A., Archibald, J. M., & Williams, T. A. (2018). Symbiosis in the microbial world: from ecology to genome evolution. *Biology Open*, 7(2), bio032524.
- Razavi, B. S., Hoang, D. T., Blagodatskaya, E., & Kuzyakov, Y. (2017). Mapping the footprint of nematodes in the rhizosphere: Cluster root formation and spatial distribution of enzyme activities. *Soil Biology and Biochemistry*, 115, 213–220.
- Relman, D. A. (2012). The human microbiome: Ecosystem resilience and health. *Nutrition Reviews*, 70, 2–9.
- Reperant, L. A., Brown, I. H., Haenen, O. L., de Jong, M. D., Osterhaus, A. D., Papa, A., Rimstad, E., Valarcher, J. F., & Kuiken, T. (2016). Companion animals as a source of viruses for hu-

- man beings and food production animals. *Journal of Comparative Pathology*, 155(1 Suppl 1), S41–S53.
- Rothman, J. M., Dierenfeld, E. S., Molina, D. O., Shaw, A. V., Hintz, H. F., & Pell, A. N. (2006). Nutritional chemistry of the diet of gorillas in the Bwindi Impenetrable National Park, Uganda. *American Journal of Primatology*, 68, 675–691.
- Schmidt, T. S., Raes, J., & Bork, P. (2018). The human microbiome: From association to modulation. *Cell*, 172(6), 1198–1215.
- Schulz, H. N., & De Beer, D. (2002). Uptake rates of oxygen and sulfide measured with individual *Thiomargarita namibiensis* cells by using microelectrodes. *Applied and Environmental Microbiology*, 68, 5746–5749.
- Shade, A., Peter, H., Allison, S., Baho, D., Berga, M., Buergermann, H., Huber, D., Langenheder, S., Lennon, J., Martiny, J., Matulich, K., Schmidt, T., & Handelsman, J. (2012). Fundamentals of microbial community resistance and resilience. *Frontiers in Microbiology*, 3, 417.
- Shreiner, A. B., Kao, J. Y., & Young, V. B. (2015). The gut microbiome in health and in disease. *Current Opinion in Gastroenterology*, 31(1), 69–75.
- Tasnim, N., Abulizi, N., Pither, J., Hart, M. M., & Gibson, D. L. (2017). Linking the gut microbial ecosystem with the environment: Does gut health depend on where we live? *Frontiers in Microbiology*, 8, 1935.
- The Human Microbiome Project Consortium. (2012). Structure, function and diversity of the healthy human microbiome. *Nature*, 486(7402), 207–214.
- Tomley, F. M., & Shirley, M. W. (2009). Livestock infectious diseases and zoonoses. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 364, 2637–2642.
- Trinh, P., Zaneveld, J. R., Safranek, S., & Rabinowitz, P. M. (2018). One health relationships between human, animal, and environmental microbiomes: A mini-review. *Frontiers in Public Health*, 6, 235.
- Valdes, A. M., Walter, J., Segal, E., & Spector, T. D. (2018). Role of the gut microbiota in nutrition and health. *BMJ*, 361, k2179.
- Vivarelli, S., Salemi, R., Candido, S., Falzone, L., Santagati, M., Stefani, S., Torino, F., Banna, G. L., Tonini, G., & Libra, M. (2019). Gut microbiota and cancer: From pathogenesis to therapy. *Cancers*, 11(1), 38.
- Wiedemann, A., Virlogeux-Payant, I., Chaussé, A. M., Schikora, A., & Velge, P. (2015). Interactions of *Salmonella* with animals and plants. *Frontiers in Microbiology*, 5, 791.
- Young, K. D. (2007). Bacterial morphology: Why have different shapes? *Current Opinion in Microbiology*, 10(6), 596–600.
- Zierer, J., Jackson, M. A., Kastenmüller, G., Mangino, M., Long, T., Telenti, A., Mohny, R. P., Small, K. S., Jordana, T., Bell, J. T., Steves, C. J., Valdes, A. M., Spector, T. D., & Menni, C. (2018). The fecal metabolome as a functional readout of the gut microbiome. *Nature Genetics*, 50, 790–795.

# Bağırsak Mikrobiyotasının Belirleyicileri

**Arunachalam Muthaiyan**

## 1. Giriş

Son yıllarda, insan mikrobiyotası, biyomedikal bilimlerdeki en sık odaklanılan dinamik araştırma alanlarından biridir. Özellikle, insan vücudunun mikrobiyotasının çoğunu barındıran gastrointestinal (GI) yolu incelemek için daha fazla çaba sarf edilmiştir (Huttenhower ve diğerleri 2014; Schmidt ve diğerleri 2018; Jalili-Firoozinezhad ve diğerleri. 2019). İnsan mikrobiyotası, bir insan vücudunun içinde ya da üzerinde yaşayan ve konağın sağlığını etkileyen bakteriler, arkeler, ökaryotik mikroplar, bakteriyofajlar ve ökaryotik virüslerin de dahil olduğu mikroorganizmalar topluluğudur (Hooper ve Gordon 2001; Huttenhower ve diğerleri 2012; D’Argenio ve Salvatore 2015; Wang ve diğerleri 2017; Hugon ve diğerleri 2017; Lederer ve diğerleri 2017). Bununla birlikte, ilginç bir şekilde, sağlıklı insan mikrobiyotası araştırmaları büyük ölçüde bakterilere odaklanmaktadır ve diğer mikrobiyal alanlara daha az önem verilmektedir (Lloyd-Price ve ark. 2016). Bu mikrobiyal toplulukla ilişkili genler, insan mikrobiyomu olarak adlandırılır ve bilim adamları, mikrobiyotanın bileşimini ve işlevini tanımlamak için mikrobiyomu kullanır (Amato 2017). İnsan mikrobiyomu; mikrobiyal genleri, gen ürünlerini ve mikrobiyotanın genomlarını içeren belirli bir mikrobiyotanın tüm genomik öğelerinin toplamını kapsar (Proctor 2011) (Kutu 1).

### **Kutu 1 Mikrobiyota mı Mikrobiyom mu?**

“Mikrobiyota” terimi, bakteriler, arkeler, ökaryotik mikroplar, bakteriyofajlar ve belirli bir ortamda (örn. deri ve gastrointestinal sistem) bulunan ökaryotik virüsler de dahil tüm mikroorganizmaları ifade eder. “Mikrobiyom”, mikrobiyota genomlarının tümü olarak tanımlanır. Bu mikroorganizmalar, bunların genleri ve metabolitleri, mikroorganizmaların birbirileri ile ve ayrıca konakçıları ile toplu olarak etkileşimleri mikrobiyomumuzu temsil eder. Bu iki terimin küçük farkları olsa da, mikrobiyota ve mikrobiyom sıklıkla birbirinin yerine kullanılır.

İnsan vücudu, biri ebeveynlerden miras kalan ve diğeri mikrobiyomdan elde edilen iki genom taşır. Bu kavram, insanların “holobiont” veya “süper organizmalar” olarak tanımlanmasının temelidir (Cavalier-Smith 1992; Grice ve Segre 2012; Walsh vd. 2014; van de Guchte vd. 2018). Ulusal Sağlık Ortak Fonu Enstitüleri, insan-mikro-

**KAYNAKLAR**

- Abdul Rahim, M. B. H., Chilloux, J., Martinez-Gili, L., et al. (2019). Diet-induced metabolic changes of the human gut microbiome: Importance of short-chain fatty acids, methylamines and indoles. *Acta Diabetologica*, 56, 493–500. <https://doi.org/10.1007/s00592-019-01312-x>.
- Abeles, S. R., Jones, M. B., Santiago-Rodriguez, T. M., et al. (2016). Microbial diversity in individuals and their household contacts following typical antibiotic courses. *Microbiome*, 4, 39. <https://doi.org/10.1186/s40168-016-0187-9>.
- Agans, R., Gordon, A., Kramer, D. L., et al. (2018). Dietary fatty acids sustain the growth of the human gut microbiota. *Applied and Environmental Microbiology*, 84, e01525-18. <https://doi.org/10.1128/AEM.01525-18>.
- Almeida, A., Mitchell, A. L., Boland, M., et al. (2019). A new genomic blueprint of the human gut microbiota. *Nature*, 568, 499–504. <https://doi.org/10.1038/s41586-019-0965-1>.
- Amato, K. R. (2017). An introduction to microbiome analysis for human biology applications. *American Journal of Human Biology*, 29, e22931. <https://doi.org/10.1002/ajhb.22931>.
- Anderson, J. R., Carroll, I., Azcarate-Peril, M. A., et al. (2017). A preliminary examination of gut microbiota, sleep, and cognitive flexibility in healthy older adults. *Sleep Medicine*, 38, 104–107. <https://doi.org/10.1016/j.sleep.2017.07.018>.
- Bahr, S. M., Tyler, B. C., Wooldridge, N., et al. (2015). Use of the second-generation antipsychotic, risperidone, and secondary weight gain are associated with an altered gut microbiota in children. *Translational Psychiatry*, 5, e652. <https://doi.org/10.1038/tp.2015.135>.
- Barton, W., Penney, N. C., Cronin, O., et al. (2017). The microbiome of professional athletes differs from that of more sedentary subjects in composition and particularly at the functional metabolic level. *Gut*, 67, 625–633. <https://doi.org/10.1136/gutjnl-2016-313627>.
- Belkaid, Y., & Hand, T. W. (2014). Role of the microbiota in immunity and inflammation. *Cell*, 157, 121–141. <https://doi.org/10.1016/J.CELL.2014.03.011>.
- Belstrøm, D., Holmstrup, P., Nielsen, C. H., et al. (2014). Bacterial profiles of saliva in relation to diet, lifestyle factors, and socioeconomic status. *Journal of Oral Microbiology*, 6, 23609. <https://doi.org/10.3402/jom.v6.23609>.
- Benedict, C., Vogel, H., Jonas, W., et al. (2016). Gut microbiota and glucometabolic alterations in response to recurrent partial sleep deprivation in normal-weight young individuals. *Molecular Metabolism*, 5, 1175–1186. <https://doi.org/10.1016/j.molmet.2016.10.003>.
- Bercik, P., Verdu, E. F., Foster, J. A., et al. (2010). Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice. *Gastroenterology*, 139, 2102–2112.e1. <https://doi.org/10.1053/J.GASTRO.2010.06.063>.
- Bezirtzoglou, E., Tsiotsias, A., & Welling, G. W. (2011). Microbiota profile in feces of breast- and formula-fed newborns by using fluorescence in situ hybridization (FISH). *Anaerobe*, 17, 478–482. <https://doi.org/10.1016/j.anaerobe.2011.03.009>.
- Bhalodi, A. A., van Engelen, T. S. R., Virk, H. S., & Wiersinga, W. J. (2019). Impact of antimicrobial therapy on the gut microbiome. *The Journal of Antimicrobial Chemotherapy*, 74, i6–i15. <https://doi.org/10.1093/jac/dky530>.
- Biasucci, G., Benenati, B., Morelli, L., et al. (2008). Cesarean delivery may affect the early biodiversity of intestinal bacteria. *The Journal of Nutrition*, 138, 1796S–1800S. <https://doi.org/10.1093/jn/138.9.1796S>.
- Bibbò, S., Ianiro, G., Giorgio, V., et al. (2016). The role of diet on gut microbiota composition. *European Review for Medical and Pharmacological Sciences*, 20, 4742–4749.
- Blaser, M. J. (2016). Antibiotic use and its consequences for the normal microbiome. *Science*, 352, 544–545. <https://doi.org/10.1126/science.aad9358>.
- Blaser, M. J., & Dominguez-Bello, M. G. (2016). The human microbiome before birth. *Cell Host & Microbe*, 20, 558–560. <https://doi.org/10.1016/j.chom.2016.10.014>.

- Blaser, M. J., & Falkow, S. (2009). What are the consequences of the disappearing human micro-biota? *Nature Reviews. Microbiology*, 7, 887–894. <https://doi.org/10.1038/nrmicro2245>.
- Blum, H. E. (2017). The human microbiome. *Advances in Medical Sciences*, 62, 414–420. <https://doi.org/10.1016/J.ADVMS.2017.04.005>.
- Boix-Amorós, A., Puente-Sánchez, F., du Toit, E., et al. (2019). Mycobiome profiles in breast milk from healthy women depend on mode of delivery, geographic location, and interaction with bacteria. *Applied and Environmental Microbiology*, 85, e02994-18. <https://doi.org/10.1128/aem.02994-18>.
- Borody, T. J., Eslick, G. D., & Clancy, R. L. (2019). Fecal microbiota transplantation as a new therapy: From Clostridioides difficile infection to inflammatory bowel disease, irritable bowel syndrome, and colon cancer. *Current Opinion in Pharmacology*, 49, 43–51.
- Bressa, C., Bailén-Andrino, M., Pérez-Santiago, J., et al. (2017). Differences in gut microbiota profile between women with active lifestyle and sedentary women. *PLoS One*, 12, e0171352. <https://doi.org/10.1371/journal.pone.0171352>.
- Browne, H. (2016). Antibiotics, gut bugs and the young. *Nature Reviews. Microbiology*, 14, 336. <https://doi.org/10.1038/nrmicro.2016.73>.
- Browne, H. P., Forster, S. C., Anonye, B. O., et al. (2016). Culturing of “unculturable” human microbiota reveals novel taxa and extensive sporulation. *Nature*, 533, 543–546. <https://doi.org/10.1038/nature17645>.
- Brüssow, H. (2015). Growth promotion and gut microbiota: Insights from antibiotic use. *Environmental Microbiology*, 17, 2216–2227. <https://doi.org/10.1111/1462-2920.12786>.
- Buffie, C. G., Bucci, V., Stein, R. R., et al. (2015). Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*. *Nature*, 517, 205–208. <https://doi.org/10.1038/nature13828>.
- Bunker, J. J., Flynn, T. M., Koval, J. C., et al. (2015). Innate and adaptive humoral responses coat distinct commensal bacteria with immunoglobulin A. *Immunity*, 43, 541–553. <https://doi.org/10.1016/J.IMMUNI.2015.08.007>.
- Cani, P. D. (2018). Human gut microbiome: Hopes, threats and promises. *Gut*, 67, 1716–1725. <https://doi.org/10.1136/gutjnl-2018-316723>.
- Cani, P.D., & Knauf, C. (2016). How gut microbes talk to organs: The role of endocrine and nervous routes. *Molecular Metabolism*, 5, 743–752. <https://doi.org/10.1016/j.molmet.2016.05.011>.
- Cao, X. (2017). Intestinal inflammation induced by oral bacteria. *Science*, 358, 308–309. <https://doi.org/10.1126/science.aap9298>.
- Cavalier-Smith, T. (1992). Symbiosis as a source of evolutionary innovation: Speciation and morphogenesis. *Trends in Ecology & Evolution*, 7, 422–423. [https://doi.org/10.1016/0169-5347\(92\)90028-A](https://doi.org/10.1016/0169-5347(92)90028-A).
- Cerf-Bensussan, N., & Gaboriau-Routhiau, V. (2010). The immune system and the gut microbiota: Friends or foes? *Nature Reviews. Immunology*, 10, 735–744. <https://doi.org/10.1038/nri2850>.
- Chakraborti, D., Rahman, M. M., Chatterjee, A., et al. (2016). Fate of over 480 million inhabitants living in arsenic and fluoride endemic Indian districts: Magnitude, health, socio-economic effects and mitigation approaches. *Journal of Trace Elements in Medicine and Biology*, 38, 33–45.
- Chen, L., Zhang, Y.-H., Huang, T., & Cai, Y.-D. (2016). Gene expression profiling gut microbiota in different races of humans. *Scientific Reports*, 6, 23075. <https://doi.org/10.1038/srep23075>.
- Chi, L., Bian, X., Gao, B., et al. (2017). The effects of an environmentally relevant level of arsenic on the gut microbiome and its functional metagenome. *Toxicological Sciences*, 160, 193–204. <https://doi.org/10.1093/toxsci/kfx174>.
- Chu, D. M., Seferovic, M., Pace, R. M., & Aagaard, K. M. (2018). The microbiome in preterm birth. *Best Practice & Research. Clinical Obstetrics & Gynaecology*, 52, 103–113.
- Chung, H., Pamp, S. J., Hill, J. A., et al. (2012). Gut immune maturation depends on coloni-

- zation with a host-specific microbiota. *Cell*, 149, 1578–1593. <https://doi.org/10.1016/j.CELL.2012.04.037>.
- Claesson, M. J., Jeffery, I. B., Conde, S., et al. (2012). Gut microbiota composition correlates with diet and health in the elderly. *Nature*, 488, 178–184. <https://doi.org/10.1038/nature11319>.
- Codagnone, M. G., Spichak, S., O'Mahony, S. M., et al. (2019). Programming bugs: Microbiota and the developmental origins of brain health and disease. *Biological Psychiatry*, 85, 150–163. <https://doi.org/10.1016/j.biopsych.2018.06.014>.
- Collado, M. C., Cernada, M., Neu, J., et al. (2015). Factors influencing gastrointestinal tract and microbiota immune interaction in preterm infants. *Pediatric Research*, 77, 726–731. <https://doi.org/10.1038/pr.2015.54>.
- Collado, M. C., Delgado, S., Maldonado, A., & Rodríguez, J. M. (2009). Assessment of the bacterial diversity of breast milk of healthy women by quantitative real-time PCR. *Letters in Applied Microbiology*, 48, 523–528. <https://doi.org/10.1111/j.1472-765X.2009.02567.x>.
- Costalos, C., Kapiki, A., Apostolou, M., & Papatoma, E. (2008). The effect of a prebiotic supplemented formula on growth and stool microbiology of term infants. *Early Human Development*, 84, 45–49. <https://doi.org/10.1016/j.earlhumdev.2007.03.001>.
- Cotten, C. M. (2016). Adverse consequences of neonatal antibiotic exposure. *Current Opinion in Pediatrics*, 28, 141–149. <https://doi.org/10.1097/MOP.0000000000000338>.
- de la Cuesta-Zuluaga, J., Kelley, S. T., Chen, Y., et al. (2019). Age- and sex-dependent patterns of gut microbial diversity in human adults. *mSystems*, 4, e00261-19. <https://doi.org/10.1128/mSystems.00261-19>.
- D'Argenio, V., & Salvatore, F. (2015). The role of the gut microbiome in the healthy adult status. *Clinica Chimica Acta*, 451, 97–102. <https://doi.org/10.1016/j.CCA.2015.01.003>.
- Daliri, E. B. M., Tango, C. N., Lee, B. H., & Oh, D. H. (2018). Human microbiome restoration and safety. *International Journal of Medical Microbiology*, 308, 487–497.
- David, L. A., Maurice, C. F., Carmody, R. N., et al. (2014). Diet rapidly and reproducibly alters the human gut microbiome. *Nature*, 505, 559–563. <https://doi.org/10.1038/nature12820>.
- De Filippis, F., Pellegrini, N., Vannini, L., et al. (2016). High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut*, 65, 1812–1821. <https://doi.org/10.1136/gutjnl-2015-309957>.
- De Filippo, C., Cavalieri, D., Di Paola, M., et al. (2010). Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proceedings of the National Academy of Sciences*, 107, 14691–14696. <https://doi.org/10.1073/pnas.1005963107>.
- Derrien, M., & Veiga, P. (2017). Rethinking diet to aid human–microbe symbiosis. *Trends in Microbiology*, 25, 100–112. <https://doi.org/10.1016/j.tim.2016.09.011>.
- Dethlefsen, L., Huse, S., Sogin, M. L., & Relman, D. A. (2008). The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biology*, 6, e280. <https://doi.org/10.1371/journal.pbio.0060280>.
- Dethlefsen, L., & Relman, D. A. (2011). Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proceedings of the National Academy of Sciences*, 108, 4554–4561. <https://doi.org/10.1073/pnas.1000087107>.
- DiGiulio, D. B., Romero, R., Amogan, H. P., et al. (2008). Microbial prevalence, diversity and abundance in amniotic fluid during preterm labor: A molecular and culture-based investigation. *PLoS One*, 3, e3056. <https://doi.org/10.1371/journal.pone.0003056>.
- Dill-McFarland, K. A., Tang, Z.-Z., Kemis, J. H., et al. (2019). Close social relationships correlate with human gut microbiota composition. *Scientific Reports*, 9, 703. <https://doi.org/10.1038/s41598-018-37298-9>.
- Dinan, T. G., Stilling, R. M., Stanton, C., & Cryan, J. F. (2015). Collective unconscious: How gut microbes shape human behavior. *Journal of Psychiatric Research*, 63, 1–9.
- Dominguez-Bello, M. G., Costello, E. K., Contreras, M., et al. (2010). Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in new-

- borns. *Proceedings of the National Academy of Sciences of the United States of America*, 107, 11971–11975. <https://doi.org/10.1073/pnas.1002601107>.
- Dominguez-Bello, M. G., De Jesus-Laboy, K. M., Shen, N., et al. (2016). Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nature Medicine*, 22, 250–253. <https://doi.org/10.1038/nm.4039>.
- Dong, T. S., & Gupta, A. (2019). Influence of early life, diet, and the environment on the microbiome. *Clinical Gastroenterology and Hepatology*, 17, 231–242.
- Duerkop, B. A., Vaishnava, S., & Hooper, L. V. (2009). Immune responses to the microbiota at the intestinal mucosal surface. *Immunity*, 31, 368–376. <https://doi.org/10.1016/J.IMMUNI.2009.08.009>.
- Ercolini, D., & Fogliano, V. (2018). Food design to feed the human gut microbiota. *Journal of Agricultural and Food Chemistry*, 66, 3754–3758. <https://doi.org/10.1021/acs.jafc.8b00456>.
- Fallani, M., Amarri, S., Uusijarvi, A., et al. (2011). Determinants of the human infant intestinal microbiota after the introduction of first complementary foods in infant samples from five European centres. *Microbiology*, 157, 1385–1392. <https://doi.org/10.1099/mic.0.042143-0>.
- Fanaro, S., Chierici, R., Guerrini, P., & Vigi, V. (2003). Intestinal microflora in early infancy: Composition and development. *Acta Paediatrica. Supplement*, 91, 48–55. <https://doi.org/10.1111/j.1651-2227.2003.tb00646.x>.
- Fernández, L., Langa, S., Martín, V., et al. (2013). The human milk microbiota: Origin and potential roles in health and disease. *Pharmacological Research*, 69, 1–10. <https://doi.org/10.1016/j.phrs.2012.09.001>.
- Ferrer, M., Martins dos Santos, V. A. P., Ott, S. J., & Moya, A. (2014). Gut microbiota disturbance during antibiotic therapy: A multi-omic approach. *Gut Microbes*, 5, 64–70. <https://doi.org/10.4161/gmic.27128>.
- Ferrer, M., Méndez-García, C., Rojo, D., et al. (2017). Antibiotic use and microbiome function. *Biochemical Pharmacology*, 134, 114–126. <https://doi.org/10.1016/j.bcp.2016.09.007>.
- Ferretti, P., Pasolli, E., Tett, A., et al. (2018). Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. *Cell Host & Microbe*, 24, 133–145.e5. <https://doi.org/10.1016/j.chom.2018.06.005>.
- Field, C. J. (2005). The immunological components of human milk and their effect on immune development in infants. *The Journal of Nutrition*, 135, 1–4. <https://doi.org/10.1093/jn/135.1.1>.
- Flint, H. J., Duncan, S. H., & Louis, P. (2017). The impact of nutrition on intestinal bacterial communities. *Current Opinion in Microbiology*, 38, 59–65. <https://doi.org/10.1016/j.mib.2017.04.005>.
- Flint, H. J., Duncan, S. H., Scott, K. P., & Louis, P. (2015). Links between diet, gut microbiota composition and gut metabolism. *The Proceedings of the Nutrition Society*, 74, 13–22. <https://doi.org/10.1017/S0029665114001463>.
- Flint, H. J., Scott, K. P., Louis, P., & Duncan, S. H. (2012). The role of the gut microbiota in nutrition and health. *Nature Reviews. Gastroenterology & Hepatology*, 9, 577–589. <https://doi.org/10.1038/nrgastro.2012.156>.
- Flowers, S. A., Evans, S. J., Ward, K. M., et al. (2017). Interaction between atypical antipsychotics and the gut microbiome in a bipolar disease cohort. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 37, 261–267. <https://doi.org/10.1002/phar.1890>.
- Food and Agriculture Organization of the United Nations WHO. (2006). *Probiotics in food: health and nutritional properties and guidelines for evaluation*. NLM Catalog – NCBI. <https://www.ncbi.nlm.nih.gov/nlmcatalog/101617803>. Accessed 22 Dec 2019.
- Francino, M. P. (2016). Antibiotics and the human gut microbiome: Dysbioses and accumulation of resistances. *Frontiers in Microbiology*, 6, 1543. <https://doi.org/10.3389/fmicb.2015.01543>.
- Fu, J., Bonder, M. J., Cenit, M. C., et al. (2015). The gut microbiome contributes to a substantial proportion of the variation in blood lipids. *Circulation Research*, 117, 817–824. <https://doi.org/10.1161/CIRCRESAHA.115.306807>.

- Fuertes, A., Pérez-Burillo, S., Apaolaza, I., et al. (2019). Adaptation of the human gut microbiota metabolic network during the first year after birth. *Frontiers in Microbiology*, *10*, 848. <https://doi.org/10.3389/fmicb.2019.00848>.
- Ghosh, T. S., Gupta, S. S., Nair, G. B., & Mande, S. S. (2013). In silico analysis of antibiotic resistance genes in the gut microflora of individuals from diverse geographies and age-groups. *PLoS One*, *8*, e83823. <https://doi.org/10.1371/journal.pone.0083823>.
- Gillings, M., Paulsen, I., Tetu, S., et al. (2015). Ecology and evolution of the human microbiota: Fire, farming and antibiotics. *Genes (Basel)*, *6*, 841–857. <https://doi.org/10.3390/genes6030841>.
- Glick-Bauer, M., & Yeh, M.-C. (2014). The health advantage of a vegan diet: Exploring the gut microbiota connection. *Nutrients*, *6*, 4822–4838. <https://doi.org/10.3390/nu6114822>.
- Gomez-Arango, L. F., Barrett, H. L., McIntyre, H. D., et al. (2017). Antibiotic treatment at delivery shapes the initial oral microbiome in neonates. *Scientific Reports*, *7*, 43481. <https://doi.org/10.1038/srep43481>.
- Gomez-Gallego, C., Garcia-Mantrana, I., Salminen, S., & Collado, M. C. (2016). The human milk microbiome and factors influencing its composition and activity. *Seminars in Fetal & Neonatal Medicine*, *21*, 400–405. <https://doi.org/10.1016/J.SINY.2016.05.003>.
- Goodrich, J. K., Davenport, E. R., Beaumont, M., et al. (2016). Genetic determinants of the gut microbiome in UK twins. *Cell Host & Microbe*, *19*, 731–743. <https://doi.org/10.1016/J.CHOM.2016.04.017>.
- Goodrich, J. K., Davenport, E. R., Clark, A. G., & Ley, R. E. (2017). The relationship between the human genome and microbiome comes into view. *Annual Review of Genetics*, *51*, 413–433. <https://doi.org/10.1146/annurev-genet-110711-155532>.
- Goodrich, J. K., Waters, J. L., Poole, A. C., et al. (2014). Human genetics shape the gut microbiome. *Cell*, *159*, 789–799. <https://doi.org/10.1016/j.cell.2014.09.053>.
- Górska, A., Peter, S., Willmann, M., et al. (2018). Dynamics of the human gut phageome during antibiotic treatment. *Computational Biology and Chemistry*, *74*, 420–427. <https://doi.org/10.1016/j.compbiolchem.2018.03.011>.
- Grady, N. G., Petrof, E. O., & Claud, E. C. (2016). Microbial therapeutic interventions. *Seminars in Fetal & Neonatal Medicine*, *21*, 418–423. <https://doi.org/10.1016/J.SINY.2016.04.005>.
- Grice, E. A., & Segre, J. A. (2012). The human microbiome: Our second genome. *Annual Review of Genomics and Human Genetics*, *13*, 151–170. <https://doi.org/10.1146/annurev-genom-090711-163814>.
- Guaraldi, F., & Salvatori, G. (2012). Effect of breast and formula feeding on gut microbiota shaping in newborns. *Frontiers in Cellular and Infection Microbiology*, *2*, 94. <https://doi.org/10.3389/fcimb.2012.00094>.
- Guarner, F. (2015). The gut microbiome: What do we know? *Clinics in Liver Disease*, *5*, 86–90. <https://doi.org/10.1002/cld.454>.
- Gurwitz, D. (2013). The gut microbiome: Insights for personalized medicine. *Drug Development Research*, *74*, 341–343. <https://doi.org/10.1002/ddr.21095>.
- Haak, B. W., Lankelma, J. M., Hugenholtz, F., et al. (2019). Long-term impact of oral vancomycin, ciprofloxacin and metronidazole on the gut microbiota in healthy humans. *The Journal of Antimicrobial Chemotherapy*, *74*, 782–786. <https://doi.org/10.1093/jac/dky471>.
- Hasan, N., & Yang, H. (2019). Factors affecting the composition of the gut microbiota, and its modulation. *PeerJ*, *7*, e7502. <https://doi.org/10.7717/peerj.7502>.
- Heintz-Buschart, A., & Wilmes, P. (2018). Human gut microbiome: Function matters. *Trends in Microbiology*, *26*, 563–574. <https://doi.org/10.1016/J.TIM.2017.11.002>.
- Hill, C., Guarner, F., Reid, G., et al. (2014). Expert consensus document: The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature Reviews. Gastroenterology & Hepatology*, *11*, 506–514. <https://doi.org/10.1038/nrgastro.2014.66>.
- Hooper, L. V., & Gordon, J. I. (2001). Commensal host-bacterial relationships in the gut. *Science*,

- 292, 1115–1118. <https://doi.org/10.1126/SCIENCE.1058709>.
- Huang, X., Fan, X., Ying, J., & Chen, S. (2019). Emerging trends and research foci in gastrointestinal microbiome. *Journal of Translational Medicine*, *17*, 67. <https://doi.org/10.1186/s12967-019-1810-x>.
- Hugon, P., Lagier, J.-C., Colson, P., et al. (2017). Repertoire of human gut microbes. *Microbial Pathogenesis*, *106*, 103–112. <https://doi.org/10.1016/j.micpath.2016.06.020>.
- Huttenhower, C., Gevers, D., Knight, R., et al. (2012). Structure, function and diversity of the healthy human microbiome. *Nature*, *486*, 207–214. <https://doi.org/10.1038/nature11234>.
- Huttenhower, C., Knight, R., Brown, C. T., et al. (2014). Advancing the microbiome research community. *Cell*, *159*, 227–230. <https://doi.org/10.1016/J.CELL.2014.09.022>.
- Ianiro, G., Tilg, H., & Gasbarrini, A. (2016). Antibiotics as deep modulators of gut microbiota: Between good and evil. *Gut*, *65*, 1906–1915. <https://doi.org/10.1136/gutjnl-2016-312297>.
- Iizumi, T., Battaglia, T., Ruiz, V., & Perez Perez, G. I. (2017). Gut microbiome and antibiotics. *Archives of Medical Research*, *48*, 727–734. <https://doi.org/10.1016/j.arcmed.2017.11.004>.
- Imhann, F., Bonder, M. J., Vila, A. V., et al. (2016). Proton pump inhibitors affect the gut microbiome. *Gut*, *65*, 740–748. <https://doi.org/10.1136/gutjnl-2015-310376>.
- Isaac, S., Scher, J. U., Djukovic, A., et al. (2017). Short- and long-term effects of oral vancomycin on the human intestinal microbiota. *The Journal of Antimicrobial Chemotherapy*, *72*, 128–136. <https://doi.org/10.1093/jac/dkw383>.
- Iyengar, S. R., & Walker, W. A. (2012). Immune factors in breast milk and the development of atopic disease. *Journal of Pediatric Gastroenterology and Nutrition*, *55*, 641–647. <https://doi.org/10.1097/MPG.0b013e3182617a9d>.
- Jackson, M. A., Goodrich, J. K., Maxan, M. E., et al. (2016). Proton pump inhibitors alter the composition of the gut microbiota. *Gut*, *65*, 749–756. <https://doi.org/10.1136/gutjnl-2015-310861>.
- Jain, A., Li, X. H., & Chen, W. N. (2018). Similarities and differences in gut microbiome composition correlate with dietary patterns of Indian and Chinese adults. *AMB Express*, *8*, 104. <https://doi.org/10.1186/s13568-018-0632-1>.
- Jacobsson, H. E., Abrahamsson, T. R., Jenmalm, M. C., et al. (2014). Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by Caesarean section. *Gut*, *63*, 559–566. <https://doi.org/10.1136/gutjnl-2012-303249>.
- Jacobsson, H. E., Jernberg, C., Andersson, A. F., et al. (2010). Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. *PLoS One*, *5*, e9836. <https://doi.org/10.1371/journal.pone.0009836>.
- Jalili-Firoozinezhad, S., Gazzaniga, F. S., Calamari, E. L., et al. (2019). A complex human gut microbiome cultured in an anaerobic intestine-on-a-chip. *Nature Biomedical Engineering*, *3*(7), 520–531. <https://doi.org/10.1038/s41551-019-0397-0>.
- Jefferson, A., & Adolphus, K. (2019). The effects of intact cereal grain fibers, including wheat bran on the gut microbiota composition of healthy adults: A systematic review. *Frontiers in Nutrition*, *6*, 33. <https://doi.org/10.3389/fnut.2019.00033>.
- Jernberg, C., Löfmark, S., Edlund, C., & Jansson, J. K. (2007). Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. *The ISME Journal*, *1*, 56–66. <https://doi.org/10.1038/ismej.2007.3>.
- Jiang, H., Ling, Z., Zhang, Y., et al. (2015). Altered fecal microbiota composition in patients with major depressive disorder. *Brain, Behavior, and Immunity*, *48*, 186–194. <https://doi.org/10.1016/j.bbi.2015.03.016>.
- Jin, Y., Wu, S., Zeng, Z., & Fu, Z. (2017). Effects of environmental pollutants on gut microbiota. *Environmental Pollution*, *222*, 1–9.
- Kamo, T., Akazawa, H., Suda, W., et al. (2017). Dysbiosis and compositional alterations with aging in the gut microbiota of patients with heart failure. *PLoS One*, *12*, e0174099. <https://doi.org/10.1371/journal.pone.0174099>.
- Kau, A. L., Ahern, P. P., Griffin, N. W., et al. (2011). Human nutrition, the gut microbiome and the

- immune system. *Nature*, 474, 327–336. <https://doi.org/10.1038/nature10213>.
- Keeney, K. M., Yurist-Doutsch, S., Arrieta, M.-C., & Finlay, B. B. (2014). Effects of antibiotics on human microbiota and subsequent disease. *Annual Review of Microbiology*, 68, 217–235. <https://doi.org/10.1146/annurev-micro-091313-103456>.
- Khangwal, I., & Shukla, P. (2019). Combinatory biotechnological intervention for gut microbiota. *Applied Microbiology and Biotechnology*, 103, 3615–3625. <https://doi.org/10.1007/s00253-019-09727-w>.
- Kho, Z. Y., & Lal, S. K. (2018). The human gut microbiome – a potential controller of wellness and disease. *Frontiers in Microbiology*, 9, 1835. <https://doi.org/10.3389/fmicb.2018.01835>.
- Kim, H., Sitarik, A. R., Woodcroft, K., et al. (2019). Birth mode, breastfeeding, pet exposure, and antibiotic use: Associations with the gut microbiome and sensitization in children. *Current Allergy and Asthma Reports*, 19, 22. <https://doi.org/10.1007/s11882-019-0851-9>.
- Kim, H. N., Yun, Y., Ryu, S., et al. (2018). Correlation between gut microbiota and personality in adults: A cross-sectional study. *Brain, Behavior, and Immunity*, 69, 374–385. <https://doi.org/10.1016/j.bbi.2017.12.012>.
- Kim, M., Qie, Y., Park, J., & Kim, C. H. (2016). Gut microbial metabolites fuel host antibody responses. *Cell Host & Microbe*, 20, 202–214. <https://doi.org/10.1016/j.chom.2016.07.001>.
- Kish, L., Hotte, N., Kaplan, G. G., et al. (2013). Environmental particulate matter induces murine intestinal inflammatory responses and alters the gut microbiome. *PLoS One*, 8, e62220. <https://doi.org/10.1371/journal.pone.0062220>.
- Kisuse, J., La-ongkham, O., Nakphaichit, M., et al. (2018). Urban diets linked to gut microbiome and metabolome alterations in children: A comparative cross-sectional study in Thailand. *Frontiers in Microbiology*, 9, 1345. <https://doi.org/10.3389/fmicb.2018.01345>.
- Koch, M. A., Reiner, G. L., Lugo, K. A., et al. (2016). Maternal IgG and IgA antibodies dampen mucosal T helper cell responses in early life. *Cell*, 165, 827–841. <https://doi.org/10.1016/j.CELL.2016.04.055>.
- Koenig, J. E., Spor, A., Scalfone, N., et al. (2011). Succession of microbial consortia in the developing infant gut microbiome. *Proceedings of the National Academy of Sciences*, 108, 4578–4585. <https://doi.org/10.1073/pnas.1000081107>.
- Korpela, K., Salonen, A., Virta, L. J., et al. (2016). Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. *Nature Communications*, 7, 10410. <https://doi.org/10.1038/ncomms10410>.
- Kovacs, A., Ben-Jacob, N., Tayem, H., et al. (2011). Genotype is a stronger determinant than sex of the mouse gut microbiota. *Microbial Ecology*, 61, 423–428. <https://doi.org/10.1007/s00248-010-9787-2>.
- Kristensen, N. B., Bryrup, T., Allin, K. H., et al. (2016). Alterations in fecal microbiota composition by probiotic supplementation in healthy adults: A systematic review of randomized controlled trials. *Genome Medicine*, 8, 52. <https://doi.org/10.1186/s13073-016-0300-5>.
- Kumbhare, S. V., Patangia, D. V., Patil, R. H., et al. (2019). Factors influencing the gut microbiome in children: From infancy to childhood. *Journal of Biosciences*, 44, 49. <https://doi.org/10.1007/s12038-019-9860-z>.
- Kump, P., Wurm, P., Gröchenig, H. P., et al. (2018). The taxonomic composition of the donor intestinal microbiota is a major factor influencing the efficacy of faecal microbiota transplantation in therapy refractory ulcerative colitis. *Alimentary Pharmacology & Therapeutics*, 47, 67–77. <https://doi.org/10.1111/apt.14387>.
- Lagier, J. C., Khelaifia, S., Alou, M. T., et al. (2016). Culture of previously uncultured members of the human gut microbiota by culturomics. *Nature Microbiology*, 1, 16203. <https://doi.org/10.1038/nmicrobiol.2016.203>.
- Lang, J. M., Pan, C., Cantor, R. M., et al. (2018). Impact of individual traits, saturated fat, and protein source on the gut microbiome. *MBio*, 9, e01604–e01618. <https://doi.org/10.1128/MBIO.01604-18>.

- Le Bastard, Q., Al-Ghalith, G. A., Grégoire, M., et al. (2018). Systematic review: Human gut dysbiosis induced by non-antibiotic prescription medications. *Alimentary Pharmacology & Therapeutics*, *47*, 332–345. <https://doi.org/10.1111/apt.14451>.
- Le Huërrou-Luron, I., Blat, S., & Boudry, G. (2010). Breast- v. formula-feeding: Impacts on the digestive tract and immediate and long-term health effects. *Nutrition Research Reviews*, *23*, 23–36. <https://doi.org/10.1017/S0954422410000065>.
- LeBlanc, J. G., Milani, C., de Giori, G. S., et al. (2013). Bacteria as vitamin suppliers to their host: A gut microbiota perspective. *Current Opinion in Biotechnology*, *24*, 160–168. <https://doi.org/10.1016/j.copbio.2012.08.005>.
- Lederer, A.-K., Pisanski, P., Kousoulas, L., et al. (2017). Postoperative changes of the microbiome: Are surgical complications related to the gut flora? A systematic review. *BMC Surgery*, *17*, 125. <https://doi.org/10.1186/s12893-017-0325-8>.
- Lee, J. A., & Stern, J. M. (2019). Understanding the link between gut microbiome and urinary stone disease. *Current Urology Reports*, *20*, 19. <https://doi.org/10.1007/s11934-019-0882-8>.
- Lee, Y.-K. (2013). Effects of diet on gut microbiota profile and the implications for health and disease. *Bioscience of Microbiota, Food and Health*, *32*, 1–12. <https://doi.org/10.12938/bmfh.32.1>.
- Lei, Y. M. K., Nair, L., & Alegre, M.-L. (2015). The interplay between the intestinal microbiota and the immune system. *Clinics and Research in Hepatology and Gastroenterology*, *39*, 9–19. <https://doi.org/10.1016/J.CLINRE.2014.10.008>.
- Lemas, D. J., Yee, S., Cacho, N., et al. (2016). Exploring the contribution of maternal antibiotics and breastfeeding to development of the infant microbiome and pediatric obesity. *Seminars in Fetal & Neonatal Medicine*, *21*, 406–409. <https://doi.org/10.1016/J.SINY.2016.04.013>.
- Ley, R. E., Peterson, D. A., & Gordon, J. I. (2006). Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell*, *124*, 837–848. <https://doi.org/10.1016/j.cell.2006.02.017>.
- Li, H., Li, T., Li, X., et al. (2018). Gut microbiota in Tibetan herders reflects the degree of urbanization. *Frontiers in Microbiology*, *9*, 1745. <https://doi.org/10.3389/fmicb.2018.01745>.
- Lieberman, T. D. (2018). Seven billion microcosms: Evolution within human microbiomes. *mSystems*, *3*, e00171-17. <https://doi.org/10.1128/mSystems.00171-17>.
- Lin, A., Bik, E. M., Costello, E. K., et al. (2013). Distinct distal gut microbiome diversity and composition in healthy children from Bangladesh and the United States. *PLoS One*, *8*, e53838. <https://doi.org/10.1371/journal.pone.0053838>.
- Lloyd-Price, J., Abu-Ali, G., & Huttenhower, C. (2016). The healthy human microbiome. *Genome Medicine*, *8*, 51. <https://doi.org/10.1186/s13073-016-0307-y>.
- Losasso, C., Eckert, E. M., Mastrorilli, E., et al. (2018). Assessing the influence of vegan, vegetarian and omnivore oriented westernized dietary styles on human gut microbiota: A cross sectional study. *Frontiers in Microbiology*, *9*, 317. <https://doi.org/10.3389/fmicb.2018.00317>.
- Lozupone, C. A., Stombaugh, J. I., Gordon, J. I., et al. (2012). Diversity, stability and resilience of the human gut microbiota. *Nature*, *489*, 220–230. <https://doi.org/10.1038/nature11550>.
- Lupp, C., Robertson, M. L., Wickham, M. E., et al. (2007). Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of Enterobacteriaceae. *Cell Host & Microbe*, *2*, 119–129. <https://doi.org/10.1016/j.chom.2007.06.010>.
- Lynch, S. V., & Pedersen, O. (2016). The human intestinal microbiome in health and disease. *The New England Journal of Medicine*, *375*, 2369–2379. <https://doi.org/10.1056/NEJM-ra1600266>.
- Lyu, Q., & Hsu, C.-C. (2018). Can diet influence our health by altering intestinal microbiota-derived fecal metabolites? *mSystems*, *3*, e00187-17. <https://doi.org/10.1128/mSystems.00187-17>.
- Macfarlane, S., Macfarlane, G. T., & Cummings, J. H. (2006). Review article: Prebiotics in the gastrointestinal tract. *Alimentary Pharmacology & Therapeutics*, *24*, 701–714.
- Magnúsdóttir, S., & Thiele, I. (2018). Modeling metabolism of the human gut microbiome. *Cur-*

- rent Opinion in Biotechnology, 51, 90–96. <https://doi.org/10.1016/J.COPBIO.2017.12.005>.
- Maier, L., Pruteanu, M., Kuhn, M., et al. (2018). Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature*, 555, 623–628. <https://doi.org/10.1038/nature25979>.
- Malys, M. K., Campbell, L., & Malys, N. (2015). Symbiotic and antibiotic interactions between gut commensal microbiota and host immune system. *Medicina (Kaunas)*, 51, 69–75.
- Mändar, R., & Mikelsaar, M. (1996). Transmission of mother's microflora to the newborn at birth. *Neonatology*, 69, 30–35. <https://doi.org/10.1159/000244275>.
- Mariat, D., Firmesse, O., Levenez, F., et al. (2009). The Firmicutes/Bacteroidetes ratio of the human microbiota changes with age. *BMC Microbiology*, 9, 123. <https://doi.org/10.1186/1471-2180-9-123>.
- Martin, R., Makino, H., Yavuz, A. C., et al. (2016). Early-life events, including mode of delivery and type of feeding, siblings and gender, shape the developing gut microbiota. *PLoS One*, 11, e0158498. <https://doi.org/10.1371/journal.pone.0158498>.
- Martin, V., Maldonado-Barragán, A., Moles, L., et al. (2012). Sharing of bacterial strains between breast milk and infant feces. *Journal of Human Lactation*, 28, 36–44. <https://doi.org/10.1177/0890334411424729>.
- Martínez, I., Lattimer, J. M., Hubach, K. L., et al. (2013). Gut microbiome composition is linked to whole grain-induced immunological improvements. *The ISME Journal*, 7, 269–280. <https://doi.org/10.1038/ismej.2012.104>.
- Matamoros, S., Gras-Leguen, C., Le Vacon, F., et al. (2013). Development of intestinal microbiota in infants and its impact on health. *Trends in Microbiology*, 21, 167–173.
- Matijašič, B. B., Obermajer, T., Lipoglavšek, L., et al. (2014). Association of dietary type with fecal microbiota in vegetarians and omnivores in Slovenia. *European Journal of Nutrition*, 53, 1051–1064. <https://doi.org/10.1007/s00394-013-0607-6>.
- Maurice, C. F., Haiser, H. J., & Turnbaugh, P. J. (2013). Xenobiotics shape the physiology and gene expression of the active human gut microbiome. *Cell*, 152, 39–50. <https://doi.org/10.1016/J.CELL.2012.10.052>.
- McDonald, D., Hyde, E., Debelius, J. W., et al. (2018). American gut: An open platform for citizen science microbiome research. *mSystems*, 3, e00031-18. <https://doi.org/10.1128/mSystems.00031-18>.
- Milani, C., Duranti, S., Bottacini, F., et al. (2017). The first microbial colonizers of the human gut: Composition, activities, and health implications of the infant gut microbiota. *Microbiology and Molecular Biology Reviews*, 81, e00036-17. <https://doi.org/10.1128/MMBR.00036-17>.
- Modi, S. R., Collins, J. J., & Relman, D. A. (2014). Antibiotics and the gut microbiota. *The Journal of Clinical Investigation*, 124, 4212–4218.
- Moschen, A. R., Wieser, V., & Tilg, H. (2012). Dietary factors: Major regulators of the gut's microbiota. *Gut and Liver*, 6, 411–416. <https://doi.org/10.5009/gnl.2012.6.4.411>.
- Moya, A., & Ferrer, M. (2016). Functional redundancy-induced stability of gut microbiota subjected to disturbance. *Trends in Microbiology*, 24, 402–413.
- Mshvildadze, M., Neu, J., & Mai, V. (2008). Intestinal microbiota development in the premature neonate: Establishment of a lasting commensal relationship? *Nutrition Reviews*, 66, 658–663. <https://doi.org/10.1111/j.1753-4887.2008.00119.x>.
- Murphy, K., O'Shea, C. A., Ryan, C. A., et al. (2015). The gut microbiota composition in dichorionic triplet sets suggests a role for host genetic factors. *PLoS One*, 10, e0122561. <https://doi.org/10.1371/journal.pone.0122561>.
- Mutlu, E. A., Comba, I. Y., Cho, T., et al. (2018). Inhalational exposure to particulate matter air pollution alters the composition of the gut microbiome. *Environmental Pollution*, 240, 817–830. <https://doi.org/10.1016/j.envpol.2018.04.130>.
- Nayfach, S., Shi, Z. J., Seshadri, R., et al. (2019). New insights from uncultivated genomes of the global human gut microbiome. *Nature*, 568, 505–510. <https://doi.org/10.1038/s41586-019-1058-x>.

- Neish, A. S. (2009). Microbes in gastrointestinal health and disease. *Gastroenterology*, *136*, 65–80. <https://doi.org/10.1053/j.gastro.2008.10.080>.
- Neu, J. (2016). The microbiome during pregnancy and early postnatal life. *Seminars in Fetal & Neonatal Medicine*, *21*, 373–379. <https://doi.org/10.1016/j.siny.2016.05.001>.
- NIH Common Fund. (2019, May 29). The Human Microbiome Project expands the toolbox for studying host and microbiome interactions. National Institutes of Health (NIH). *News Releases*. <https://www.nih.gov/news-events/news-releases/human-microbiome-project-expands-tool-box-studying-host-microbiome-interactions>. Accessed 29 May 2019.
- Nogueira, T., David, P. H. C., & Pothier, J. (2019). Antibiotics as both friends and foes of the human gut microbiome: The microbial community approach. *Drug Development Research*, *80*, 86–97.
- Odamaki, T., Kato, K., Sugahara, H., et al. (2016). Age-related changes in gut microbiota composition from newborn to centenarian: A cross-sectional study. *BMC Microbiology*, *16*, 90. <https://doi.org/10.1186/s12866-016-0708-5>.
- Oliphant, K., Parreira, V. R., Cochrane, K., & Allen-Vercoe, E. (2019). Drivers of human gut microbial community assembly: Coadaptation, determinism and stochasticity. *The ISME Journal*, *13*, 3080–3092. <https://doi.org/10.1038/s41396-019-0498-5>.
- Ooi, J. H., Li, Y., Rogers, C. J., & Cantorna, M. T. (2013). Vitamin D regulates the gut microbiome and protects mice from dextran sodium sulfate-induced colitis. *The Journal of Nutrition*, *143*, 1679–1686. <https://doi.org/10.3945/jn.113.180794>.
- Palmeira, P., Carneiro-Sampaio, M., Palmeira, P., & Carneiro-Sampaio, M. (2016). Immunology of breast milk. *Revista da Associação Médica Brasileira*, *62*, 584–593. <https://doi.org/10.1590/1806-9282.62.06.584>.
- Palmer, C., Bik, E. M., DiGiulio, D. B., et al. (2007). Development of the human infant intestinal microbiota. *PLoS Biology*, *5*, e177. <https://doi.org/10.1371/journal.pbio.0050177>.
- Park, G.-S., Park, M. H., Shin, W., et al. (2017). Emulating host-microbiome ecosystem of human gastrointestinal tract in vitro. *Stem Cell Reviews and Reports*, *13*, 321–334. <https://doi.org/10.1007/s12015-017-9739-z>.
- Paololi, E., Asnicar, F., Manara, S., et al. (2019). Extensive unexplored human microbiome diversity revealed by over 150,000 genomes from metagenomes spanning age, geography, and life-style. *Cell*, *176*, 649–662.e20. <https://doi.org/10.1016/j.cell.2019.01.001>.
- Peñalver Bernabé, B., Cralle, L., & Gilbert, J. A. (2018). Systems biology of the human microbiome. *Current Opinion in Biotechnology*, *51*, 146–153.
- Penders, J., Thijs, C., Vink, C., et al. (2006). Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics*, *118*, 511–521. <https://doi.org/10.1542/peds.2005-2824>.
- Petersen, L. M., Bautista, E. J., Nguyen, H., et al. (2017). Community characteristics of the gut microbiomes of competitive cyclists. *Microbiome*, *5*, 98. <https://doi.org/10.1186/s40168-017-0320-4>.
- Poole, A. C., Goodrich, J. K., Youngblut, N. D., et al. (2019). Human salivary amylase gene copy number impacts oral and gut microbiomes. *Cell Host & Microbe*, *25*, 553–564.e7. <https://doi.org/10.1016/j.chom.2019.03.001>.
- Poroyko, V. A., Carreras, A., Khalyfa, A., et al. (2016). Chronic sleep disruption alters gut microbiota, induces systemic and adipose tissue inflammation and insulin resistance in mice. *Scientific Reports*, *6*, 35405. <https://doi.org/10.1038/srep35405>.
- Proctor, L. M. (2011). The human microbiome project in 2011 and beyond. *Cell Host & Microbe*, *10*, 287–291. <https://doi.org/10.1016/J.CHOM.2011.10.001>.
- Proctor, L. M. (2016). The National Institutes of Health human microbiome project. *Seminars in Fetal & Neonatal Medicine*, *21*, 368–372. <https://doi.org/10.1016/J.SINY.2016.05.002>.
- Rahim, H., Taylor, M. R., Hirota, S. A., & Greenway, S. C. (2018). Microbiome alterations following solid-organ transplantation: Consequences, solutions, and prevention. *Transplant Research and Risk Management*, *10*, 1–11. <https://doi.org/10.2147/TRRM.S143063>.

- Rajilić-Stojanović, M., & de Vos, W. M. (2014). The first 1000 cultured species of the human gastrointestinal microbiota. *FEMS Microbiology Reviews*, 38, 996–1047. <https://doi.org/10.1111/1574-6976.12075>.
- Rajilić-Stojanović, M., Heilig, H. G. H. J., Tims, S., et al. (2013). Long-term monitoring of the human intestinal microbiota composition. *Environmental Microbiology*, 15, 1146–1159. <https://doi.org/10.1111/1462-2920.12023>.
- Rashid, M.-U., Zaura, E., Buijs, M. J., et al. (2015). Determining the long-term effect of antibiotic administration on the human normal intestinal microbiota using culture and pyrosequencing methods. *Clinical Infectious Diseases*, 60, S77–S84. <https://doi.org/10.1093/cid/civ137>.
- Rastall, R. A., Gibson, G. R., Gill, H. S., et al. (2005). Modulation of the microbial ecology of the human colon by probiotics, prebiotics and synbiotics to enhance human health: An overview of enabling science and potential applications. *FEMS Microbiology Ecology*, 52, 145–152.
- Reveles, K. R., Ryan, C. N., Chan, L., et al. (2018). Proton pump inhibitor use associated with changes in gut microbiota composition. *Gut*, 67, 1369–1370.
- Richards, A. L., Burns, M. B., Alazizi, A., et al. (2016). Genetic and transcriptional analysis of human host response to healthy gut microbiota. *mSystems*, 1, e00067-16. <https://doi.org/10.1128/mSystems.00067-16>.
- Rieder, R., Wisniewski, P. J., Alderman, B. L., & Campbell, S. C. (2017). Microbes and mental health: A review. *Brain, Behavior, and Immunity*, 66, 9–17. <https://doi.org/10.1016/j.bbi.2017.01.016>.
- Rogers, M. A. M., & Aronoff, D. M. (2016). The influence of non-steroidal anti-inflammatory drugs on the gut microbiome. *Clinical Microbiology and Infection*, 22, 178.e1–178.e9. <https://doi.org/10.1016/j.cmi.2015.10.003>.
- Rojo, D., Méndez-García, C., Raczkowska, B. A., et al. (2017). Exploring the human microbiome from multiple perspectives: Factors altering its composition and function. *FEMS Microbiology Reviews*, 41, 453–478. <https://doi.org/10.1093/femsre/fuw046>.
- Rosenwald, A. G., Arora, G. S., Madupu, R., et al. (2012). The human microbiome project: An opportunity to engage undergraduates in research. *Procedia Computer Science*, 9, 540–549. <https://doi.org/10.1016/J.PROCS.2012.04.058>.
- Rothschild, D., Weissbrod, O., Barkan, E., et al. (2018). Environment dominates over host genetics in shaping human gut microbiota. *Nature*, 555, 210–215. <https://doi.org/10.1038/nature25973>.
- Round, J. L., & Mazmanian, S. K. (2009). The gut microbiota shapes intestinal immune responses during health and disease. *Nature Reviews. Immunology*, 9, 313–323. <https://doi.org/10.1038/nri2515>.
- Ruengsomwong, S., La-ongkham, O., Jiang, J., et al. (2016). Microbial community of healthy Thai vegetarians and non-vegetarians, their Core gut microbiota, and pathogen risk. *Journal of Microbiology and Biotechnology*, 26, 1723–1735. <https://doi.org/10.4014/jmb.1603.03057>.
- Rutayisire, E., Huang, K., Liu, Y., & Tao, F. (2016). The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: A systematic review. *BMC Gastroenterology*, 16, 86. <https://doi.org/10.1186/s12876-016-0498-0>.
- Salim, S. Y., Kaplan, G. G., & Madsen, K. L. (2014). Air pollution effects on the gut microbiota. *Gut Microbes*, 5, 215–219. <https://doi.org/10.4161/gmic.27251>.
- Sassone-Corsi, M., & Raffatellu, M. (2015). No vacancy: How beneficial microbes cooperate with immunity to provide colonization resistance to pathogens. *Journal of Immunology*, 194, 4081–4087. <https://doi.org/10.4049/jimmunol.1403169>.
- Savin, Z., Kivity, S., Yonath, H., & Yehuda, S. (2018). Smoking and the intestinal microbiome. *Archives of Microbiology*, 200, 677–684. <https://doi.org/10.1007/s00203-018-1506-2>.
- Schmidt, T. S. B., Raes, J., & Bork, P. (2018). The human gut microbiome: From association to modulation. *Cell*, 172, 1198–1215. <https://doi.org/10.1016/J.CELL.2018.02.044>.
- Scholten, P. A. M. J., Oozeer, R., Martin, R., et al. (2012). The early settlers: Intestinal microbiology in early life. *Annual Review of Food Science and Technology*, 3, 425–447. <https://doi.org/10.1146/annurev-food-070811-103433>.

- org/10.1146/annurev-food-022811-101120.
- Scott, K. P., Duncan, S. H., & Flint, H. J. (2008). Dietary fibre and the gut microbiota. *Nutrition Bulletin*, 33, 201–211. <https://doi.org/10.1111/j.1467-3010.2008.00706.x>.
- Scott, K. P., Gratz, S. W., Sheridan, P. O., et al. (2013). The influence of diet on the gut microbiota. *Pharmacological Research*, 69, 52–60. <https://doi.org/10.1016/j.phrs.2012.10.020>.
- Sender, R., Fuchs, S., & Milo, R. (2016). Revised estimates for the number of human and bacteria cells in the body. *PLoS Biology*, 14(8), e1002533. <https://doi.org/10.1371/journal.pbio.1002533>.
- Sheflin, A. M., Melby, C. L., Carbonero, F., & Weir, T. L. (2017). Linking dietary patterns with gut microbial composition and function. *Gut Microbes*, 8, 113–129. <https://doi.org/10.1080/19490976.2016.1270809>.
- Simpson, H. L., & Campbell, B. J. (2015). Review article: Dietary fibre-microbiota interactions. *Alimentary Pharmacology & Therapeutics*, 42, 158–179. <https://doi.org/10.1111/apt.13248>.
- Singh, R. K., Chang, H.-W., Yan, D., et al. (2017). Influence of diet on the gut microbiome and implications for human health. *Journal of Translational Medicine*, 15, 73. <https://doi.org/10.1186/s12967-017-1175-y>.
- Sitaraman, R. (2018). Prokaryotic horizontal gene transfer within the human holobiont: Ecological-evolutionary inferences, implications and possibilities. *Microbiome*, 6, 163. <https://doi.org/10.1186/s40168-018-0551-z>.
- Smith, R. P., Easson, C., Lyle, S. M., et al. (2019). Gut microbiome diversity is associated with sleep physiology in humans. *PLoS One*, 14, e0222394. <https://doi.org/10.1371/journal.pone.0222394>.
- Song, S. J., Lauber, C., Costello, E. K., et al. (2013). Cohabiting family members share microbiota with one another and with their dogs. *eLife*, 2, e00458. <https://doi.org/10.7554/eLife.00458>.
- Sonnenburg, E. D., Smits, S. A., Tikhonov, M., et al. (2016). Diet-induced extinctions in the gut microbiota compound over generations. *Nature*, 529, 212–215. <https://doi.org/10.1038/nature16504>.
- Sun, L., Zhang, X., Zhang, Y., et al. (2019). Antibiotic-induced disruption of gut microbiota alters local metabolomes and immune responses. *Frontiers in Cellular and Infection Microbiology*, 9, 99. <https://doi.org/10.3389/fcimb.2019.00099>.
- Sung, J., Hale, V., Merkel, A. C., et al. (2016). Metabolic modeling with Big Data and the gut microbiome. *Applied & Translational Genomics*, 10, 10–15. <https://doi.org/10.1016/j.ATG.2016.02.001>.
- Suzuki, K., Meek, B., Doi, Y., et al. (2004). Aberrant expansion of segmented filamentous bacteria in IgA-deficient gut. *Proceedings of the National Academy of Sciences of the United States of America*, 101, 1981–1986. <https://doi.org/10.1073/pnas.0307317101>.
- Taddei, C. R., Cortez, R. V., Mattar, R., et al. (2018). Microbiome in normal and pathological pregnancies: A literature overview. *American Journal of Reproductive Immunology*, 80, e12993. <https://doi.org/10.1111/aji.12993>.
- Tanaka, M., & Nakayama, J. (2017). Development of the gut microbiota in infancy and its impact on health in later life. *Allergology International*, 66, 515–522.
- Tap, J., Mondot, S., Levenez, F., et al. (2009). Towards the human intestinal microbiota phylogenetic core. *Environmental Microbiology*, 11, 2574–2584. <https://doi.org/10.1111/j.1462-2920.2009.01982.x>.
- Tasnim, N., Abulizi, N., Pither, J., et al. (2017). Linking the gut microbial ecosystem with the environment: Does gut health depend on where we live? *Frontiers in Microbiology*, 8, 1935. <https://doi.org/10.3389/fmicb.2017.01935>.
- Thaiss, C. A., Zeevi, D., Levy, M., et al. (2014). Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell*, 159, 514–529. <https://doi.org/10.1016/j.cell.2014.09.048>.
- Thursby, E., & Juge, N. (2017). Introduction to the human gut microbiota. *The Biochemical Jour-*

- nal*, 474, 1823–1836. <https://doi.org/10.1042/BCJ20160510>.
- Ticinesi, A., Lauretani, F., Milani, C., et al. (2017). Aging gut microbiota at the cross-road between nutrition, physical frailty, and sarcopenia: Is there a gut–muscle axis? *Nutrients*, 9, 1303. <https://doi.org/10.3390/nu9121303>.
- Tomova, A., Bukovsky, I., Rembert, E., et al. (2019). The effects of vegetarian and vegan diets on gut microbiota. *Frontiers in Nutrition*, 6, 47. <https://doi.org/10.3389/fnut.2019.00047>.
- Touchefeu, Y., Montassier, E., Nieman, K., et al. (2014). Systematic review: The role of the gut microbiota in chemotherapy- or radiation-induced gastrointestinal mucositis – current evidence and potential clinical applications. *Alimentary Pharmacology & Therapeutics*, 40, 409–421.
- Turnbaugh, P.J., Hamady, M., Yatsunencko, T., et al. (2009). A core gut microbiome in obese and lean twins. *Nature*, 457, 480–484. <https://doi.org/10.1038/nature07540>.
- Turta, O., & Rautava, S. (2016). Antibiotics, obesity and the link to microbes – what are we doing to our children? *BMC Medicine*, 14, 57. <https://doi.org/10.1186/s12916-016-0605-7>.
- Umberson, D., Crosnoe, R., & Reczek, C. (2010). Social relationships and health behavior across the life course. *Annual Review of Sociology*, 36, 139–157. <https://doi.org/10.1146/annurev-soc-070308-120011>.
- van de Guchte, M., Blottière, H. M., & Doré, J. (2018). Humans as holobionts: Implications for prevention and therapy. *Microbiome*, 6, 81. <https://doi.org/10.1186/s40168-018-0466-8>.
- Vuillermin, P. J., Macia, L., Nanan, R., et al. (2017). The maternal microbiome during pregnancy and allergic disease in the offspring. *Seminars in Immunopathology*, 39, 669–675. <https://doi.org/10.1007/s00281-017-0652-y>.
- Walker, A. W. (2016). Studying the human microbiota. *Advances in Experimental Medicine and Biology*, 902, 5–32. [https://doi.org/10.1007/978-3-319-31248-4\\_2](https://doi.org/10.1007/978-3-319-31248-4_2).
- Walsh, C. J., Guinane, C. M., O’Toole, P. W., & Cotter, P. D. (2014). Beneficial modulation of the gut microbiota. *FEBS Letters*, 588, 4120–4130. <https://doi.org/10.1016/j.febslet.2014.03.035>.
- Wampach, L., Heintz-Buschart, A., Hogan, A., et al. (2017). Colonization and succession within the human gut microbiome by archaea, bacteria, and microeukaryotes during the first year of life. *Frontiers in Microbiology*, 8, 738. <https://doi.org/10.3389/fmicb.2017.00738>.
- Wang, B., Yao, M., Lv, L., et al. (2017). The human microbiota in health and disease. *Engineering*, 3, 71–82. <https://doi.org/10.1016/J.ENG.2017.01.008>.
- Weber, D., Hiergeist, A., Weber, M., et al. (2019). Detrimental effect of broad-spectrum antibiotics on intestinal microbiome diversity in patients after allogeneic stem cell transplantation: Lack of commensal sparing antibiotics. *Clinical Infectious Diseases*, 68, 1303–1310. <https://doi.org/10.1093/cid/ciy711>.
- Whiteson, K. L. (2018). Vive la persistence: engineering human microbiomes in the 21st century. *mSystems*, 3, e00166-17. <https://doi.org/10.1128/mSystems.00166-17>.
- WHO. (2017). *Depression*. World Health Organization. [https://www.who.int/mental\\_health/man-agement/depression/en/](https://www.who.int/mental_health/man-agement/depression/en/). Accessed 18 Jun 2019.
- WHO. (2018). *Ambient (outdoor) air pollution*. World Health Organization. [https://www.who.int/news-room/fact-sheets/detail/ambient-\(outdoor\)-air-quality-and-health](https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health). Accessed 18 Dec 2019.
- Wilson, B. C., Vatanen, T., Cutfield, W. S., & O’Sullivan, J. M. (2019). The super-donor phenomenon in fecal microbiota transplantation. *Frontiers in Cellular and Infection Microbiology*, 9, 2.
- Winter, G., Hart, R. A., Charlesworth, R. P. G., & Sharpley, C. F. (2018). Gut microbiome and depression: What we know and what we need to know. *Reviews in the Neurosciences*, 29, 629–643. <https://doi.org/10.1515/revneuro-2017-0072>.
- Wipperman, M. F., Fitzgerald, D. W., Juste, M. A. J., et al. (2017). Antibiotic treatment for tuberculosis induces a profound dysbiosis of the microbiome that persists long after therapy is completed. *Scientific Reports*, 7, 10767. <https://doi.org/10.1038/s41598-017-10346-6>.
- Wong, M.-W., Yi, C.-H., Liu, T.-T., et al. (2018). Impact of vegan diets on gut microbiota: An up-

- date on the clinical implications. *Tzu Chi Medical Journal*, 30, 200. [https://doi.org/10.4103/tcmj.tcmj\\_21\\_18](https://doi.org/10.4103/tcmj.tcmj_21_18).
- Xia, Y., & Sun, J. (2017). Hypothesis testing and statistical analysis of microbiome. *Genes & Diseases*, 4, 138–148. <https://doi.org/10.1016/J.GENDIS.2017.06.001>.
- Yamashita, T., Hayashi, T., Yoshida, N., & Hirata, K. I. (2018). Gut microbial dysbiosis in heart failure – is it a future therapeutic target or not? *Circulation Journal*, 82, 1507–1509.
- Yatsunenکو, T., Rey, F. E., Manary, M. J., et al. (2012). Human gut microbiome viewed across age and geography. *Nature*, 486, 222–227. <https://doi.org/10.1038/nature11053>.
- Yoshida, N., Yamashita, T., & Hirata, K. (2018). Gut microbiome and cardiovascular diseases. *Diseases*, 6, 56. <https://doi.org/10.3390/diseases6030056>.
- Younes, J. A., Lievens, E., Hummelen, R., et al. (2018). Women and their microbes: The unexpected friendship the impact of microbes on the vaginal niche. *Trends in Microbiology*, 26, 16–32. <https://doi.org/10.1016/j.tim.2017.07.008>.
- Zimmermann, P., & Curtis, N. (2018). Factors influencing the intestinal microbiome during the first year of life. *The Pediatric Infectious Disease Journal*, 37, e315–e335. <https://doi.org/10.1097/INF.0000000000002103>.
- Zinöcker, M., & Lindseth, I. (2018). The western diet–microbiome–host interaction and its role in metabolic disease. *Nutrients*, 10, 365. <https://doi.org/10.3390/nu10030365>.
- Zmora, N., Suez, J., & Elinav, E. (2019). You are what you eat: Diet, health and the gut microbiota. *Nature Reviews. Gastroenterology & Hepatology*, 16, 35–56. <https://doi.org/10.1038/s41575-018-0061-2>.

# Diyetin İnsan Bağırsak Mikrobiyomu Üzerindeki Etkileri ve Sonrasında Konak Fizyolojisi ve Metabolizması Üzerindeki Etkisi

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## 1 Giriş

Bağırsak mikrobiyomu, insan ve hayvanların gastrointestinal sisteminde yaşayan temel olarak bakterilerden oluşan bir mikrobiyal ekosistemdir. Konak genetiğinin, diyet ve çevre de dahil olmak üzere çeşitli faktörlerden etkilendiği düşünülmektedir (Zoetendal ve ark. 2001). Bağırsak mikrobiyomu, bağışıklık sisteminin düzenlenmesi, organ gelişimi, konak metabolizması (Sommer ve Bäckhed 2013), ve bağırsak mukozasının yapısal bütünlüğünün korunması da dahil olmak üzere konak için hayati önem taşıyan birçok işlevi yerine getirir (Jandhyala ve ark. 2015). Son zamanlarda, bağırsak mikrobiyomunun davranışları bile değiştirebildiği bulunmuştur (Sommer ve Bäckhed 2013). Bağırsak mikrobiyotasının metabolik gücü karaciğerinkine eşittir ve genetik potansiyeli, tek başına insan vücudununkinden iki kat daha fazladır (Sommer ve Bäckhed 2013); bu nedenle, insan bağırsak mikrobiyomu genellikle ek bir organ olarak kabul edilmektedir (Sommer ve Bäckhed 2013; O'Hara ve Shanahan 2006; Quigley 2013; Clarke ve ark. 2014). Bağırsak mikrobiyomunun inflamatuvar bağırsak hastalığı (IBD), astım, obezite, diyabet (Shen ve Wong 2016) ve kardiyovasküler hastalıklar (Sandoval ve Seeley 2010) gibi hastalıklarda rol oynadığı düşünülmektedir. Mikrop-lardan yoksun hayvanlar üzerinde yapılan çalışmalarla, bağırsak mikrobiyomunun gerçekten de bağışıklıkta rol oynadığı belirlenmiştir (O'Hara ve Shanahan 2006; Shen ve Wong 2016). Normal bağırsak mikrobiyomu öncelikle Firmicutes ve Bacteroidetes filumlarından oluşur (Sommer ve Bäckhed 2013; Jandhyala ve diğerleri 2015), ancak Proteobacteria, Verrucomicrobia, Aktinobakteriler, Fusobacteria ve Cyanobacteria üyeleri de mevcuttur (Sommer ve Bäckhed 2013).

Bağırsak mikrobiyomunun konak metabolizması işlevlerine yoğun katkısının bilinmesine rağmen (Sommer ve Bäckhed 2013; Quigley 2013; Clarke ve diğerleri 2014; Faderl ve diğerleri 2015), mekanizma tam olarak anlaşılamamıştır (Sommer ve Bäckhed 2013). Bağırsak mikrobiyotası besinler, ksenobiyotikler ve safra asitleri de dahil olmak üzere bileşenlerin metabolizmasına yaptığı katkının yanı sıra kısa zincirli yağ asitleri, K vitamini, B vitamini bileşenleri gibi diğer önemli bileşenlerin üretimine de

## Kaynaklar

- Arora, T., Singh, S., & Sharma, R. (2013). Probiotics: Interaction with gut microbiome and anti-obesity potential. *Nutrition*, 29(4), 591–596.
- Azcrate-Peril, M., Ritter, A., & Savaiano, D. (2017). Impact of short-chain galactooligosaccharides on the gut microbiome of lactose-intolerant individuals. *Proc Natl Acad Sci U S A*, 114(3), E367–E375.
- Baer, D., Stote, K. S., Henderson, T., et al. (2014). The metabolizable energy of dietary resistant maltodextrin is variable and alters fecal microbiota composition in adult men. *The Journal of Nutrition*, 144(7), 1023–1029.
- Berg, G., Erlacher, A., & Grube, M. (2015). The Edible plant microbiome: importance and health issues. In B. Lugtenberg (Ed.), *Principles of plant-microbe interactions* (pp. 419–426). Switzerland: Springer.
- Butt, M., & Sultan, T. (2011). Coffee and its consumption: Benefits and risks. *Critical Reviews in Food Science and Nutrition*, 51(4), 363–373.
- Cabello-Olmo, M., Oneca, M., Torre, P., Sainz, N., et al. (2019). A fermented food product containing lactic acid bacteria protects ZDF rats from the development of Type 2 diabetes. *Nutrients*, 11(10), 2530.
- Centanni, M., Lawley, B., Butts, C., et al. (2018). Bifidobacterium pseudolongum in the ceca of rats fed hi-maize starch has characteristics of a keystone species in Bifidobacterial blooms. *Applied and Environmental Microbiology*, 84(15), 1–13.
- Chamba, J. F., & Irlinger, F. (2004). Secondary and adjunct cultures. In P. Fox, P. McSweeney, T. Cogan, & T. Guinee (Eds.), *Cheese: Chemistry, physics and microbiology* (pp. 191–206). Amsterdam: Academic Press.
- Clarke, G., Stilling, R. M., & Kennedy, P. J. (2014). Minireview: gut microbiota: the neglected endocrine organ. *Journal of Molecular Endocrinology*, 28(8), 1221–1238.
- Cowan, T., Palmnäs, M., Yang, J., et al. (2014). Chronic coffee consumption in the diet-induced obese rat: Impact on gut microbiota and serum metabolomics. *The Journal of Nutritional Biochemistry*, 25(4), 489–495.
- Davenport, R., Mizrahi-Man, O., Michelini, K., et al. (2014). Seasonal variation in human gut microbiome composition. *PLoS One*, 9(3), e90731.
- David, L., Maurice, C., Carmody, R., et al. (2014). Diet rapidly and reproducibly alters the human gut microbiome. *Nature*, 505(7484), 559–563.
- De Filippis, F., Pellegrini, N., Vannini, L., et al. (2016). High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut*, 65, 1–10.
- Deehan, E., & Walter, J. (2016). The fiber gap and the disappearing gut microbiome: Implications for human nutrition. *Trends in Endocrinology and Metabolism*, 27(5), 239–242.
- Del Chierico, F., Vernocchi, P., Dallapiccola, B., et al. (2014). Mediterranean diet and health: Food effects on gut microbiota and disease control. *International Journal of Molecular Sciences*, 5(7), 11678–11699.
- Dutheil, S., Ota, K., Wohleb, E., et al. (2016). High-fat diet induced anxiety and anhedonia: Impact on brain homeostasis and inflammation. *Neuropsychopharmacology*, 41(7), 1874–1887.
- Faderl, M., Noti, M., Corazza, N., et al. (2015). Keeping bugs in check: The mucus layer as a critical component in maintaining intestinal homeostasis. *IUBMB Life*, 67, 275–285.
- Feng, W., Wang, H., Zhang, P., et al. (2017). Modulation of gut microbiota contributes to curcumin-mediated attenuation of hepatic steatosis in rats. *Biochimica et Biophysica Acta*, 1861(7), 1801–1812.
- Francavilla, R., Calasso, M., & Calace, L. (2012). Effect of lactose on gut microbiota and metabolome of infants with cow's milk allergy. *Pediatric Allergy and Immunology*, 23(5), 420–427.
- Goldbohm, R. A., Hertog, M., Brants, H., et al. (1996). Consumption of black tea and cancer risk: A prospective cohort study. *Journal of the National Cancer Institute*, 88(2), 93–100.

- González-Sarriás, A., Espín, J., & Tomás-Barberán, F. (2017). Non-extractable polyphenols produce gut microbiota metabolites that persist in circulation and show anti-inflammatory and free radical-scavenging effects. *Trends in Food Science and Technology*, 69, 281–288.
- Graf, D., Di Cagno, R., Fåk, F., et al. (2015). Contribution of diet to the composition of the human gut microbiota. *Microbial Ecology in Health and Disease*, 26(26164), 1–11.
- Guarner, F., & Malagelada, J. R. (2003). Gut flora in health and disease. *The Lancet*, 361, 512–519.
- Gurley, B., Miousse, I., Nookaew, I., et al. (2019). Decaffeinated green tea extract does not elicit hepatotoxic effects and modulates the gut microbiome in lean B6C3F1 mice. *Nutrients*, 11(776), 1–14.
- Heiman, M., & Greenway, F. (2016). A healthy gastrointestinal microbiome is dependent on dietary diversity. *Molecular Metabolism*, 5(5), 317–320.
- Hemarajata, P., & Versalovic, J. (2013). Effects of probiotics on gut microbiota: Mechanisms of intestinal immunomodulation and neuromodulation. *Therapeutic Advances in Gastroenterology*, 6(1), 39–51.
- Hollman, P., Van Het Hof, K., Tijburg, L., et al. (2001). Addition of milk does not affect the absorption of flavonols from tea in man. *Free Radical Research*, 34, 293–300.
- ISAPP. (2016). *ISAPP videos*. <https://isappscience.org/resources/isapp-videos/>. Accessed 7 Jul 2019.
- Jami, E., White, B., & Mizrahi, I. (2014). Potential role of the Bovine Rumen microbiome in modulating milk composition and feed efficiency. *PLoS One*, 9(1), e85423.
- Jandhyala, S., Talukdar, R., Subramanyam, C., et al. (2015). Role of the normal gut microbiota. *World Journal of Gastroenterology*, 21(29), 8787–8803.
- Janssens, P. L. H. R., Penders, J., Hursel, R., Budding, A. E., Savelkoul, P. H. M., & Westerterp-Plantenga, M. S. (2016). Long-term green tea supplementation does not change the human gut microbiota. *PLoS One*, 11(4), e0153134.
- Jin, Y., Wu, S., Zeng, Z., et al. (2017). Effects of environmental pollutants on gut microbiota. *Environmental Pollution*, 222, 1–9.
- Jones, M., Martoni, C. J., & Prakash, S. (2012a). Cholesterol lowering inhibition of sterol absorption by *Lactobacillus reuteri* NCIMB 30242 a randomized controlled trial. *European Journal of Clinical Nutrition*, 66, 1234–1241.
- Jones, M., Martoni, J., Parent, M., et al. (2012b). Cholesterol-lowering efficacy of a microencapsulated bile salt hydrolase-active *Lactobacillus reuteri* NCIMB 30242 yoghurt formulation in hypercholesterolaemic adults. *The British Journal of Nutrition*, 107, 1505–1513.
- Jy, K., & Ey, C. (2016). Changes in Korean adult females' intestinal microbiota resulting from Kimchi Intake. *Journal of Nutrition & Food Sciences*, 06(02), 1–9.
- Kakumanu, M., Reeves, A., Anderson, D., et al. (2016). Honey bee gut microbiome is altered by in-hive pesticide exposures. *Frontiers in Microbiology*, 7, 1–11.
- Kashtanova, D., Popenko, A., Tkacheva, O., et al. (2016). Association between the gut microbiota and diet: Fetal life, early childhood, and further life. *Nutrition*, 32(6), 620–627.
- Kemperman, R., Gross, G., Mondot, S., et al. (2013). Impact of polyphenols from black tea and red wine grape juice on a gut model microbiome. *Food Research International*, 53(2), 659–669. join.
- Long, S., Gahan, G., & Joyce, S. (2017). Interactions between gut bacteria and bile in health and disease. *Molecular Aspects of Medicine*, 56, 54–65.
- Lu, C., Sun, T., Li, Y., et al. (2017). Modulation of the gut microbiota by krill oil in mice fed a high-sugar high-fat diet. *Frontiers in Microbiology*, 8(905), 1–11.
- Luna, R. A., & Foster, J. A. (2015). Gut brain axis: Diet microbiota interactions and implications for modulation of anxiety and depression. *Current Opinion in Biotechnology*, 32, 35–41.
- Ma, D., Wang, A. C., Parikh, I., et al. (2018). Ketogenic diet enhances neurovascular function with altered gut microbiome in young healthy mice. *Scientific Reports*, 8(6670), 1–10.
- Mao, Q., Manservigi, F., Panzacchi, S., et al. (2018). The Ramazzini Institute 13-week pilot study

- on glyphosate and Roundup administered at human-equivalent dose to Sprague Dawley rats: effects on the microbiome. *Environmental Health*, 17(1), 50.
- Newell, C., Bomhof, M., Reimer, R., et al. (2016). Ketogenic diet modifies the gut microbiota in a murine model of autism spectrum disorder. *Molecular Autism*, 7(37), 2–6.
- Neyrinck, A., Hiel, S., Bouzin, C., et al. (2018). Wheat-derived arabinoxylan oligosaccharides with bifidogenic properties abolishes metabolic disorders induced by western diet in mice. *The Journal of Nutrition*, 144(7), 1023–1029.
- Nickerson, K., & McDonald, C. (2012). Crohn's disease-associated adherent-invasive *Escherichia coli* adhesion is enhanced by exposure to the ubiquitous dietary polysaccharide maltodextrin. *PLoS One*, 7(12), e52132.
- Nishitsuji, K., Watanabe, S., Xiao, J., et al. (2018). Effect of coffee or coffee components on gut microbiome and short-chain fatty acids in a mouse model of metabolic syndrome. *Scientific Reports*, 8(16173), 1–10.
- Nemiri, A., Ribière, C., Stanton, C., et al. (2019). Retention of microbiota diversity by lactose-free milk in a mouse model of elderly gut microbiota. *Journal of Agricultural and Food Chemistry*, 67(7), 2098–2112.
- O'Hara, A. M., & Shanahan, F. (2006). The gut flora as a forgotten organ. *EMBO Reports*, 7(7), 688–693.
- O'Shea, E., Cotter, P., Stanton, C., et al. (2012). Production of bioactive substances by intestinal bacteria as a basis for explaining probiotic mechanisms: Bacteriocins and conjugated linoleic acid. *International Journal of Food Microbiology*, 152(3), 189–205.
- Olson, C., Vuong, H., Yano, J., et al. (2018). The gut microbiota mediates the anti-seizure effects of the ketogenic diet. *Cell*, 173(7), 1728–1741.e1–e6.
- Pandey, K., Naik, S., & Vakil, B. (2015). Probiotics, prebiotics and synbiotics – A review. *Journal of Food Science and Technology*, 52(12), 7577–7587.
- Paul Ross, R., Morgan, S., & Hill, C. (2002). Preservation and fermentation: Past, present and future. *International Journal of Food Microbiology*, 79(1), 3–16.
- Piwożarek, K., Lipińska, E., Hać-Szymańczuk, E., et al. (2018). Propionibacterium spp.-source of propionic acid, vitamin B12, and other metabolites important for the industry. *Applied Microbiology and Biotechnology*, 102(2), 515–538.
- Piwożarski, J. P., Kiss, A. K., Granica, S., et al. (2015). Urolithins, gut microbiota-derived metabolites of ellagitannins, inhibit LPS-induced inflammation in RAW 264.7 murine macrophages. *Molecular Nutrition & Food Research*, 59(11), 2168–2177.
- Quigley, E. (2013). Gut bacteria in health and disease. *Gastroenterología y Hepatología*, 9(9), 560–569.
- Quigley, L., O'Sullivan, O., Stanton, C., et al. (2013a). The complex microbiota of raw milk. *FEMS Microbiology Reviews*, 37(5), 664–698.
- Quigley, L., McCarthy, R., O'Sullivan, O., et al. (2013b). The microbial content of raw and pasteurized cow milk as determined by molecular approaches. *Journal of Dairy Science*, 96(8), 4928–4937.
- Rettedal, A., Altermann, E., Roy, N., et al. (2019). The effects of unfermented and fermented cow and sheep milk on the gut microbiota. *Frontiers in Microbiology*, 10(458), 1–12.
- Richardson, T. (1978). The hypocholesteremic effect of milk – A review. *Journal of Food Protection*, 41(3), 226–235.
- Rissato, S., Galhiane, M., de Almeida, M., et al. (2007). Multiresidue determination of pesticides in honey samples by gas chromatography–mass spectrometry and application in environmental contamination. *Food Chemistry*, 101(4), 1719–1726.
- Robertson, R., Seira Oriach, C., Murphy, K., et al. (2017). Omega-3 polyunsaturated fatty acids critically regulate behaviour and gut microbiota development in adolescence and adulthood. *Brain, Behavior, and Immunity*, 59, 21–37.
- Ryan, L., & Petit, S. (2010). Addition of whole, semiskimmed, and skimmed bovine milk reduces

- the total antioxidant capacity of black tea. *Nutrition Research*, 40(1), 14–20.
- Saad, M. J. A., Santos, A., & Prada, P. O. (2016). Linking gut microbiota and inflammation to obesity and insulin resistance. *Physiology*, 31(4), 283–293.
- Sandoval, D., & Seeley, R. (2010). The microbes made me eat it. *Science*, 328(5975), 179–180.
- Sasaki, A., de Vega, W., Sivanathan, S., et al. (2014). Maternal high-fat diet alters anxiety behavior and glucocorticoid signaling in adolescent offspring. *The Journal of Neuroscience*, 27(2), 92–101.
- Saxe, L. (2019). Fermented Foods are up to 149%: As long as they're unfamiliar. *Forbes*. Available via <https://www.forbes.com/sites/lizzysaxe/2019/02/06/fermented-foods-are-up-149-percent-as-long-as-theyre-unfamiliar/#59cac643673f>. Accessed 7 Jul 2019.
- Seo, D.-B., Jeong, H., Cho, D., et al. (2018). Fermented green tea extract alleviates obesity and related complications and alters gut microbiota composition in diet-induced obese mice. *Journal of Medicinal Food*, 18(5), 1–8.
- Shen, S., & Wong, C. (2016). Bugging inflammation: role of the gut microbiota. *Clinical and Translational Immunology*, 5, e72.
- Shen, L., Liu, L., & Ji, H.-F. (2017). Regulatory effects of curcumin spice administration on gut microbiota and its pharmacological implications. *Food & Nutrition Research*, 61(1), 1361780.
- Sommer, F., & Bäckhed, F. (2013). The gut microbiota — masters of host development and physiology. *Nature Reviews Microbiology*, 11, 227–238.
- Sun, H., Chen, Y., Cheng, M., et al. (2018). The Modulatory effect of polyphenols from green tea, oolong tea, and black tea on human intestinal microbiota in vitro. *Journal of Food Science and Technology*, 55(1), 399–407.
- Tannock, G., Lawley, B., Munro, K., et al. (2012). Comparison of the compositions of the stool microbiotas of infants fed goat milk formula, cow milk-based formula, or breast milk. *Applied and Environmental Microbiology*, 79(9), 3040–3048.
- Trinchese, G., Cavaliere, G., Canani, R. B., et al. (2015). Human, donkey and cow milk differently affects energy efficiency and inflammatory state by modulating mitochondrial function and gut microbiota. *The Journal of Nutritional Biochemistry*, 26(11), 1136–1146.
- van het Hof, K., Kivits, G., Tijburg, W., et al. (1998). Bioavailability of catechins from tea the effect of milk. *European Journal of Clinical Nutrition*, 52, 356–359.
- Van Doorn, G., Wullemijn, D., & Spence, C. (2014). Does the colour of the mug influence the taste of the coffee? *Flavour*, 3(10), 1–7.
- Veiga, P., Pons, N., Agrawal, A., et al. (2014). Changes of the human gut microbiome induced by a fermented milk product. *Scientific Reports*, 4(1), 6328.
- Vijayakuma, R., Sagar, G. V., Sreeramulu, D., et al. (2005). Addition of milk does not alter the antioxidant activity of black tea. *Annals of Nutrition & Metabolism*, 49(3), 189–195.
- Vitaglione, P., Mazzone, G., Lembo, V., et al. (2019). Coffee prevents fatty liver disease induced by a high-fat diet by modulating pathways of the gut-liver axis. *Journal of Nutritional Science*, 8(e15), 1–11.
- Wahlqvist, M. (2015). Lactose nutrition in lactase nonpersisters. *Asia Pacific Journal of Clinical Nutrition*, 24(1), S21–S25.
- Wahlström, A., Sayin, S., Marschall, H.-U., et al. (2016). Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. *Cell Metabolism*, 24(1), 41–50.
- Wang, Y., & Ho, C.-T. (2009). Polyphenolic chemistry of tea and coffee: A century of progress. *Journal of Agricultural and Food Chemistry*, 57(18), 8109–8114.
- Wang, Z., Zhang, W., Wang, B., et al. (2018a). Influence of Bactrian camel milk on the gut microbiota. *Journal of Dairy Science*, 101(7), 5758–5769.
- Wang, J., Tang, L., Hongyuan, Z., et al. (2018b). Long term treatment with green tea polyphenols modifies the gut microbiome of female sprague dawley rats. *The Journal of Nutritional Biochemistry*, 56, 55–64.
- Weitkunat, K., Stuhlmann, C., Postel, A., et al. (2017). Short-chain fatty acids and inulin, but not guar gum, prevent diet-induced obesity and insulin resistance through differential mecha-

- nisms in mice. *Scientific Reports*, 7(6109), 1–13.
- Wen, Y., He, Q., Ding, J., et al. (2017). Cow, yak, and camel milk diets differentially modulated the systemic immunity and fecal microbiota of rats. *Science Bulletin*, 62(6), 405–414.
- Wu, G., Compher, C., Chen, E., et al. (2016). Comparative metabolomics in vegans and omnivores reveal constraints on diet-dependent gut microbiota metabolite production. *Gut*, 65(1), 63–72.
- Yang, J., Martínez, I., Walter, J., et al. (2013). In vitro characterization of the impact of selected dietary fibers on fecal microbiota composition and short chain fatty acid production. *Anaerobe*, 23, 74–81.
- Yu, H.-S., Lee, N.-K., Choi, A.-J., et al. (2019). Anti-inflammatory potential of probiotic strain *Weissella cibaria* JW15 isolated from Kimchi through regulation of NF- $\kappa$ B and MAPKs pathways in LPS-Induced RAW 264.7 cells. *Journal of Microbiology and Biotechnology*, 29(7), 1022–1032.
- Zhang, X., Zhang, M., Ho, C.-T., et al. (2018). Metagenomics analysis of gut microbiota modulatory effect of green tea polyphenols by high fat diet-induced obesity mice model. *Journal of Functional Foods*, 46, 268–277.
- Zimmer, J., Lange, B., Frick, J.-S., et al. (2012). A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. *European Journal of Clinical Nutrition*, 66(1), 53–60.
- Zoetendal, E., Akkermans, A., Akkermans-van Vliet, W., et al. (2001). The host genotype affects the bacterial community in the human gastrointestinal tract. *Microbial Ecology in Health and Disease*, 13(3), 129–134

# Bağırsak Florası ve Bağırsak Sağlığı Üzerine Probiyotikler ve Prebiyotikler

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## 1. Giriş

Bağırsaktaki tüm bakteri türleri simbiyotik ilişki içinde yaşar ve diğer bağırsak mikropları ve konakçıları ile karşılıklı mutualistik ilişkiler paylaşır. Bağırsak mikroflora simbiyozunun en büyük etkenlerinden biri diyetdir. Sağlıklı bir gastrointestinal mikrobiyom, diyet çeşitliliğine bağlıdır. Bağırsak, sindirilmemiş veya sindirilmiş, bağırsakta bulunan milyonlarca mikrobiyotik türün her biri tarafından farklı şekillerde dönüştürülebilir enerji ile doludur. İnsanlar, anne sütünü tüketirken ilk bağırsak mikrofloralarını geliştirmeye başlarlar, bu sırada bağırsak mikroorganizmasındaki çeşitlilik, özellikle de kommensal bakteriler dengeli bir bağırsak mikrobiyomu oluşmasını sağlar. Katı yiyecekler sunulduğunda, daha egzotik bakteriler ortaya çıkar ve bağırsakların yerleşik ortamı değişmeye başlar. Sıvı bir diyetten katı bir yetişkin diyetine geçiş yapan küçük çocuklar, süreç boyunca yeni yiyeceklerin test edilmesi nedeniyle potansiyel olarak kendi ebeveynlerinden daha çeşitli bir bağırsak mikrobiyomuna sahip olabilirler. Ebeveynlerin yaşam tarzlarının bir sonucu olarak alışlagelmiş diyetleri de çocuklarının kişiselleştirilmiş mikrobiyomunu yaratmaya katkıda bulunabilir.

Çalışmalar, lif ve polifenoller gibi birçok diyet faktörünün bağırsak bakterilerinin dengesini değiştirebileceğini göstermiştir. Örneğin, lif karışımına sahip diyet uygulayan denekler üzerinde yapılan bir çalışmada, bağırsak sıkışmalarına ilişkin daha az olumsuz semptom bulunmuştur, özellikle lifsiz bir diyet uygulayan kontrol grubuna kıyasla bağırsak bakteri kaybı miktarında daha küçük bir azalma görülmüştür (Koecher ve ark. 2015). Ayrı bir çalışmada, diyet polifenollerinin, orijinal bitki ürünlerine kıyasla dönüşüm ürünleri aracılığıyla bağırsak bakteri dengesini dolaylı olarak etkileyebileceği bulunmuş ve kontrol grubuna kıyasla bağırsakta bakteri çoğalmasının artmasına neden olabileceği ifade edilmiştir (Zhang ve ark. 2015). Karbonhidratlar, proteinler ve yağlar çoğu diyetle dahil edilen ana bileşenlerdir. Yağ, protein ve karbonhidrat miktarı ve türünün bağırsak mikrobiyotasının bileşiminde büyük rol oynadığı bilinmektedir. Bütirat ve asetatın; proteinlerin, yağların ve karbonhidratların mikrobiyal bozunmasının biyoaktif metabolitleri olduğu ve ayrıca konakçıda bağırsak sağlığı üzerinde olumlu etkileri olduğu bilinmektedir (Riaz Rajoka ve ark. 2017).

şitli çalışmalar, prebiyotikler ve probiyotikler birlikte uygulandığında olumlu gelişmiş etkiler göstermiştir (Markowiak ve Ślizewska 2017). Sinbiyotiklerin etkileri hakkında sınırlı sayıda çalışma olduğundan, prebiyotikler ile probiyotikleri birleştirmenin etkilerini anlamak için daha fazla çalışmaya ihtiyaç vardır (Markowiak ve Ślizewska 2017). Fekal mikrobiyota ve bakteriyel konsorsiyum nakilleri söz konusu olduğunda, bağırsak florasının başarılı bir şekilde düzenlendiğini gösteren çalışmalar vardır, ancak bağışıklık tepkisi prosedürünün nasıl etkilediğini anlamak için daha ileri çalışmalara hala ihtiyaç vardır ve ayrıca enterik enfeksiyonların ve kronik bağırsak iltihaplarının gelecekteki tedavisi için transplantasyonun iyileştirilmiş dağıtım/uygulama yöntemleri de gereklidir (Li ve ark. 2015, 2016).

## 6. Sonuç

Bağırsak mikrobiyotasına bakıldığında, bağırsağın homeostaz yeteneğinden,bağırsağın genel bağışıklığına, geniş düzenlemelerin bağırsak mikroflora simbiyozuna yol açmasına ve bağırsak mikrobiyal disbiyozunun insanlarda akut ve kronik sağlık sorunları üzerindeki etkilerine kadar değişen birçok faktör analiz edilebilir. Hastalık tedavisi ve müdahale stratejileri için kullanılmak üzere bağırsak mikrobiyotamızı değiştirme ve düzenleme kabiliyeti son derece güçlüdür ve sürekli olarak gelişmektedir. Probiyotik suşların ve prebiyotik benzeri gıda bileşenlerinin kullanımında gözlemlenen çeşitli faydalar arasında; bağırsak sağlığının iyileştirilmesi, bağışıklık tepkisinin güçlendirilmesi, serum kolesterolünün düşürülmesi ve kanserin önlenmesine yardımcı olunması yer alır. Yararlı mikropların hedefi, SCFA'lar ve K vitamini gibi biyoaktif metabolitlerin üretildiği mekanizmalar olabilir. Ayrıca yararlı mikroplar; lenfoid dokularla etkileşim yoluyla bağışıklık sistemini geliştirirler; teepitel, fagositöz ve IgA salgılanmasını indükler, T-hücre yanıtlarını değiştirir ve Th1 hücrelerini artırır ve Th2 yanıtlarını değiştirirler. Ayrıca, yeni bir alan olan fekal mikrobiyota transplantasyonu ve şu anda geliştirilmekte olan ve iyileştirilmekte olan bakteriyel konsorsiyum transplantasyonu da bağırsak mikrobiyotasını disbiyozdan kurtarmak için umut verici terapötik stratejilerdir.

## Kaynaklar

- Al-Sheraji, S. H., Ismail, A., Manap, M. Y., Mustafa, S., Yusof, R. M., Hassan, F. A. (2013). Prebiotics as functional foods: A review, *Journal of Functional Foods*, 5(4), 1542–1553, ISSN 1756-4646, <https://doi.org/10.1016/j.jff.2013.08.009>.
- Aroniadis, O. C. (2013). Fecal microbiota transplantation: Past, present and future. *Current Opinion in Gastroenterology*, 29(1), 79–84.
- Bandyopadhyay, B., & Mandal, N. C. (2014). Probiotics, prebiotics and synbiotics – In health improvement by modulating gut microbiota: The concept revisited. *International Journal of*

*Current Microbiology and Applied Sciences*, 3, 410–420.

- Barbara, G., Cremon, C., Carini, G., Bellacosa, L., Zecchi, L., De Giorgio, R., Corinaldesi, R., & Stanghellini, V. (2011). The immune system in irritable bowel syndrome. *Journal of Neurogastroenterology and Motility*, 17(4), 349–359.
- Beto, J. A. (2015). The role of calcium in human aging. *Clinical Nutrition Research*. <https://doi.org/10.7762/cnr.2015.4.1.1>.
- Bian, X., Chi, L., Gao, B., Tu, P., Ru, H., & Lu, K. (2017). Gut microbiome response to sucralose and its potential role in inducing liver inflammation in mice. *Frontiers in Physiology*. <https://doi.org/10.3389/fphys.2017.00487>.
- Bosscher, D. (2009). Fructan prebiotics derived from inulin. In: *Prebiotics and probiotics science and technology*. Springer, New York, NY. [https://doi.org/10.1007/978-0-387-79058-9\\_6](https://doi.org/10.1007/978-0-387-79058-9_6).
- Carabin, I. G., & Gary Flamm, W. (1999). Evaluation of safety of inulin and oligofructose as dietary fiber. *Regulatory Toxicology and Pharmacology*. <https://doi.org/10.1006/rtp.1999.1349>.
- Carding, S., Verbeke, K., Vipond, D. T., Corfe, B. M., & Owen, L. J. (2015). Dysbiosis of the gut microbiota in disease. *Microbial Ecology in Health and Disease*. <https://doi.org/10.3402/mehd.v26.26191>.
- Chassaing, B., Koren, O., Goodrich, J. K., Poole, A. C., Srinivasan, S., Ley, R. E., & Gewirtz, A. T. (2015). Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature*. <https://doi.org/10.1038/nature14232>.
- Chong, C. Y. L., Bloomfield, F. H., & O'Sullivan, J. M. (2018). Factors affecting gastrointestinal microbiome development in neonates. *Nutrients*, 10(3), 274.
- Collins, M. D., & Gibson, G. R. (1999). Probiotics, prebiotics, and synbiotics: Approaches for modulating the microbial ecology of the gut. *American Journal of Clinical Nutrition*, 69(5), 1052S–1057S.
- Conlon, M. A., & Bird, A. R. (2015). The impact of diet and lifestyle on gut microbiota and human health. *Nutrients*, 7(1), 17–44.
- Crout, D. H. G., & Vic, G. (1998). Glycosidases and glycosyl transferases in glycoside and oligosaccharide synthesis. *Current Opinion in Chemical Biology*. [https://doi.org/10.1016/S1367-5931\(98\)80041-0](https://doi.org/10.1016/S1367-5931(98)80041-0).
- Cummings, J. H., Macfarlane, G. T., & Englyst, H. N. (2001). Prebiotic digestion and fermentation. *American Journal of Clinical Nutrition*, 73(2 Suppl), 415S–420S.
- Falony, G., Joossens, M., Vieira-Silva, S., Wang, J., Darzi, Y., Faust, K., Kurilshikov, A., Bonder, M. J., Valles-Colomer, M., Vandeputte, D., Tito, R. Y., Chaffron, S., Rymenans, L., Verspecht, C., De Sutter, L., Lima-Mendez, G., D'hoel, K., Jonckheere, K., Homola, D., Garcia, R., Tigchelaar, E. F., Eeckhaut, L., Fu, J., Henckaerts, L., Zhernakova, A., Wijmenga, C., & Raes, J. (2016). Population-level analysis of gut microbiome variation. *Science*. <https://doi.org/10.1126/science.aad3503>.
- Fei, N., & Zhao, L. (2013). An opportunistic pathogen isolated from the gut of an obese human causes obesity in germfree mice. *The ISME Journal*. <https://doi.org/10.1038/ismej.2012.153>.
- Ferrere, G., Wrzosek, L., Cailleux, F., Turpin, W., Puchois, V., Spatz, M., Ciocan, D., Rainteau, D., Humbert, L., Hugot, C., Gaudin, F., Noordine, M. L., Robert, V., Berrebi, D., Thomas, M., Naveau, S., Perlemuter, G., & Cassard, A. M. (2017). Fecal microbiota manipulation prevents dysbiosis and alcohol-induced liver injury in mice. *Journal of Hepatology*. <https://doi.org/10.1016/j.jhep.2016.11.008>.
- Fioramonti, J., Theodorou, V., & Bueno, L. (2003). Probiotics: What are they? What are their effects on gut physiology? *Best Practice and Research Clinical Gastroenterology*, 17(5), 711–724.
- Flint, H. J., Scott, K. P., Louis, P., & Duncan, S. H. (2012). The role of the gut microbiota in nutrition and health. *Nature Reviews. Gastroenterology & Hepatology*, 9, 577–589. <https://doi.org/10.1038/nrgastro.2012.156>.

- Florowska, A., Krygier, K., Florowski, T., & Dłuzewska, E. (2016). Prebiotics as functional food ingredients preventing diet-related diseases. *Food & Function*, 7(5), 2147–2155.
- Gagliardi, A., Totino, V., Cacciotti, F., Iebba, V., Neroni, B., Bonfiglio, G., Trancassini, M., Pasariello, C., Pantanella, F., & Schippa, S. (2018). Rebuilding the gut microbiota ecosystem. *International Journal of Environmental Research and Public Health*, 15(8), 1679.
- Gibson, G. R. (1999). Dietary modulation of the human gut microflora using the prebiotics Oligofructose and inulin. *The Journal of Nutrition*. <https://doi.org/10.1093/jn/129.7.1438s>.
- Goodrich, J. K., Waters, J. L., Poole, A. C., Sutter, J. L., Koren, O., Blekhan, R., Beaumont, M., Van Treuren, W., Knight, R., Bell, J. T., Spector, T. D., Clark, A. G., & Ley, R. E. (2014). Human genetics shape the gut microbiome. *Cell*. <https://doi.org/10.1016/j.cell.2014.09.053>.
- Govender, M., Choonara, Y. E., Kumar, P., Du Toit, L. C., Van Vuuren, S., & Pillay, V. (2014). A review of the advancements in probiotic delivery: Conventional vs. Non-conventional formulations for intestinal flora supplementation. *AAPS PharmSciTech*, 15(1), 29–43.
- Haller D. (eds) *The Gut Microbiome in Health and Disease*. Springer, Cham. <https://doi.org/10.1007/978-3-319-90545-7>.
- Harmsen, H. J. M., Wildeboer-Veloo, A. C. M., Raangs, G. C., Wagendorp, A. A., Klijn, N., Bindels, J. G., & Welling, G. W. (2000). Analysis of intestinal flora development in breast-fed and formula-fed infants by using molecular identification and detection methods. *Journal of Pediatric Gastroenterology and Nutrition*. <https://doi.org/10.1097/00005176-200001000-00019>.
- Hasenhuettl G., Hartel R. (eds) *Food Emulsifiers and Their Applications*. Springer, Cham. <https://doi.org/10.1007/978-3-030-29187-7>.
- Hayes, S. R., & Vargas, A. J. (2016). Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Explore: The Journal of Science & Healing*. <https://doi.org/10.1016/j.explore.2016.08.015>.
- Jackson, M. A., Goodrich, J. K., Maxan, M. E., Freedberg, D. E., Abrams, J. A., Poole, A. C., Sutter, J. L., Welter, D., Ley, R. E., Bell, J. T., Spector, T. D., & Steves, C. J. (2016). Proton pump inhibitors alter the composition of the gut microbiota. *Gut*. <https://doi.org/10.1136/gutjnl-2015-310861>.
- Jandhyala, S. M., Talukdar, R., Subramanyam, C., Vuyyuru, H., Sasikala, M., & Reddy, D. N. (2015). Role of the normal gut microbiota. *World Journal of Gastroenterology*. <https://doi.org/10.3748/wjg.v21.i29.8787>.
- Kechagia, M., Basoulis, D., Konstantopoulou, S., Dimitriadi, D., Gyftopoulou, K., Skarmoutsou, N., & Fakiri, E. M. (2013). Health benefits of probiotics: A review. *ISRN Nutrition*. <https://doi.org/10.5402/2013/481651>.
- Kelly, D., King, T., & Aminov, R. (2007). Importance of microbial colonization of the gut in early life to the development of immunity. *Mutation Research*. <https://doi.org/10.1016/j.mrfmm.2007.03.011>.
- Kennedy, P. J., Cryan, J. F., Dinan, T. G., & Clarke, G. (2014). Irritable bowel syndrome: A microbiome-gut-brain axis disorder? *World Journal of Gastroenterology*, 20(39), 14105–14125.
- Koehler, K. J., Thomas, W., & Slavin, J. L. (2015). Healthy subjects experience bowel changes on enteral diets: Addition of a fiber blend attenuates stool weight and gut bacteria decreases without changes in gas. *Journal of Parenteral and Enteral Nutrition*. <https://doi.org/10.1177/0148607113510523>.
- Lee, S. O., Kim, C. S., Cho, S. K., Choi, H. J., Ji, G. E., & Oh, D. K. (2003). Bioconversion of linoleic acid into conjugated linoleic acid during fermentation and by washed cells of *Lactobacillus reuteri*. *Biotechnology Letters*, 25, 935–938. <https://doi.org/10.1023/A:1024084203052>.
- Lee, S. M., Donaldson, G. P., Mikulski, Z., Boyajian, S., Ley, K., & Mazmanian, S. K. (2013). Bacterial colonization factors control specificity and stability of the gut microbiota. *Nature*, 501, 426–429. <https://doi.org/10.1038/nature12447>.
- Li, M., Liang, P., Li, Z., Wang, Y., Zhang, G., Gao, H., Wen, S., & Tang, L. (2015). Fecal microbiota transplantation and bacterial consortium transplantation have comparable effects on the

- re-establishment of mucosal barrier function in mice with intestinal dysbiosis. *Frontiers in Microbiology*. <https://doi.org/10.3389/fmicb.2015.00692>.
- Li, M., Li, Z., Wen, S., Liu, Y., Wang, Y., & Tang, L. (2016). Transplantation of a bacterial consortium ameliorates trinitrobenzenesulfonic acid-induced colitis and intestinal dysbiosis in rats. *Future Microbiology*. <https://doi.org/10.2217/fmb-2015-0002>.
- Magge, S., & Lembo, A. (2012). Low-FODMAP diet for treatment of irritable bowel syndrome. *Gastroenterología y Hepatología*, 8(11), 739–745.
- Marietta, E. V., Gomez, A. M., Yeoman, C., Tilahun, A. Y., Clark, C. R., Luckey, D. H., Murray, J. A., White, B. A., Kudva, Y. C., & Rajagopalan, G. (2013). Low incidence of spontaneous type 1 diabetes in non-obese diabetic mice raised on gluten-free diets is associated with changes in the intestinal microbiome. *PLoS One*. <https://doi.org/10.1371/journal.pone.0078687>.
- Markowiak, P., & Ślizewska, K. (2017). Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients*, 9(9), 1021.
- Martin, B. R., Braun, M. M., Wigertz, K., Bryant, R., Zhao, Y., Lee, W. H., Kempa-Steczko, A., & Weaver, C. M. (2010). Fructo-oligosaccharides and calcium absorption and retention in adolescent girls. *Journal of the American College of Nutrition*. <https://doi.org/10.1080/07315724.2010.10719855>.
- Meneghin, F., Fabiano, V., Mameli, C., & Zuccotti, G. V. (2012). Probiotics and atopic dermatitis in children. *Pharmaceuticals (Basel)*, 5(7), 727–744.
- Nettleton, J. E., Reimer, R. A., & Shearer, J. (2016). Reshaping the gut microbiota: Impact of low calorie sweeteners and the link to insulin resistance? *Physiology & Behavior*, 164(Pt B), 488–493.
- Nicholson, J. K., Holmes, E., Kinross, J., Burcelin, R., Gibson, G., Jia, W., & Pettersson, S. (2012). Host-gut microbiota metabolic interactions. *Science*, 336(6086), 1262–1267.
- Patel, S., & Goyal, A. (2012). The current trends and future perspectives of prebiotics research: A review. *3 Biotech*. <https://doi.org/10.1007/s13205-012-0044-x>.
- Peng, M., & Biswas, D. (2017). Short chain and polyunsaturated fatty acids in host gut health and foodborne bacterial pathogen inhibition. *Critical Reviews in Food Science and Nutrition*. <https://doi.org/10.1080/10408398.2016.1203286>.
- Peng, M., Patel, P., Vinod, N., Cassandra, B., Michael, C., & Debabrata, B. (2018). Feasible options to control colonization of enteric pathogens with designed synbiotics. In R. R. Watson & V. R. Preedy (Eds.), *Dietary interventions in gastrointestinal diseases*. Elsevier Academic Press, 135–149, ISBN 9780128144688, <https://doi.org/10.1016/B978-0-12-814468-8.00011-9>.
- Reijnders, D., Goossens, G. H., Hermes, G. D. A., Neis, E. P. J. G., van der Beek, C. M., Most, J., Holst, J. J., Lenaerts, K., Kootte, R. S., Nieuwdorp, M., Groen, A. K., Olde Damink, S. W. M., Boekschoten, M. V., Smidt, H., Zoetendal, E. G., Dejong, C. H. C., & Blaak, E. E. (2016). Effects of gut microbiota manipulation by antibiotics on host metabolism in obese humans: A randomized double-blind placebo-controlled trial. *Cell Metabolism*. <https://doi.org/10.1016/j.cmet.2016.06.016>.
- Rezac, S., Kok, C. R., Heermann, M., & Hutkins, R. (2018). Fermented foods as a dietary source of live organisms. *Frontiers in Microbiology*, 9, 1785.
- Riaz Rajoka, M. S., Shi, J., Mehwish, H. M., Zhu, J., Li, Q., Shao, D., Huang, Q., & Yang, H. (2017). Interaction between diet composition and gut microbiota and its impact on gastrointestinal tract health. *Food Science and Human Wellness*. <https://doi.org/10.1016/j.fshw.2017.07.003>.
- Samuel, B. S., Shaito, A., Motoike, T., Rey, F. E., Backhed, F., Manchester, J. K., Hammer, R. E., Williams, S. C., Crowley, J., Yanagisawa, M., & Gordon, J. I. (2008). Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proceedings of the National Academy of Sciences*. <https://doi.org/10.1073/pnas.0808567105>.
- Saxelin, M. (2008). Probiotic formulations and applications, the current probiotics market, and changes in the marketplace: A European perspective. *Clinical Infectious Diseases*. <https://doi.org/10.1093/cid/cin511>.

- doi.org/10.1086/523337.
- Sidnell, A. (2008). Essentials of human nutrition. *Nutrition Bulletin*. <https://doi.org/10.1111/j.1467-3010.2008.00698.x>.
- Slavin, J. (2013). Fiber and prebiotics: Mechanisms and health benefits. *Nutrients*, 5(4), 1417–1435.
- Sreeja, V., & Prajapati, J. B. (2013). Probiotic formulations: Application and status as pharmaceuticals-a review. *Probiotics and Antimicrobial Proteins*. <https://doi.org/10.1007/s12602-013-9126-2>.
- Sridharan, G. V., Choi, K., Klemashevich, C., Wu, C., Prabakaran, D., Pan, L. B., Steinmeyer, S., Mueller, C., Yousofshahi, M., Alaniz, R. C., Lee, K., & Jayaraman, A. (2014). Prediction and quantification of bioactive microbiota metabolites in the mouse gut. *Nature Communications*. <https://doi.org/10.1038/ncomms6492>.
- Su, P., Henriksson, A., & Mitchell, H. (2007). Prebiotics enhance survival and prolong the retention period of specific probiotic inocula in an in vivo murine model. *Journal of Applied Microbiology*. <https://doi.org/10.1111/j.1365-2672.2007.03469.x>.
- Topping, D. L., & Clifton, P.M. (2001). Short-chain fatty acids and human colonic function: Roles of resistant starch and nonstarch polysaccharides. *Physiological Reviews*, 81, 1031–1064. <https://doi.org/10.1152/physrev.2001.81.3.1031>.
- Turnbaugh, P.J., Bäckhed, F., Fulton, L., & Gordon, J. I. (2008). Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host & Microbe*. <https://doi.org/10.1016/j.chom.2008.02.015>.
- Valdes, A. M., Walter, J., Segal, E., & Spector, T. D. (2018). Role of the gut microbiota in nutrition and health. *BMJ*. <https://doi.org/10.1136/bmj.k2179>.
- Zhang, Y. J., Li, S., Gan, R. Y., Zhou, T., Xu, D. P., & Li, H. B. (2015). Impacts of gut bacteria on human health and diseases. *International Journal of Molecular Sciences*, 16(4), 7493–7519.

# İnsan Beslenmesinde ve Bağırsak Sağlığında Bağırsak Florasının Rolü

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## 1. Giriş

Bağırsak mikrobiyomu üzerine yapılan çalışmaların artmasıyla birlikte, bağırsak mikrobiyomunun hayvan ve insan sağlığını koruyan en önemli faktörlerden biri olduğunu gösteren daha fazla veri ortaya çıkmıştır. Bağırsak mikrobiyomunun rolleri son derece çeşitlidir, ancak sindirim sürecine nasıl dahil olduğuna ve konakçı beslenmesine nasıl katkıda bulunduğuna çok dikkat edilmiştir (Laparra ve Sanz 2010). Konak ve onun mikrobiyomu arasında gerçekleşen dinamikleri ve bu etkileşimin spesifik sonucunun ne olacağını tam olarak anlamak için hala pek çok araştırma yapılmaktadır (Hillman ve ark. 2017). Bağırsak mikrobiyomu, gastrointestinal sistem içinde belirli bölgelerde yaşayan çok çeşitli bir mikrop ekosisteminden oluşur, ancak dış faktörlerden büyük ölçüde etkilenebilir, bu da bağırsak mikrobiyomunu çok değişken ve çeşitli hale getirir. İklim, kimyasallara, minerallere ve kirliliklere maruz kalma gibi çevresel faktörlerin dikkate alınması önemlidir, ancak konakçının tükettiği gıda, gastrointestinal sistemdeki mikroplarla doğrudan temasa geçerek, potansiyel olarak metabolizmalarını ve büyümelerini etkiler. Benzer nedenlerle, mikrobiyom, belirli alanlarda bulunacak mikrop grupları ve sayılarının ne olabileceği açısından bireyden bireye farklılık gösterebilir. Buna ek olarak, genetik gibi konakçıya özgü faktörler ve konakçı hücrelerle etkileşim ve bunların ne gibi bir etki yaratacağı gibi faktörler de bulunmaktadır.

Konağı ve mikrobiyomunu etkileyecek birçok değişkeni dikkate alırken, bağırsak mikrobiyotasında olması gereken mikroorganizmaların optimal oranları için evrensel bir standart bulmanın çok zor olduğunu ve bu sistemlerde sürekli olarak rol oynayan birçok dış ve iç faktörün hesaba katılması gerektiğini belirtmek önemlidir. Bununla birlikte, şimdiye kadar birikmiş olan toplu bilgi ile, sağlıklı bir bağırsak mikrobiyomunu teşvik etmek için genel kılavuzlar olarak kullanılacak belirli parametreler tanımlanmıştır. Bu yönergeler göz önünde bulundurularak, dengeli bir bağırsak mikrobiyomunun faydalarını ortaya çıkarmak için belirli kişiler tarafından belirli önlemler uygulamaya konulabilir (Hemarajata ve Versalovic 2013). Ayrıca, belirli mikrop gruplarının topluluk içinde sahip oldukları farklı rolleri anlamak; konakçıya fayda sağlama potansiyelleri ve sağlığa zararlı olabilecek bu mikropların etkisini nasıl azaltılacağı hakkında önemli bilgiler verir.

iyileşmeyecektir, buna soğuk algınlığı, grip (grip), bronşit, çoğu öksürük türü, bazı kulak enfeksiyonları, çoğu sinüs enfeksiyonları ve mide gribi de dahildir (Yoon ve Yoon 2018). Antibiyotiklerin ne zaman, hangi yaşta, ne sıklıkta, ne dozajda ve hangi hastalıklar için kullanılması gerektiğinin farkında olmak önemlidir.

## 10 Sonuç

Bağırsak mikrobiyomunun beslenmeyi iyileştirmede ve konakçının sağlığını geliştirmede oynadığı rol çok yönlü ve karmaşıktır. Yıllar boyunca, egzersiz, stresin azaltılması, daha iyi bir diyet ve belirli bileşiklerin tüketimi gibi birçok alışkanlık, daha sağlıklı yaşam tarzlarının destekleyicileri olmakla ilişkilendirilmiştir. Ancak mikrobiyomun konakçı ile nasıl etkileşime girdiğinin daha iyi anlaşılmasıyla, bu uygulamaların insan bağırsağında yaşayan mikrobiyal popülasyonu doğrudan nasıl etkileyebileceği hakkında daha fazla bilgi keşfedilmiştir. Bu eylemlerden elde edilen faydaların çoğu, mikrobiyotadan doğrudan yanıt olarak ortaya çıkar. Ancak, bu süreçlerin çoğunun uzun vadeli etkilerini anlamak için hala çok fazla araştırmaya ihtiyaç olduğunu belirtmek önemlidir. Mikrobiyom içinde bir denge olması gerekir ve araştırmalar, bağırsaktaki herhangi bir bakteri grubunun aşırı bolluğunun, bağırsak mikrobiyomunun faydalarından yararlanmak için yapılan her türlü çabayı boşa çıkaran disbiyozaya yol açabileceğini göstermiştir. Aynı doğrultuda, bu faydaların çoğunun, belirli mikrobiyal profillere ve diğer dış faktörlere bağlı olarak kişiden kişiye değişeceğini belirtmek önemlidir. Bazı bireylerin sağlıklarını iyileştirmek için özel ihtiyaçları olabilir veya farklı bir yaklaşım gerektirecek bir durumda olabilir. Daha fazla araştırma, konakçı için daha iyi bir sonuç elde etmek üzere bağırsak mikrobiyomunu korumak ve etkilemek amacı ile daha iyi yönlendirilmiş uygulamaların geliştirilmesine yardımcı olacaktır, ancak şu anda kesinlikle yararlı olduğu kanıtlanmış ve bireylerin günlük yaşamlarında uygulanabilecek birçok önlem vardır.

## References

- Azzam, H., & Malnick, S. (2015). Non-alcoholic fatty liver disease – The heart of the matter. *World Journal of Hepatology*, 7(10), 1369–1376. <https://doi.org/10.4254/wjh.v7.i10.1369>.
- Bailey, M. T., Dowd, S. E., Galley, J. D., Hufnagle, A. R., Allen, R. G., & Lyte, M. (2011). Exposure to a social stressor alters the structure of the intestinal microbiota: Implications for stressor-induced immunomodulation. *Brain, Behavior, and Immunity*, 25(3), 397–407. <https://doi.org/10.1016/j.bbi.2010.10.023>.
- Begley, M., Hill, C., & Gahan, C. G. (2006). Bile salt hydrolase activity in probiotics. *Applied and Environmental Microbiology*, 72(3), 1729–1738.
- Braune, A., & Blaut, M. (2016). Bacterial species involved in the conversion of dietary flavonoids in the human gut. *Gut Microbes*. <https://doi.org/10.1080/19490976.2016.1158395>.
- Bugaut, M. (1987). Occurrence, absorption and metabolism of short chain fatty acids in the di-

- gestive tract of mammals. *Comparative Biochemistry and Physiology -- Part B: Biochemistry And*. [https://doi.org/10.1016/0305-0491\(87\)90433-0](https://doi.org/10.1016/0305-0491(87)90433-0).
- Campbell, S. C., Wisniewski, P. J., Noji, M., McGuinness, L. R., Häggblom, M. M., Lightfoot, S. A., & Kerkhof, L. J. (2016). The effect of diet and exercise on intestinal integrity and microbial diversity in mice. *PLoS One*, *11*(3), e0150502. <https://doi.org/10.1371/journal.pone.0150502>.
- Chen, M., Zhang, H., Liu, W., & Zhang, W. (2014). The global pattern of urbanization and economic growth: Evidence from the last three decades. *PLoS One*, *9*(8), e103799. <https://doi.org/10.1371/journal.pone.0103799>.
- Chumpitazi, B. (2018). Update on dietary management of childhood functional abdominal pain disorders. *Gastroenterology Clinics of North America*, *47*(4), 715–726.
- Clemente-Postigo, M., Queipo-Ortuño, M. I., Boto-Ordoñez, M., Coin-Aragüez, L., Roca-Rodriguez, M. D. M., Delgado-Lista, J., & Tinahones, F. J. (2013). Effect of acute and chronic red wine consumption on lipopolysaccharide concentrations. *The American Journal of Clinical Nutrition*, *97*(5), 1053–1061. <https://doi.org/10.3945/ajcn.112.051128>.
- Connors, J., Dawe, N., & Van Limbergen, J. (2019). The role of succinate in the regulation of intestinal inflammation. *Nutrients*. <https://doi.org/10.3390/nu11010025>.
- den Besten, G., van Eunen, K., Groen, A. K., Venema, K., Reijngoud, D. J., & Bakker, B. M. (2013). The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *Journal of Lipid Research*, *54*(9), 2325–2340.
- Davies, J., & Davies, D. (2010). Origins and evolution of antibiotic resistance. *Microbiology and Molecular Biology Reviews: MMBR*, *74*(3), 417–433. <https://doi.org/10.1128/MMBR.00016-10>.
- Dhingra, D., Michael, M., Rajput, H., & Patil, R. T. (2011). Dietary fiber in foods: A review. *Journal of Food Science and Technology*, *49*(3), 255–266.
- Dominianni, C., Sinha, R., Goedert, J. J., Pei, Z., Yang, L., Hayes, R. B., et al. (2015). Sex, body mass index, and dietary Fiber intake influence the human gut microbiome. *PLoS One*, *10*(4), e0124599. <https://doi.org/10.1371/journal.pone.0124599>.
- Dongowski, G., Lorenz, A., & Anger, H. (2000). Degradation of pectins with different degrees of esterification by *Bacteroides Applied and Environmental Microbiology*, *66*(4), 1321–1327.
- Duda-Chodak, A., Tarko, T., Satora, P., & Sroka, P. (2015). Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: a review. *European Journal of Nutrition* *54*(3), 325–341. <https://doi.org/10.1007/s00394-015-0852-y>.
- Elleuch, L., Shaaban, M., Smaoui, S., Mellouli, L., Karray-Rebai, I., Fourati-Ben Fguira, L., et al. (2010). Bioactive secondary metabolites from a new terrestrial streptomyces sp. TN262. *Applied Biochemistry and Biotechnology*. <https://doi.org/10.1007/s12010-009-8808-4>.
- El Kaoutari, A., Armougom, F., Gordon, J. I., Raoult, D., & Henrissat, B. (2013). The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. *Nature Reviews Microbiology*, *11*(7), 497.
- Esakkiraj, P., Rajkumarbarathi, M., Palavesam, A., & Immanuel, G. (2010). Lipase production by *Staphylococcus epidermidis* CMST-Pi 1 isolated from the gut of shrimp *Penaeus indicus*. *Annals of Microbiology*, *60*(1), 37–42.
- Fadl, A. A., Sha, J., Klimpel, G. R., Olano, J. P., Niesel, D. W., & Chopra, A. K. (2005). Murein lipoprotein is a critical outer membrane component involved in *Salmonella enterica* serovar typhimurium systemic infection. *Infection and Immunity*, *73*(2), 1081–1096. <https://doi.org/10.1128/IAI.73.2.1081-1096.2005>.
- Fetzner, S. (2012). Ring-cleaving dioxygenases with a cupin fold. *Applied and Environmental Microbiology*. <https://doi.org/10.1128/AEM.07651-11>.
- Flint, H. J., Scott, K. P., Duncan, S. H., Louis, P., & Forano, E. (2012). Microbial degradation of complex carbohydrates in the gut. *Gut Microbes*, *3*(4), 289–306.

- Foster, J. A., Rinaman, L., & Cryan, J. F. (2017). Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiology of Stress*, 7, 124–136. <https://doi.org/10.1016/j.ynstr.2017.03.001>.
- Fritsch, C., Heinrich, V., Vogel, R. F., & Toelstede, S. (2016). Phenolic acid degradation potential and growth behavior of lactic acid bacteria in sunflower substrates. *Food Microbiology*. <https://doi.org/10.1016/j.fm.2016.03.003>.
- Gaci, N., Borrel, G., Tottey, W., O'Toole, P. W., & Brugère, J. F. (2014). Archaea and the human gut: New beginning of an old story. *World Journal of Gastroenterology*, 20(43), 16062–16078.
- García-Ruiz, A., González de Llano, D., Esteban-Fernández, A., Requena, T., Bartolomé, B., & Moreno-Arribas, M. V. (2014). Assessment of probiotic properties in lactic acid bacteria isolated from wine. *Food Microbiology*, 44, 220–225. <https://doi.org/10.1016/j.fm.2014.06.015>.
- Gérard, P. (2013). Metabolism of cholesterol and bile acids by the gut microbiota. *Pathogens*, 3(1), 14–24.
- Glick-Bauer, M., & Yeh, M.-C. (2014). The health advantage of a vegan diet: Exploring the gut microbiota connection. *Nutrients*, 6(11), 4822–4838. <https://doi.org/10.3390/nu6114822>.
- Grajek, W., Olejnik, A., & Sip, A. (2005). Probiotics, prebiotics and antioxidants as functional foods. *Acta Biochimica Polonica-English Edition*, 52(3), 665.
- Gramenzi, A., Caputo, F., Biselli, M., Kuria, F., Loggi, E., Andreone, P., & Bernardi, M. (2006). Review article: Alcoholic liver disease—pathophysiological aspects and risk factors. *Alimentary Pharmacology & Therapeutics*, 24(8), 1151–1161. <https://doi.org/10.1111/j.1365-2036.2006.03110.x>.
- Gu, Q., & Li, P. (2016, July 13). *Biosynthesis of vitamins by probiotic bacteria*. Retrieved from <https://www.intechopen.com/books/probiotics-and-prebiotics-in-human-nutrition-and-health/biosynthesis-of-vitamins-by-probiotic-bacteria>
- Hamaker, B. R., & Tuncil, Y. E. (2014). A perspective on the complexity of dietary fiber structures and their potential effect on the gut microbiota. *Journal of Molecular Biology*, 426(23), 3838–3850. <https://doi.org/10.1016/j.jmb.2014.07.028>.
- Hemarajata, P., & Versalovic, J. (2013). Effects of probiotics on gut microbiota: Mechanisms of intestinal immunomodulation and neuromodulation. *Therapeutic Advances in Gastroenterology*, 6(1), 39–51. <https://doi.org/10.1177/1756283X12459294>.
- Hillman, E. T., Lu, H., Yao, T., & Nakatsu, C. H. (2017). Microbial ecology along the gastrointestinal tract. *Microbes and Environments*, 32(4), 300–313.
- Hoffmann, C., Dollive, S., Grunberg, S., Chen, J., Li, H., Wu, G. D., et al. (2013). Archaea and fungi of the human gut microbiome: Correlations with diet and bacterial residents. *PLoS One*, 8(6), e66019.
- Hofmann, A. F., Hagey, L. R., & Krasowski, M. D. (2010). Bile salts of vertebrates: Structural variation and possible evolutionary significance. *Journal of Lipid Research*, 51(2), 226–246.
- Hosseini, E., Grootaert, C., Verstraete, W., & Van de Wiele, T. (2011). Propionate as a health-promoting microbial metabolite in the human gut. *Nutrition Reviews*, 69(5), 245–258.
- Howarth, N. C., Saltzman, E., & Roberts, S. B. (2001). Dietary fiber and weight regulation. *Nutrition Reviews*, 59(5), 129–139.
- Jandhyala, S. M., Talukdar, R., Subramanyam, C., Vuyyuru, H., Sasikala, M., & Nageshwar Reddy, D. (2015). Role of the normal gut microbiota. *World Journal of Gastroenterology*, 21(29), 8787–8803.
- Jiang, T., Gao, X., Wu, C., Tian, F., Lei, Q., Bi, J., Xie, B., Wang, H. Y., Chen, S., & Wang, X. (2016). Apple-derived pectin modulates gut microbiota, improves gut barrier function, and attenuates metabolic endotoxemia in rats with diet-induced obesity. *Nutrients*, 8(3), 126. <https://doi.org/10.3390/nu8030126>.
- Johansson, M. E., Sjövall, H., & Hansson, G. C. (2013). The gastrointestinal mucus system in health and disease. *Nature reviews. Gastroenterology & Hepatology*, 10(6), 352–361.
- Joyce, S. A., MacSharry, J., Casey, P. G., Kinsella, M., Murphy, E. F., Shanahan, F., & Gahan, C.

- G. (2014). Regulation of host weight gain and lipid metabolism by bacterial bile acid modification in the gut. *Proceedings of the National Academy of Sciences*, 201323599.
- Jung, J. Y., Lee, S. H., Kim, J. M., Park, M. S., Bae, J.-W., Hahn, Y., & Jeon, C. O. (2011). Metagenomic analysis of kimchi, a traditional Korean fermented food. *Applied and Environmental Microbiology*, 77(7), 2264–2274. <https://doi.org/10.1128/AEM.02157-10>.
- Kekkonen, R. A., Kajasto, E., Miettinen, M., Veckman, V., Korpela, R., & Julkunen, I. (2008). Probiotic *Leuconostoc mesenteroides* ssp. *cremoris* and *Streptococcus thermophilus* induce IL-12 and IFN- $\gamma$  production. *World Journal of Gastroenterology*, 14(8), 1192–1203. <https://doi.org/10.3748/wjg.14.1192>.
- Kuo, L. E., Kitlinska, J. B., Tilan, J. U., Li, L., Baker, S. B., Johnson, M. D., & Zukowska, Z. (2007). Neuropeptide Y acts directly in the periphery on fat tissue and mediates stress-induced obesity and metabolic syndrome. *Nature Medicine*, 13(7), 803–811. <https://doi.org/10.1038/nm1611>.
- Laparra, J. M., & Sanz, Y. (2010). Interactions of gut microbiota with functional food components and nutraceuticals. *Pharmacological Research*, 61(3), 219–225.
- LeBlanc, J. G., Chain, F., Martín, R., Bermúdez-Humarán, L. G., Courau, S., & Langella, P. (2017). Beneficial effects on host energy metabolism of short-chain fatty acids and vitamins produced by commensal and probiotic bacteria. *Microbial Cell Factories*, 16(1), 79.
- Lima, G. P. P., Vianello, F., Corrêa, C. R., Campos, R. A. D. S., & Borguini, M. G. (2014). Polyphenols in fruits and vegetables and its effect on human health. *Food and Nutrition Sciences*, 1065–1082.
- Lima-Ojeda, J. M., Rupprecht, R., & Baghai, T. C. (2017). “I am I and my bacterial circumstances”: Linking gut microbiome, neurodevelopment, and depression. *Frontiers in Psychiatry*, 8. <https://doi.org/10.3389/fpsy.2017.00153>.
- Lovegrove, A., Edwards, C. H., De Noni, I., Patel, H., El, S. N., Grassby, T., Zielke, C., Ulmius, M., Nilsson, L., Butterworth, P. J., Ellis, P. R., & Shewry, P. R. (2015). Role of polysaccharides in food, digestion, and health. *Critical Reviews in Food Science and Nutrition*, 57(2), 237–253.
- Lurie-Weinberger, M. N., & Gophna, U. (2015). Archaea in and on the human body: Health implications and future directions. *PLoS Pathogens*, 11(6), e1004833.
- Ma, N., & Ma, X. (2019). *Dietary amino acids and the gut-microbiome-immune axis: Physiological metabolism and therapeutic prospects*. Comprehensive Reviews in Food Science and Food Safety. <https://doi.org/10.1111/1541-4337.12401>.
- Mach, N., & Fuster-Botella, D. (2017). Endurance exercise and gut microbiota: A review. *Journal of Sport and Health Science*, 6(2), 179–197.
- Magnúsdóttir, S., Ravcheev, D., de Crécy-Lagard, V., & Thiele, I. (2015). Systematic genome assessment of B-vitamin biosynthesis suggests co-operation among gut microbes. *Frontiers in Genetics*, 6, 148.
- Mallett, A. K., & Rowland, I. R. (1990). Bacterial enzymes: Their role in the formation of mutagens and carcinogens in the intestine. *Digestive Diseases*, 8(2), 71–79.
- Manrique, P., Dills, M., & Young, M. (2017). The human gut phage community and its implications for health and disease. *Viruses*, 9(6), 141.
- Mar Rodríguez, M., Pérez, D., Javier Chaves, F., Esteve, E., Marin-García, P., Xifra, G., Vendrell, J., Jové, M., Pamplona, R., Ricart, W., Portero-Otin, M., Chacón, M. R., & Fernández Real, J. M. (2015). Obesity changes the human gut mycobiome. *Scientific Reports*, 5, 14600. <https://doi.org/10.1038/srep14600>.
- Matsumoto, M., Inoue, R., Tsukahara, T., Ushida, K., Chiji, H., Matsubara, N., & Hara, H. (2008). Voluntary running exercise alters microbiota composition and increases n-Butyrate concentration in the rat cecum. *Bioscience, Biotechnology, and Biochemistry* 72(2), 572–576. <https://doi.org/10.1271/bbb.70474>.
- Messaoudi, M., Violle, N., Bisson, J.-F., Desor, D., Javelot, H., & Rougeot, C. (2011). Beneficial psychological effects of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifi-*

- dobacterium longum R0175) in healthy human volunteers. *Gut Microbes*, 2(4), 256–261. <https://doi.org/10.4161/gmic.2.4.16108>.
- Mika, A., Van Treuren, W., González, A., Herrera, J. J., Knight, R., & Fleshner, M. (2015). Exercise is more effective at altering gut microbial composition and producing stable changes in lean mass in juvenile versus adult male F344 rats. *PLoS One*, 10(5), e0125889. <https://doi.org/10.1371/journal.pone.0125889>.
- Milani, C., Duranti, S., Bottacini, F., Casey, E., Turrone, F., Mahony, J., & Lugli, G. A. (2017). The first microbial colonizers of the human gut: Composition, activities, and health implications of the infant gut microbiota. *Microbiology and Molecular Biology Reviews*, 81(4), e00036–e00017.
- Minot, S., Bryson, A., Chehoud, C., Wu, G. D., Lewis, J. D., & Bushman, F. D. (2013). Rapid evolution of the human gut virome. *Proceedings of the National Academy of Sciences*, 110(30), 12450–12455.
- Monda, V., Villano, I., Messina, A., Valenzano, A., Esposito, T., Moscatelli, F., & Messina, G. (2017). Exercise modifies the gut microbiota with positive health effects. *Oxidative Medicine and Cellular Longevity*, 2017. <https://doi.org/10.1155/2017/3831972>.
- Morrison, D. J., & Preston, T. (2016). Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes*, 7(3), 189–200.
- Mudgil, D., & Barak, S. (2013). Composition, properties and health benefits of indigestible carbohydrate polymers as dietary fiber: A review. *International Journal of Biological Macromolecules*, 61, 1–6.
- Murphy, E. F., Cotter, P.D., Healy, S., Marques, T.M., O'sullivan, O., Fouhy, F., & Ross, P.R. (2010). Composition and energy harvesting capacity of the gut microbiota: relationship to diet, obesity and time in mouse models. *Gut*, gut-2010.
- Mutzel, M. (2014). *Saccharomyces boulardii: The probiotic yeast that is great for your gut and immune system*. Retrieved from <https://mikemutzel.com/saccharomyces-boulardii-the-probiotic-yeast-that-is-great-for-your-gut-and-immune-system/>
- Parthasarathy, A., Cross, P. J., Dobson, R. C. J., Adams, L. E., Savka, M. A., & Hudson, A. O. (2018). A three-ring circus: Metabolism of the three proteogenic aromatic amino acids and their role in the health of plants and animals. *Frontiers in Molecular Biosciences*. <https://doi.org/10.3389/fmolb.2018.00029>.
- Parvez, S., Malik, K. A., Kang, S. A., & Kim, H.-Y. (2006). Probiotics and their fermented food products are beneficial for health. *Journal of Applied Microbiology*, 100(6), 1171–1185. <https://doi.org/10.1111/j.1365-2672.2006.02963.x>.
- Patel, S., Behara, R., Swanson, G. R., Forsyth, C. B., Voigt, R. M., & Keshavarzian, A. (2015). Alcohol and the intestine. *Biomolecules*, 5(4), 2573–2588. <https://doi.org/10.3390/biom5042573>.
- Phillips, M. L. (2009). Gut reaction: Environmental Effects on the Human Microbiota. *Environmental Health Perspectives*, 117(5), A198–A205.
- Probiotics: In Depth. (2011, November 21). Retrieved December 10, 2018, from <https://nccih.nih.gov/health/probiotics/introduction.htm>
- Raskov, H., Burchard, J., & Pommergaard, H. C. (2017). Linking gut microbiota to colorectal cancer. *Journal of Cancer*. <https://doi.org/10.7150/jca.20497>.
- Ridlon, J. M., Kang, D. J., & Hylemon, P. B. (2006). Bile salt biotransformations by human intestinal bacteria. *Journal of Lipid Research*, 47(2), 241–259.
- Ríos-Covián, D., Ruas-Madiedo, P., Margolles, A., Gueimonde, M., de Los Reyes-Gavilán, C. G., & Salazar, N. (2016). Intestinal short chain fatty acids and their link with diet and human health. *Frontiers in Microbiology*, 7, 185. <https://doi.org/10.3389/fmicb.2016.00185>.
- Roager, H. M., & Licht, T. R. (2018). Microbial tryptophan catabolites in health and disease. *Nature Communications*. <https://doi.org/10.1038/s41467-018-05470-4>.
- Rosselot, A. E., Hong, C. I., & Moore, S. R. (2016). Rhythm and bugs: Circadian clocks, gut mic-

- robiota, and enteric infections. *Current Opinion in Gastroenterology*, 32(1), 7–11. <https://doi.org/10.1097/MOG.0000000000000227>.
- Rytioja, J., Hildén, K., Yuzon, J., Hatakka, A., de Vries, R. P., & Mäkelä, M. R. (2014). Plant- polysaccharide-degrading enzymes from basidiomycetes. *Microbiology and Molecular Biology Reviews: MMBR*, 78(4), 614–649.
- Sam, Q. H., Chang, M. W., & Chai, L. Y. (2017). The fungal Mycobiome and its interaction with gut bacteria in the host. *International Journal of Molecular Sciences*, 18(2), 330. <https://doi.org/10.3390/ijms18020330>.
- Sánchez-Maldonado, A. F., Schieber, A., & Gänzle, M. G. (2011). Structure-function relationships of the antibacterial activity of phenolic acids and their metabolism by lactic acid bacteria. *Journal of Applied Microbiology*. <https://doi.org/10.1111/j.1365-2672.2011.05141.x>.
- Scalbert, A., Morand, C., Manach, C., & Rémésy, C. (2002). Absorption and metabolism of polyphenols in the gut and impact on health. *Biomedicine & Pharmacotherapy*, 56(6), 276–282. [https://doi.org/10.1016/S0753-3322\(02\)00205-6](https://doi.org/10.1016/S0753-3322(02)00205-6).
- Schaab, M. R., Barney, B. M., & Francisco, W. A. (2006). Kinetic and spectroscopic studies on the quercetin 2,3-dioxygenase from *Bacillus subtilis*. *Biochemistry*. <https://doi.org/10.1021/bi051571c>.
- Schmidt, K., Cowen, P. J., Harmer, C. J., Tzortzis, G., Errington, S., & Burnet, P. W. (2015). Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. *Psychopharmacology*, 232(10), 1793–1801.
- Selma, M. V., Espin, J. C., & Tomas-Barberan, F. A. (2009). Interaction between phenolics and gut microbiota: Role in human health. *Journal of Agricultural and Food Chemistry*, 57(15), 6485–6501.
- Singh, A., Zapata, R. C., Pezeshki, A., Reidelberger, R. D., & Chelikani, P. K. (2018). Inulin fiber dose-dependently modulates energy balance, glucose tolerance, gut microbiota, hormones and diet preference in high-fat fed male rats. *The Journal of Nutritional Biochemistry*.
- Slavin, J. (2013). Fiber and prebiotics: Mechanisms and health benefits. *Nutrients*, 5(4), 1417–1435.
- Stevens, J. F., & Maier, C. S. (2016). The chemistry of gut microbial metabolism of polyphenols. *Phytochemistry Reviews*. <https://doi.org/10.1007/s11101-016-9459-z>.
- Stojković, D. S., Davidović, S., Živković, J., Glamočlija, J., Ćirić, A., Stevanović, M., et al. (2013). Comparative evaluation of antimutagenic and antimutagenic effects of *Morchella esculenta* extracts and protocatechuic acid. *Frontiers in Life Science*. <https://doi.org/10.1080/2155376.9.2014.901925>.
- Tasnim, N., Abulizi, N., Pither, J., Hart, M. M., & Gibson, D. L. (2017). Linking the gut microbial ecosystem with the environment: Does gut health depend on where we live? *Frontiers in Microbiology*, 8. <https://doi.org/10.3389/fmicb.2017.01935>.
- Thursby, E., & Juge, N. (2017). Introduction to the human gut microbiota. *The Biochemical Journal*, 474(11), 1823–1836. <https://doi.org/10.1042/BCJ20160510>.
- Tiso, M., & Schechet, A. N. (2015). Nitrate reduction to nitrite, nitric oxide and ammonia by gut bacteria under physiological conditions. *PLoS One*, 10(5), e0127490.
- University of Jyväskylä. (2018). *Endurance exercise training has beneficial effects on gut microbiota composition*. Retrieved December 10, 2018, from <https://www.sciencedaily.com/releases/2018/10/181015105451.htm>
- University of Michigan Health System. (2016). *High-fiber diet keeps gut microbes from eating the colon's lining, protects against infection, animal study shows*. ScienceDaily.
- van de Pol, J. A., van Best, N., Mbakwa, C. A., Thijs, C., Savelkoul, P. H., Arts, I. C., Hornef, M. W., Mommers, M., & Penders, J. (2017). Gut colonization by methanogenic archaea is associated with organic dairy consumption in children. *Frontiers in Microbiology*, 8, 355. <https://doi.org/10.3389/fmicb.2017.00355>.
- Vinardell, M. P., & Mitjans, M. (2017). Lignins and their derivatives with beneficial effects on human health. *International Journal of Molecular Sciences*, 18(6), 1219. <https://doi.org/10.3390/ijms18061219>.

# Enflamasyon ve Kronik Enterik Enfeksiyonlarda Bağırsak Mikrobiyomu

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## 1. Giriş

İnsan vücudu, kendi hücrelerinden ortalama 10 kat fazla olan yaklaşık 10.000 türde trilyonlarca mikroorganizma barındırır (Eckburg ve ark. 2005; Savage 1977). Bu mikroplar topluca insan mikrobiyomu olarak bilinir ve bunlar genellikle insan vücudunun olası her bölümünde uyum içinde yaşayan bakterileri, virüsleri, protozoaları ve mantarları içerir; mikrobiyom, insan beyninin ağırlığından 2 kg daha ağırdır (Hallen-Adams ve Suhr 2016). İnsan vücudunun yaklaşık %2'sini oluşturan küçücük bir kiracı olan bu mikroorganizmalar, konakçıya bazen “ekstra organ” olarak kabul edilen pek çok fayda sağlar. İnsan Mikrobiyom Projesi (HMP), insan bağırsak mikrobiyotası hakkında kapsamlı bilgi edinmek için 2007 yılında başlatılmıştır. HMP'nin sonuçlarının, mikrobiyomun insan sağlığı, bağışıklık, beslenme ve hastalığındaki rolünün daha iyi bir açıklamasını vermesi beklenmektedir.

Sağlıklı bir şekilde dengelenmiş bir bağırsak mikroflorası; bağırsak bariyer fonksiyonunun korunmasına, bağışıklık sistemini eğitmeye ve olgunlaştırmaya, iltihabı önlemeye, besinler ve reseptör proteinler için patojenlere karşı doğrudan rekabet etmeye, hormon ve vitaminler (örneğin, K vitamini, biyotin ve folat) üretmeye yardımcı olur (Marchesi 2014). ; McKenney ve Pamer 2015). Üç ana bileşen (konak bağışıklığı, patojen ve konağın bağırsak mikrobiyotası) arasındaki karmaşık sürekli etkileşim, enterik enfeksiyonlara yol açabilir. Karmaşık etkileşimin verimliliğine bağlı olarak, enterik enfeksiyon çözülebilir veya enfekte konağın kronik patojen kolonizasyonuna ve hatta konağın ölümüne yol açabilir (Sekirov ve Finlay 2009). Bağırsak mikrobiyotası, beklenmedik bir şekilde patojenlerin kolonizasyonunu destekleyen metabolitler üreterek akut veya kronik enterik enfeksiyonları teşvik edebilir. Simbiyotik *Bacteroides thetaiotaomicron*, *Clostridium rodentium*'u rekabetçi bir şekilde dışlayabilir, ancak bağırsak epitel dokusunun müsünin sialik asit parçalarından süksinat üreterek *Clostridium difficile*'nin kolonizasyonuna yardımcı olabilir (Ferreya ve diğerleri 2014; Ng ve diğerleri. 2013; Rolhion ve Chassaing 2016). *C. difficile* ayrıca bağırsak ortamındaki endosporlardan gelişmek için safra tuzunu da kullanabilir (Giel ve ark. 2010). Dihidrojen ve etanolamin (bir nitrojen kaynağı olarak) gibi bağırsak mikrobiyomunun çeşitli diğer

kan sonuçlar, gıda alerjileri ve hassasiyetlerinin kaynağı olarak bağırsak mikrobiyomunu işaret etmeye devam etmektedir. Bağırsak bariyerinin nasıl çalıştığını ve nasıl hasar görebileceğini anlamak, alerjilerin nasıl ortaya çıktığını açıklayabilir. Bu aynı zamanda romatoid artrit ve lupus gibi otoimmün hastalıkların daha iyi anlaşılmasını sağlayabilir (Mudd ve Brenchley 2016). Bu, bugünün tedavi edilemeyen hastalıklarına gelecekte çare bulma ümidini göstermektedir.

## 5. Sonuç

İnsan vücudunun önemli bir bileşeni olarak bağırsak mikroorganizmalarının rolü, sağlık ve hastalıklarda daha belirgin hale gelmektedir. Bunların uygun biyoaktif metabolitler ve farmabiyotik molekül kaynakları oldukları zaten tespit edilmiştir. Ancak belirtmek gerekir ki, insan modellemesi olmadıkları için bugüne kadar edindiğimiz bilgiler öncelikle in vitro ve in vivo hayvan modeli çalışmalarına dayanmaktadır. Bir insan vücudu, bağışıklık sistemindeki, genetik arka plandaki, çevredeki, yaştaki, bağırsak yapısındaki ve en önemlisi, kronik metabolik hastalıklardan nöronal bozukluklara kadar birçok komplikasyona yol açabilen yerli bağırsak mikrobiyal bileşimindeki varyasyonla ilişkili olabilecek bağırsak mikrobiyal bileşiminde oluşan herhangi bir bozulmaya farklı tepkiler gösterir. İnsanlarda mikrobiyal kolonizasyon tarihinin tam olarak anlaşılmasının, öbiyozu sürdürmek ve birçok istenmeyen hastalığı önlemek için etkili stratejiler tasarlamaya yardımcı olacağı varsayılmaktadır.

## Kaynaklar

- Aditya, A., Alvarado-Martinez, Z., Nagarajan, V., Peng, M., & Biswas, D. (2019). Antagonistic effects of phenolic extracts of Chokeberry pomace on *E. coli* O157: H7 but not on probiotic and normal bacterial flora. *Journal of Berry Research*, 9, 459–472.
- Aguilar-Toalá, J. E., Garcia-Varela, R., Garcia, H. S., Mata-Haro, V., González-Córdova, A. F., Vallejo-Cordoba, B., & Hernández-Mendoza, A. (2018). Postbiotics: An evolving term within the functional foods field. *Trends in Food Science and Technology*, 75, 105–114.
- Akil, L., & Ahmad, H. A. (2011). Relationships between obesity and cardiovascular diseases in four southern states and Colorado. *Journal of Health Care for the Poor and Underserved*, 22, 61–72.
- Alipour, M., Zaidi, D., Valcheva, R., Jovel, J., Martínez, I., Sergi, C., Walter, J., Mason, A. L., Wong, G. K.-S., Dieleman, L. A., et al. (2016). Mucosal barrier depletion and loss of bacterial diversity are primary abnormalities in paediatric ulcerative colitis. *Journal of Crohn's and Colitis*, 10, 462–471.
- Andreatti Filho, R. L., Higgins, J. P., Higgins, S. E., Gaona, G., Wolfenden, A. D., Tellez, G., & Hargis, B. M. (2007). Ability of bacteriophages isolated from different sources to reduce *Salmonella enterica* Serovar Enteritidis in vitro and in vivo. *Poultry Science*, 86, 1904–1909.
- Arrieta, M. C., Bistritz, L., & Meddings, J. B. (2006). Alterations in intestinal permeability. *Gut*, 55, 1512–1520.
- Ashida, H., Ogawa, M., Kim, M., Mimuro, H., & Sasakawa, C. (2012). Bacteria and host interac-

- tions in the gut epithelial barrier. *Nature Chemical Biology*, 8, 36–45.
- Association, A.D. (2004). Gestational diabetes mellitus. *Diabetes Care Alex*, 27, S88–S90.
- Atarashi, K., Tanoue, T., Oshima, K., Suda, W., Nagano, Y., Nishikawa, H., Fukuda, S., Saito, T., Narushima, S., Hase, K., et al. (2013). Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. *Nature*, 500, 232–236.
- Bäckhed, F., Ding, H., Wang, T., Hooper, L. V., Koh, G. Y., Nagy, A., Semenkovich, C. F., & Gordon, J. I. (2004). The gut microbiota as an environmental factor that regulates fat storage. *Proceedings of the National Academy of Sciences of the United States of America*, 101, 15718–15723.
- Bajer, L., Kverka, M., Kostovcik, M., Macinga, P., Dvorak, J., Stehlikova, Z., Brezina, J., Wohl, P., Spicak, J., & Drastich, P. (2017). Distinct gut microbiota profiles in patients with primary sclerosing cholangitis and ulcerative colitis. *World Journal of Gastroenterology*, 23, 4548–4558.
- Balakireva, A. V., & Zamyatnin, A. A. (2016). Properties of gluten intolerance: Gluten structure, evolution, pathogenicity and detoxification capabilities. *Nutrients*, 8, 644.
- Balfour Sartor, R. (1997). Enteric microflora in IBD: Pathogens or commensals? *Inflammatory Bowel Diseases*, 3, 230–235.
- Berg, R. D. (1996). The indigenous gastrointestinal microflora. *Trends in Microbiology*, 4, 430–435.
- Bertin, Y., Girardeau, J. P., Chaucheyras-Durand, F., Lyan, B., Pujos-Guillot, E., Harel, J., & Martin, C. (2011). Enterohaemorrhagic *Escherichia coli* gains a competitive advantage by using ethanolamine as a nitrogen source in the bovine intestinal content. *Environmental Microbiology*, 13, 365–377.
- Bertram, S., Kurland, M., Lydick, E., Locke, G. R. I., & Yawn, B. P. (2001). The Patient's perspective of irritable bowel syndrome. *The Journal of Family Practice*, 50, 521.
- Bornstein, J., & Lawrence, R. D. (1951). Two types of diabetes mellitus, with and without available plasma insulin. *British Medical Journal*, 1, 732.
- Borody, T. J., & Khoruts, A. (2012). Fecal microbiota transplantation and emerging applications. *Nature Reviews. Gastroenterology & Hepatology*, 9, 88–96.
- Borody, T. J., Paramsothy, S., & Agrawal, G. (2013). Fecal microbiota transplantation: Indications, methods, evidence, and future directions. *Current Gastroenterology Reports*, 15, 337.
- Boyle, E. C., & Finlay, B. B. (2005). Leaky guts and lipid rafts. *Trends in Microbiology*, 13, 560–563.
- Bruwer, M., Luegering, A., Kucharzik, T., Parkos, C. A., Madara, J. L., Hopkins, A. M., & Nusrat, A. (2003). Proinflammatory cytokines disrupt epithelial barrier function by apoptosis-independent mechanisms. *Journal of Immunology*, 171, 6164–6172.
- Cammarota, G., Ianiro, G., Bibbò, S., & Gasbarrini, A. (2014). Fecal microbiota transplantation: A new old kid on the block for the management of gut microbiota-related disease. *Journal of Clinical Gastroenterology*, 48, S80–S84.
- Marcelo Campos (2017). Leaky gut: What is it, and what does it mean for you? Cani, P.D., Amar, J., Iglesias, M. A., Poggi, M., Knauf, C., Bastelica, D., Neyrinck, A. M., Fava, F., Tuohy, K. M., Chabo, C., et al. (2007). Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*, 56, 1761–1772.
- Cani, P. D., Delzenne, N. M., Amar, J., & Burcelin, R. (2008). Role of gut microflora in the development of obesity and insulin resistance following high-fat diet feeding. *Pathologie et Biologie*, 56, 305–309.
- Carrillo, C. L., Atterbury, R. J., El-Shibiny, A., Connerton, P. L., Dillon, E., Scott, A., & Connerton, F. (2005). Bacteriophage therapy to reduce campylobacter jejuni colonization of broiler chickens. *Applied and Environmental Microbiology*, 71, 6554–6563.
- Chakraborti, C. K. (2015). New-found link between microbiota and obesity. *World Journal of Gastrointestinal Pathophysiology*, 6, 110–119.
- Chassaing, B., Koren, O., Carvalho, F. A., Ley, R. E., & Gewirtz, A. T. (2014). AIEC pathobiont

- instigates chronic colitis in susceptible hosts by altering microbiota composition. *Gut*, 63, 1069–1080.
- Cheadle, G. A., Costantini, T. W., Lopez, N., Bansal, V., Eliceiri, B. P., & Coimbra, R. (2013). Enteric glia cells attenuate cytomix-induced intestinal epithelial barrier breakdown. *PLoS One*, 8, e69042.
- Chey, W. D., Kurlander, J., & Eswaran, S. (2015). Irritable bowel syndrome: A clinical review. *JAMA*, 313, 949–958.
- Chhibber, S., Kaur, S., & Kumari, S. (2008). Therapeutic potential of bacteriophage in treating *Klebsiella pneumoniae* B5055-mediated lobar pneumonia in mice. *Journal of Medical Microbiology*, 57, 1508–1513.
- Cohen, R. D., Woseth, D. M., Thisted, R. A., & Hanauer, S. B. (2000). A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *The American Journal of Gastroenterology*, 95, 1263–1276.
- Collado, M. C., Calabuig, M., & Sanz, Y. (2007). Differences between the fecal microbiota of coeliac infants and healthy controls. *Current Issues in Intestinal Microbiology*, 8, 9–14.
- Collado, M. C., Donat, E., Ribes-Koninckx, C., Calabuig, M., & Sanz, Y. (2009). Specific duodenal and faecal bacterial groups associated with paediatric coeliac disease. *Journal of Clinical Pathology*, 62, 264–269.
- Conrad, K., Roggenbuck, D., & Laass, M. W. (2014). Diagnosis and classification of ulcerative colitis. *Autoimmunity Reviews*, 13, 463–466.
- d'Herelle, F. (1931). Bacteriophage as a treatment in acute medical and surgical infections. *Bulletin of the New York Academy of Medicine*, 7, 329–348.
- Daliri, E. B.-M., & Lee, B. H. (2015). New perspectives on probiotics in health and disease. *Food Science and Human Wellness*, 4, 56–65.
- Darfeuille-Michaud, A., Neut, C., Barnich, N., Lederman, E., Di Martino, P., Desreumaux, P., Gambiaz, L., Joly, B., Cortot, A., & Colombel, J.-F. (1998). Presence of adherent *Escherichia coli* strains in ileal mucosa of patients with Crohn's disease. *Gastroenterology*, 115, 1405–1413.
- de Vrieze, J. (2013). The promise of poop. *Science*, 341, 954–957.
- Duboc, H., Rajca, S., Rainteau, D., Benarous, D., Maubert, M.-A., Quervain, E., Thomas, G., Barbu, V., Humbert, L., Despras, G., et al. (2013). Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases. *Gut*, 62, 531–539.
- Eckburg, P. B., Bik, E. M., Bernstein, C. N., Purdom, E., Dethlefsen, L., Sargent, M., Gill, S. R., Nelson, K. E., & Relman, D. A. (2005). Diversity of the human intestinal microbial flora. *Science*, 308, 1635–1638.
- Ellekilde, M., Selfjord, E., Larsen, C. S., Jaksevic, M., Rune, I., Tranberg, B., Vogensen, F. K., Nielsen, D. S., Bahl, M. I., Licht, T. R., et al. (2014). Transfer of gut microbiota from lean and obese mice to antibiotic-treated mice. *Scientific Reports*, 4, 5922.
- Ferreira, J. A., Wu, K. J., Hryckowian, A. J., Bouley, D. M., Weimer, B. C., & Sonnenburg, J. L. (2014). Gut microbiota-produced succinate Promotes *C. difficile* infection after antibiotic treatment or motility disturbance. *Cell Host & Microbe*, 16, 770–777.
- Ferrier, L., Bérard, F., Debrauwer, L., Chabo, C., Langella, P., Buéno, L., & Fioramonti, J. (2006). Impairment of the intestinal barrier by ethanol involves enteric microflora and mast cell activation in rodents. *The American Journal of Pathology*, 168, 1148–1154.
- Gaboriau-Routhiau, V., Rakotobe, S., Lécuyer, E., Mulder, I., Lan, A., Bridonneau, C., Rochet, V., Pisi, A., De Paepe, M., Brandi, G., et al. (2009). The key role of segmented filamentous bacteria in the coordinated maturation of gut helper T cell responses. *Immunity*, 31, 677–689.
- Gagliardi, A., Totino, V., Cacciotti, F., Iebba, V., Neroni, B., Bonfiglio, G., Trancassini, M., Pasariello, C., Pantanella, F., & Schippa, S. (2018). Rebuilding the gut microbiota ecosystem. *International Journal of Environmental Research and Public Health*, 15, 1679.
- Gareau, M. G., Sherman, P. M., & Walker, W. A. (2010). Probiotics and the gut microbiota in intestinal health and disease. *Nature Reviews. Gastroenterology & Hepatology*, 7, 503–514.

- Ghoshal, U. C., Shukla, R., Ghoshal, U., Gwee, K.-A., Ng, S. C., & Quigley, E. M. M. (2012). The gut microbiota and irritable bowel syndrome: Friend or foe? *International Journal of Inflammation*, 2012, 151085.
- Giel, J. L., Sorg, J. A., Sonenshein, A. L., & Zhu, J. (2010). Metabolism of bile salts in mice influences spore germination in *Clostridium difficile*. *PLoS One*, 5, e8740.
- Hallen-Adams, H. E., & Suhr, M. J. (2016). Fungi in the healthy human gastrointestinal tract. *Virulence*, 8, 352–358.
- Han, J.-L., and Lin, H.-L. (2014). Intestinal microbiota and type 2 diabetes: from mechanism insights to therapeutic perspective. *World J Gastroenterol*, 20, 17737–17745.
- Harris, L. A., Park, J. Y., Voltaggio, L., & Lam-Himlin, D. (2012). Celiac disease: Clinical, endoscopic, and histopathologic review. *Gastrointestinal Endoscopy*, 76, 625–640.
- Hawrelak, J. A. (2004). The causes of intestinal dysbiosis: A review. *Alternative Medicine Review*, 9, 18.
- Head, K. A., & Jurenka, J. S. (2003). Inflammatory bowel disease Part I: Ulcerative colitis–patho- physiology and conventional and alternative treatment options. *Alternative Medicine Review – A Journal of Clinical Therapeutics*, 8, 247–283.
- Head, K., & Jurenka, J. S. (2004). Inflammatory bowel disease. Part II: Crohn’s disease–patho- physiology and conventional and alternative treatment options. *Alternative Medicine Review – A Journal of Clinical Therapeutics*, 9, 360–401.
- Hollander, D. (1986). Increased intestinal permeability in patients with Crohn’s disease and their relatives: A possible etiologic factor. *Annals of Internal Medicine*, 105, 883.
- Hota, S. S., McNamara, I., Jin, R., Kissoon, M., Singh, S., & Poutanen, S. M. (2019). Challenges establishing a multi-purpose fecal microbiota transplantation stool donor program in Toronto, Canada. *The Official Journal of the Association of Medical Microbiology and Infectious Disease Canada*, 4, 1–9.
- Hotamisligil, G. S., Shargill, N. S., & Spiegelman, B. M. (1993). Adipose expression of tumor necrosis factor- $\alpha$ : Direct role in obesity-linked insulin resistance. *Science*, 259, 87–91.
- Huff, W. E., Huff, G. R., Rath, N. C., Balog, J. M., & Donoghue, A. M. (2002). Prevention of *Escherichia coli* infection in broiler chickens with a bacteriophage aerosol spray. *Poultry Science*, 81, 1486–1491.
- Ibbotson, J. P., Lowes, J. R., Chahal, H., Gaston, J. S. H., Life, P., Kumararatne, D. S., Sharif, H., Alexander-Williams, J., & Allan, R. N. (1992). Mucosal cell-mediated immunity to mycobac- terial, enterobacterial and other microbial antigens in inflammatory bowel disease. *Clinical and Experimental Immunology*, 87, 224–230.
- Jeffery, I. B., O’Toole, P. W., Öhman, L., Claesson, M. J., Deane, J., Quigley, E. M. M., & Simrén, M. (2012). An irritable bowel syndrome subtype defined by species-specific alterations in fae- cal microbiota. *Gut*, 61, 997–1006.
- Joseph, B., Przybilla, K., Stühler, C., Schauer, K., Slaghuis, J., Fuchs, T. M., & Goebel, W. (2006). Identification of *Listeria monocytogenes* genes contributing to intracellular replication by expression profiling and mutant screening. *Journal of Bacteriology*, 188, 556–568.
- Kamdar, K., Khakpour, S., Chen, J., Leone, V., Brulc, J., Mangatu, T., Antonopoulos, D. A., Chang, E. B., Kahn, S. A., Kirschner, B. S., et al. (2016). Genetic and metabolic signals during acute enteric bacterial infection alter the microbiota and drive progression to chronic inflammatory disease. *Cell Host & Microbe*, 19, 21–31.
- Kerckhoffs, A. P., Samsom, M., van der Rest, M. E., de Vogel, J., Knol, J., Ben-Amor, K., & Akker- mans, L. M. (2009). Lower Bifidobacteria counts in both duodenal mucosa-associated and fecal microbiota in irritable bowel syndrome patients. *World Journal of Gastroenterology*, 15, 2887–2892.
- Khosravi, Y., Seow, S. W., Amoyo, A. A., Chiow, K. H., Tan, T. L., Wong, W. Y., Poh, Q. H., Sen- tosa, I. M. D., Bunte, R. M., Pettersson, S., et al. (2015). *Helicobacter pylori* infection can affect energy modulating hormones and body weight in germ free mice. *Scientific Reports*,

- 5, 8731.
- Lacy, B. E., Mearin, F., Chang, L., Chey, W. D., Lembo, A. J., Simren, M., & Spiller, R. (2016). Bowel disorders. *Gastroenterology*, *150*, 1393–1407.e5.
- Lane, J. A., Murray, L. J., Harvey, I. M., Donovan, J. L., Nair, P., & Harvey, R. F. (2011). Randomised clinical trial: *Helicobacter pylori* eradication is associated with a significantly increased body mass index in a placebo-controlled study. *Alimentary Pharmacology & Therapeutics*, *33*, 922–929.
- Larsen, N., Vogensen, F. K., van den Berg, F. W. J., Nielsen, D. S., Andreasen, A. S., Pedersen, B. K., Al-Soud, W. A., Sørensen, S. J., Hansen, L. H., & Jakobsen, M. (2010). Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One*, *5*, e9085.
- Lazar, V., Ditu, L.-M., Pircalabioru, G. G., Gheorghe, I., Curutiu, C., Holban, A. M., Picu, A., Petcu, L., & Chifiriuc, M. C. (2018). Aspects of gut microbiota and immune system interactions in infectious diseases, immunopathology, and cancer. *Frontiers in Immunology*, *9*, 1830.
- Lender, N., Talley, N. J., Enck, P., Haag, S., Zipfel, S., Morrison, M., & Holtmann, G. J. (2014). Review article: Associations between *Helicobacter pylori* and obesity—An ecological study. *Alimentary Pharmacology & Therapeutics*, *40*, 24–31.
- Leverentz, B., Conway, W. S., Alavidze, Z., Janisiewicz, W. J., Fuchs, Y., Camp, M. J., Chighladze, E., & Sulakvelidze, A. (2001). Examination of bacteriophage as a biocontrol method for *Salmonella* on fresh-cut fruit: A model study. *Journal of Food Protection*, *64*, 1116–1121.
- Lewin, R. A. (2001). More on merde. *Perspectives in Biology and Medicine*, *44*, 594–607.
- Ley, R. E., Turnbaugh, P. J., Klein, S., & Gordon, J. I. (2006). Microbial ecology: Human gut microbes associated with obesity. *Nature*, *444*, 1022–1023.
- Li, M., Liang, P., Li, Z., Wang, Y., Zhang, G., Gao, H., Wen, S., & Tang, L. (2015). Fecal microbiota transplantation and bacterial consortium transplantation have comparable effects on the re-establishment of mucosal barrier function in mice with intestinal dysbiosis. *Frontiers in Microbiology*, *6*, 692.
- Lin, D. M., Koskella, B., & Lin, H. C. (2017). Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. *World Journal of Gastrointestinal Pharmacology and Therapeutics*, *8*, 162–173.
- Liu, H.-N., Wu, H., Chen, Y.-Z., Chen, Y.-J., Shen, X.-Z., & Liu, T.-T. (2017). Altered molecular signature of intestinal microbiota in irritable bowel syndrome patients compared with healthy controls: A systematic review and meta-analysis. *Digestive and Liver Disease*, *49*, 331–337.
- Loc-Carrillo, C., & Abedon, S. T. (2011). Pros and cons of phage therapy. *Bacteriophage*, *1*, 111–114.
- Logan, I., & Bowlus, C. L. (2010). The geoepidemiology of autoimmune intestinal diseases. *Autoimmunity Reviews*, *9*, A372–A378.
- Lovell, R. M., & Ford, A. C. (2012). Global prevalence of and risk factors for irritable bowel syndrome: A meta-analysis. *Clinical Gastroenterology and Hepatology*, *10*, 712–721.e4.
- Macfarlane, G. T., Steed, H., & Macfarlane, S. (2008). Bacterial metabolism and health-related effects of galacto-oligosaccharides and other prebiotics. *Journal of Applied Microbiology*, *104*, 305–344.
- Machiels, K., Joossens, M., Sabino, J., De Preter, V., Arijs, I., Eeckhaut, V., Ballet, V., Claes, K., Van Immerseel, F., Verbeke, K., et al. (2014). A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. *Gut*, *63*, 1275–1283.
- Maier, L., Barthel, M., Stecher, B., Maier, R. J., Gunn, J. S., & Hardt, W.-D. (2014). *Salmonella typhimurium* strain ATCC14028 requires H<sub>2</sub>-hydrogenases for growth in the gut, but not at systemic sites. *PLoS One*, *9*, e110187.
- Marasco, G., Di Biase, A. R., Schiumerini, R., Eusebi, L. H., Iughetti, L., Ravaoli, F., Scaioli, E., Colecchia, A., & Festi, D. (2016). Gut microbiota and celiac disease. *Digestive Diseases and*

- Sciences*, 61, 1461–1472.
- Marchesi, J. R. (2014). *The human microbiota and microbiome*. Wallingford: CABI.
- Marsh, M. N. (1997). Transglutaminase, gluten and celiac disease: Food for thought. *Nature Medicine*, 3, 725–726.
- Martin, H. M., Campbell, B. J., Hart, C. A., Mpofu, C., Nayar, M., Singh, R., Englyst, H., Williams, H. F., & Rhodes, J. M. (2004). Enhanced *Escherichia coli* adherence and invasion in Crohn's disease and colon cancer 11The authors thank Professor T. K. Korhonen (Division of General Microbiology, University of Helsinki, Finland), who kindly donated *Escherichia coli* IH11165; Professor J.-F. Colombel (Laboratoire de Recherche sur les Maladies Inflammatoires de l'Intestine, Centre Hospitalier Universitaire, Lille, France) and Professor A. Darfeuille-Michaud (Faculte de Pharmacie, Clermont-Ferrand, France), who kindly donated the Crohn's disease ileal isolates LF10 and LF82; and Dr. Keith Leiper (Gastroenterology Unit, Royal Liverpool & Broadgreen University Hospitals Trust, Liverpool, UK) for his cooperation in obtaining colorectal tissue specimens. As a consequence of the work described herein, a patent application has been filed by the University of Liverpool regarding the use of soluble plantain fiber in Crohn's disease. *Gastroenterology*, 127, 80–93.
- McKenney, P. T., & Pamer, E. G. (2015). From hype to hope: The gut microbiota in enteric infectious disease. *Cell*, 163, 1326–1332.
- McVay, C. S., Velásquez, M., & Fralick, J. A. (2007). Phage therapy of *Pseudomonas aeruginosa* infection in a mouse burn wound model. *Antimicrobial Agents and Chemotherapy*, 51, 1934–1938.
- Michail, S., Durbin, M., Turner, D., Griffiths, A. M., Mack, D. R., Hyams, J., Leleiko, N., Kenche, H., Stolfi, A., & Wine, E. (2012). Alterations in the gut microbiome of children with severe ulcerative colitis. *Inflammatory Bowel Diseases*, 18, 1799–1808.
- Mitchell, N. S., Catenacci, V. A., Wyatt, H. R., & Hill, J. O. (2011). Obesity: Overview of an epidemic. *The Psychiatric Clinics of North America*, 34, 717–732.
- Miyoshi, J., & Takai, Y. (2005). Molecular perspective on tight-junction assembly and epithelial polarity. *Advanced Drug Delivery Reviews*, 57, 815–855.
- Moal, V. L.-L., & Servin, A. L. (2014). Anti-infective activities of *Lactobacillus* strains in the human intestinal microbiota: From probiotics to gastrointestinal anti-infectious biotherapeutic agents. *Clinical Microbiology Reviews*, 27, 167–199.
- Mu, Q., Kirby, J., Reilly, C. M., & Luo, X. M. (2017). Leaky gut as a danger signal for autoimmune diseases. *Frontiers in Immunology*, 8, 598.
- Mudd, J. C., & Brenchley, J. M. (2016). Gut mucosal barrier dysfunction, microbial dysbiosis, and their role in HIV-1 disease progression. *The Journal of Infectious Diseases*, 214, S58–S66.
- Musso, G., Gambino, R., & Cassader, M. (2011). Interactions between gut microbiota and host metabolism predisposing to obesity and diabetes. *Annual Review of Medicine*, 62, 361–380.
- Ng, K. M., Ferreyra, J. A., Higginbottom, S. K., Lynch, J. B., Kashyap, P. C., Gopinath, S., Naidu, N., Choudhury, B., Weimer, B. C., Monack, D. M., et al. (2013). Microbiota-liberated host sugars facilitate post-antibiotic expansion of enteric pathogens. *Nature*, 502, 96–99.
- NIH Human Microbiome Project (2018). Institute for Genome Sciences, University of Maryland School of Medicine, <https://www.hmpdacc.org/overview/>
- O'Shea, E. F., Cotter, P. D., Stanton, C., Ross, R. P., & Hill, C. (2012). Production of bioactive substances by intestinal bacteria as a basis for explaining probiotic mechanisms: Bacteriocins and conjugated linoleic acid. *International Journal of Food Microbiology*, 152, 189–205.
- Ohkusa, T., Okayasu, I., Ogihara, T., Morita, K., Ogawa, M., & Sato, N. (2003). Induction of experimental ulcerative colitis by *Fusobacterium varium* isolated from colonic mucosa of patients with ulcerative colitis. *Gut*, 52, 79–83.
- Parkes, G. C., Rayment, N. B., Hudspith, B. N., Petrovska, L., Lomer, M. C., Brostoff, J., Whelan, K., & Sanderson, J. D. (2012). Distinct microbial populations exist in the mucosa-asso-

- ciated microbiota of sub-groups of irritable bowel syndrome. *Neurogastroenterology and Motility*, 24, 31–39.
- Pascal, V., Pozuelo, M., Borruel, N., Casellas, F., Campos, D., Santiago, A., Martinez, X., Varela, E., Sarrabayrouse, G., Machiels, K., et al. (2017). A microbial signature for Crohn's disease. *Gut*, 66, 813–822.
- Peng, M., Tabashsum, Z., Patel, P., Bernhardt, C., & Biswas, D. (2018). Linoleic acids overproducing *Lactobacillus casei* limits growth, survival, and virulence of *Salmonella typhimurium* and *Enterohaemorrhagic Escherichia coli*. *Frontiers in Microbiology*, 9, 2663.
- Petritz, B. A., Castro, A. P., Almeida, J. A., Gomes, C. P., Fernandes, G. R., Kruger, R. H., Pereira, R. W., & Franco, O. L. (2014). Exercise induction of gut microbiota modifications in obese, non-obese and hypertensive rats. *BMC Genomics*, 15, 511.
- Petrof, E. O., Gloor, G. B., Vanner, S. J., Weese, S. J., Carter, D., Daigneault, M. C., Brown, E. M., Schroeter, K., & Allen-Vercoe, E. (2013). Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut. *Microbiome*, 1, 3.
- Pimentel, M., Chow, E. J., & Lin, H. C. (2000). Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. *The American Journal of Gastroenterology*, 95, 3503–3506.
- Qin, J., Li, Y., Cai, Z., Li, S., Zhu, J., Zhang, F., Liang, S., Zhang, W., Guan, Y., Shen, D., et al. (2012). A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature*, 490, 55–60.
- Ramesh, V., Fralick, J. A., & Rolfe, R. D. (1999). Prevention of *Clostridium difficile* -induced ileocecolitis with bacteriophage. *Anaerobe*, 5, 69–78.
- Rastelli, M., Knauf, C., & Cani, P.D. (2018). Gut microbes and health: A focus on the mechanisms linking microbes, obesity, and related disorders. *Obesity*, 26, 792–800.
- Rios, A. C., Moutinho, C. G., Pinto, F. C., Del Fiol, F. S., Jozala, A., Chaud, M. V., Vila, M. M. D. C., Teixeira, J. A., & Balcão, V.M. (2016). Alternatives to overcoming bacterial resistances: State-of-the-art. *Microbiological Research*, 191, 51–80.
- Roberfroid, M. (2007). Prebiotics: The concept revisited. *The Journal of Nutrition*, 137, 830S–837S.
- Rolhion, N., & Chassaing, B. (2016). When pathogenic bacteria meet the intestinal microbiota. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 371, 20150504.
- Round, J. L., & Mazmanian, S. K. (2009). The gut microbiota shapes intestinal immune responses during health and disease. *Nature Reviews. Immunology*, 9, 313–323.
- Salaheen, S., Jaiswal, E., Joo, J., Peng, M., Ho, R., O'Connor, D., Adlerz, K., Aranda-Espinoza, J. H., & Biswas, D. (2016). Bioactive extracts from berry byproducts on the pathogenicity of *Salmonella typhimurium*. *International Journal of Food Microbiology*, 237, 128–135.
- Santacruz, A., Collado, M. C., García-Valdés, L., Segura, M. T., Martín-Lagos, J. A., Anjos, T., Martí-Romero, M., Lopez, R. M., Florido, J., Campoy, C., et al. (2010). Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. *The British Journal of Nutrition*, 104, 83–92.
- Sanz, Y., Sánchez, E., Marzotto, M., Calabuig, M., Torriani, S., & Dellaglio, F. (2007). Differences in faecal bacterial communities in coeliac and healthy children as detected by PCR and denaturing gradient gel electrophoresis. *FEMS Immunology and Medical Microbiology*, 51, 562–568.
- Sanz, Y., Palma, G. D., & Laparra, M. (2011). Unraveling the ties between coeliac disease and intestinal microbiota. *International Reviews of Immunology*, 30, 207–218.
- Sato, J., Kanazawa, A., Ikeda, F., Yoshihara, T., Goto, H., Abe, H., Komiya, K., Kawaguchi, M., Shimizu, T., Ogihara, T., et al. (2014). Gut dysbiosis and detection of "live gut bacteria" in blood of Japanese patients with type 2 diabetes. *Diabetes Care*, 37(8), 2343–2350.
- Saulnier, D. M., Riehle, K., Mistretta, T., Diaz, M., Mandal, D., Raza, S., Weidler, E. M., Qin, X., Coarfa, C., Milosavljevic, A., et al. (2011). Gastrointestinal microbiome signatures of pediatric patients with irritable bowel syndrome. *Gastroenterology*, 141, 1782–1791.

- Savage, D. C. (1977). Microbial ecology of the gastrointestinal tract. *Annual Review of Microbiology*, 31, 107–133.
- Scaldaferri, F., Gerardi, V., Lopetuso, L. R., Del Zompo, F., Mangiola, F., Boškoski, I., Bruno, G., Petito, V., Laterza, L., Cammarota, G., et al. (2013). Gut microbial flora, prebiotics, and pro-biotics in IBD: Their current usage and utility. *BioMed Research International*, 2013, 435268.
- Schwan, A., Sjolín, S., Trottestam, U., & Aronsson, B. (1983). Relapsing clostridium difficile enterocolitis cured by rectal infusion of homologous faeces. *The Lancet*, 322, 845.
- Sekirov, I., & Finlay, B. B. (2009). The role of the intestinal microbiota in enteric infection. *The Journal of Physiology*, 587, 4159–4167.
- Shang, Q., Sun, W., Shan, X., Jiang, H., Cai, C., Hao, J., Li, G., & Yu, G. (2017). Carrageenan-induced colitis is associated with decreased population of anti-inflammatory bacterium, *Akkermansia muciniphila*, in the gut microbiota of C57BL/6J mice. *Toxicology Letters*, 279, 87–95.
- Shen, Z.-H., Zhu, C.-X., Quan, Y.-S., Yang, Z.-Y., Wu, S., Luo, W.-W., Tan, B., & Wang, X.-Y. (2018). Relationship between intestinal microbiota and ulcerative colitis: Mechanisms and clinical application of probiotics and fecal microbiota transplantation. *World Journal of Gastroenterology*, 24, 5–14.
- Shendure, J., & Ji, H. (2008). Next-generation DNA sequencing. *Nature Biotechnology*, 26, 1135–1145.
- Shin, J.-H., Sim, M., Lee, J.-Y., & Shin, D.-M. (2016). Lifestyle and geographic insights into the distinct gut microbiota in elderly women from two different geographic locations. *Journal of Physiological Anthropology*, 35, 31.
- Stappenbeck, T. S., Hooper, L. V., & Gordon, J. I. (2002). Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells. *Proceedings of the National Academy of Sciences of the United States of America*, 99, 15451–15455.
- Sugi, K., Musch, M. W., Chang, E. B., & Field, M. (2001). Inhibition of Na<sup>+</sup>,K<sup>+</sup>-ATPase by interferon  $\gamma$  down-regulates intestinal epithelial transport and barrier function. *Gastroenterology*, 120, 1393–1403.
- Szebeni, B., Veres, G., Dezsöfi, A., Rusai, K., Vannay, A., Bokodi, G., Vásárhelyi, B., Korponay-Szabó, I. R., Tulassay, T., & Arató, A. (2007). Increased mucosal expression of Toll-like receptor (TLR)2 and TLR4 in coeliac disease. *Journal of Pediatric Gastroenterology and Nutrition*, 45, 187–193.
- Tabashsum, Z., Peng, M., Salaheen, S., Comis, C., & Biswas, D. (2018). Competitive elimination and virulence property alteration of *Campylobacter jejuni* by genetically engineered *Lactobacillus casei*. *Food Control*, 85, 283–291.
- Tanji, Y., Shimada, T., Fukudomi, H., Miyanaga, K., Nakai, Y., & Unno, H. (2005). Therapeutic use of phage cocktail for controlling *Escherichia coli* O157:H7 in gastrointestinal tract of mice. *Journal of Bioscience and Bioengineering*, 100, 280–287.
- Thiennimitr, P., Winter, S. E., Winter, M. G., Xavier, M. N., Tolstikov, V., Huseby, D. L., Sterzenbach, T., Tsolis, R. M., Roth, J. R., & Bäuml, A. J. (2011). Intestinal inflammation allows *Salmonella* to use ethanolamine to compete with the microbiota. *Proceedings of the National Academy of Sciences*, 108, 17480–17485.
- Timmer, A., McDonald, J. W., & MacDonald, J. K. (2007). Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews*. <https://doi.org/10.1002/14651858.CD000478.pub2>.
- Transparency Market Research (TMR) (2019). Published on Apr 8, 2019, <https://www.transparencymarketresearch.com/pressrelease/human-microbiome-market.htm>
- Viazis, S., Akhtar, M., Feirtag, J., & Diez-Gonzalez, F. (2011). Reduction of *Escherichia coli* O157:H7 viability on leafy green vegetables by treatment with a bacteriophage mixture and trans-cinnamaldehyde. *Food Microbiology*, 28, 149–157.

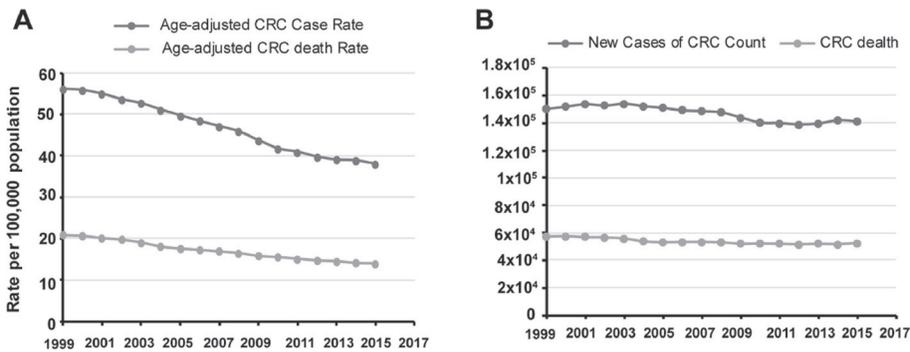
- Walter, J. (2008). Ecological role of lactobacilli in the gastrointestinal tract: Implications for fundamental and biomedical research. *Applied and Environmental Microbiology*, 74, 4985–4996.
- Wang, Q., McLoughlin, R. M., Cobb, B. A., Charrel-Dennis, M., Zaleski, K. J., Golenbock, D., Tzianabos, A. O., & Kasper, D. L. (2006). A bacterial carbohydrate links innate and adaptive responses through Toll-like receptor 2. *The Journal of Experimental Medicine*, 203, 2853–2863.
- Weisberg, S. P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R. L., & Ferrante, A. W. (2003). Obesity is associated with macrophage accumulation in adipose tissue. *The Journal of Clinical Investigation*, 112, 1796–1808.
- Wellen, K. E., & Hotamisligil, G. S. (2005). Inflammation, stress, and diabetes. *The Journal of Clinical Investigation*, 115, 1111–1119.
- White, H. E., & Orlova, E. V. (2019). Bacteriophages: Their structural organisation and function. In R. Savva (Ed.), *Bacteriophages: Perspect and future*. London: IntechOpen.
- Wills, Q. F., Kerrigan, C., & Soothill, J. S. (2005). Experimental bacteriophage protection against *Staphylococcus aureus* abscesses in a rabbit model. *Antimicrobial Agents and Chemotherapy*, 49, 1220–1221.
- Yoo, S.-R., Kim, Y.-J., Park, D.-Y., Jung, U.-J., Jeon, S.-M., Ahn, Y.-T., Huh, C.-S., McGregor, R., & Choi, M. S. (2013). Probiotics *L. plantarum* and *L. curvatus* in combination alter hepatic lipid metabolism and suppress diet-induced obesity. *Obesity (Silver Spring Md)*, 21, 2571–2578.
- Zhang, X., Shen, D., Fang, Z., Jie, Z., Qiu, X., Zhang, C., Chen, Y., & Ji, L. (2013). Human gut microbiota changes reveal the progression of glucose intolerance. *PLoS One*, 8, e71108.
- Zimmerman, J. (2003). Extraintestinal symptoms in irritable bowel syndrome and inflammatory bowel diseases: Nature, severity, and relationship to gastrointestinal symptoms. *Digestive Diseases and Sciences*, 48, 743–749.
- Zou, J., Chassaing, B., Singh, V., Pellizzon, M., Ricci, M., Fythe, M. D., Kumar, M. V., & Gewirtz, T. (2018). Fiber-mediated nourishment of gut microbiota protects against diet-induced obesity by restoring IL-22-mediated colonic health. *Cell Host & Microbe*, 23, 41–53.e4.

# Kolorektal Kanserde Bağırsak Mikrobiyomunun Rolü

Xiaolun Sun

## 1 Kolorektal kanser (CRC) epidemiyolojisi

Kalın bağırsak, sindirim sistemi uzunluğunun sadece %20'sini ve mukozal yüzey alanının %6'sını oluşturmasına rağmen (Helander ve Fandriks 2014), kolorektal kanser (CRC), gastrointestinal (GI) kanalda teşhis edilen bir numaralı kanserdir ve kolorektal kanser; Amerika Birleşik Devletleri'ndeki (ABD) yeni GI kanserleri vakalarının %44'ünden fazlasını oluşturmaktadır (Siegel ve diğerleri 2019). Neyse ki, yaygın kolonoskopi taraması ve araştırmaların ilerlemesiyle, yaşa göre düzeltilmiş yeni CRC vakalarının oranı 1999'da 100.000 nüfusta 56'dan 2015'te 100.000 nüfusta 38'e (CDC2019) tutarlı bir şekilde düşmüş, ancak toplam vaka sayıları 1999'da 150.014'ten 2015'te 140.788'e kadar gerilemiştir (Şekil 1a). Tutarlı bir şekilde, yaşa göre ayarlanmış CRC ölüm oranı, 1999'da 100.000 nüfus başına 21'den 2015'te 100.000 nüfus başına 14'e düşmüş, ancak toplam vaka sayıları 1999'da 57.222'den 2015'te 52.396'ya kadar gerilemiştir (Şekil 1b). Sonuç olarak kolorektal kanser, hem erkek hem de kadınlarda tüm kanserlerin üçüncü en yaygın nedenidir ve ABD'de kansere bağlı ölümlerin ikinci önde gelen nedenidir (Siegel ve ark. 2019). Bu nedenle, CRC'nin yeni vakalarını ve ölüm oranlarını önemli ölçüde azaltmak için gidilecek uzun bir yol olduğu görülmektedir ve CRC'nin altında yatan mekanizmayı araştırmak ve yeni terapötik yaklaşımları keşfetmek acil bir meseledir.



**Şekil 1.** 1999-2015 yılları arasında yaşa göre belirlenmiş CRC yeni vakaları ve ölümleri. (a) Amerika Birleşik Devletleri'ndeki yeni CRC vakalarının ve ölümlerin oranları. (b) CRC'den kaynaklanan yeni vaka ve ölümlerin toplam sayıları

## Kaynaklar

- Ahn, J., Sinha, R., Pei, Z., Dominianni, C., Wu, J., Shi, J., Goedert, J. J., Hayes, R. B., & Yang, L. (2013). Human gut microbiome and risk for colorectal cancer. *Journal of the National Cancer Institute*, 105, 1907–1911.
- Armelaio, F., & de Pretis, G. (2014). Familial colorectal cancer: a review. *World Journal of Gastroenterology*, 20, 9292–9298.
- Arthur, J. C., Perez-Chanona, E., Muhlbauer, M., Tomkovich, S., Uronis, J. M., Fan, T. J., Campbell, B. J., Abujamel, T., Dogan, B., Rogers, A. B., et al. (2012). Intestinal inflammation targets cancer-inducing activity of the microbiota. *Science*, 338, 120–123.
- Attene-Ramos, M. S., Wagner, E. D., Plewa, M. J., & Gaskins, H. R. (2006). Evidence that hydrogen sulfide is a genotoxic agent. *Molecular Cancer Research*, 4, 9–14.
- Aykan, N. F. (2015). Red Meat and Colorectal Cancer. *Oncology Reviews*, 9, 288.
- Bartosch, S., Woodmansey, E. J., Paterson, J. C., McMurdo, M. E., & Macfarlane, G. T. (2005). Microbiological effects of consuming a synbiotic containing *Bifidobacterium bifidum*, *Bifidobacterium lactis*, and oligofructose in elderly persons, determined by real-time polymerase chain reaction and counting of viable bacteria. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, 40, 28–37.
- Bellam, N., & Pasche, B. (2010). Tgf-beta signaling alterations and colon cancer. *Cancer Treatment and Research*, 155, 85–103.
- Bonnet, M., Buc, E., Sauvanet, P., Darcha, C., Dubois, D., Pereira, B., Dechelotte, P., Bonnet, R., Pezet, D., & Darfeuille-Michaud, A. (2014). Colonization of the human gut by *E. coli* and colorectal cancer risk. *Clinical Cancer Research*, 20, 859–867.
- Botteri, E., Iodice, S., Bagnardi, V., Raimondi, S., Lowenfels, A. B., & Maisonneuve, P. (2008). Smoking and colorectal cancer: a meta-analysis. *JAMA*, 300, 2765–2778.
- Bouvard, V., Loomis, D., Guyton, K. Z., Grosse, Y., Ghissassi, F. E., Benbrahim-Tallaa, L., Guha, N., Mattock, H., Straif, K., & International Agency for Research on Cancer Monograph Working, G. (2015). Carcinogenicity of consumption of red and processed meat. *The Lancet Oncology*, 16, 1599–1600.
- Boyle, T., Keegel, T., Bull, F., Heyworth, J., & Fritschi, L. (2012). Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. *Journal of the National Cancer Institute*, 104, 1548–1561.
- Canavan, C., Abrams, K. R., & Mayberry, J. (2006). Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. *Alimentary Pharmacology & Therapeutics*, 23, 1097–1104.
- CDC. (2019). Changes over time: All types of cancer (Centers for Disease Control and Prevention). <https://gis.cdc.gov/Cancer/USCS/DataViz.html>.
- Chassard, C., Delmas, E., Robert, C., & Bernalier-Donadille, A. (2010). The cellulose-degrading microbial community of the human gut varies according to the presence or absence of methanogens. *FEMS Microbiology Ecology*, 74, 205–213.
- Cockburn, D. W., Orlovsky, N. I., Foley, M. H., Kwiatkowski, K. J., Bahr, C. M., Maynard, M., Demeler, B., & Koropatkin, N. M. (2015). Molecular details of a starch utilization pathway in the human gut symbiont *Eubacterium rectale*. *Molecular Microbiology*, 95, 209–230.
- Colussi, D., Brandi, G., Bazzoli, F., & Ricciardiello, L. (2013). Molecular pathways involved in colorectal cancer: implications for disease behavior and prevention. *International Journal of Molecular Sciences*, 14, 16365–16385.
- Cougnoux, A., Dalmasso, G., Martinez, R., Buc, E., Delmas, J., Gibold, L., Sauvanet, P., Darcha, C., Dechelotte, P., Bonnet, M., et al. (2014). Bacterial genotoxin colibactin promotes colon tumour growth by inducing a senescence-associated secretory phenotype. *Gut*, 63, 1932–1942.
- Cuevas-Ramos, G., Petit, C. R., Marcq, I., Boury, M., Oswald, E., & Nougayrede, J. P. (2010). *Escherichia coli* induces DNA damage in vivo and triggers genomic instability in

- mammalian cells. *Proceedings of the National Academy of Sciences of the United States of America*, 107,11537–11542.
- Danielsen, S. A., Eide, P. W., Nesbakken, A., Guren, T., Leithe, E., & Lothe, R. A. (2015). Portrait of the PI3K/AKT pathway in colorectal cancer. *Biochimica et Biophysica Acta*, 1855, 104–121.
- Ekbom, A., Helmick, C., Zack, M., & Adami, H. O. (1990). Ulcerative colitis and colorectal cancer. A population-based study. *The New England Journal of Medicine*, 323, 1228–1233.
- Fedirko, V., Tramacere, I., Bagnardi, V., Rota, M., Scotti, L., Islami, F., Negri, E., Straif, K., Romieu, I., La Vecchia, C., et al. (2011). Alcohol drinking and colorectal cancer risk: an over- all and dose-response meta-analysis of published studies. *Annals of Oncology*, 22, 1958–1972.
- Feng, Q., Liang, S., Jia, H., Stadlmayr, A., Tang, L., Lan, Z., Zhang, D., Xia, H., Xu, X., Jie, Z., et al. (2015). Gut microbiome development along the colorectal adenoma-carcinoma sequence. *Nature Communications*, 6, 6528.
- Flanagan, L., Schmid, J., Ebert, M., Soucek, P., Kunicka, T., Liska, V., Bruha, J., Neary, P., Dezeu-uw, N., Tommasino, M., et al. (2014). *Fusobacterium nucleatum* associates with stages of colorectal neoplasia development, colorectal cancer and disease outcome. *European Journal of Clinical Microbiology & Infectious Diseases*, 33, 1381–1390.
- Flemer, B., Lynch, D. B., Brown, J. M., Jeffery, I. B., Ryan, F. J., Claesson, M. J., O’Riordain, M., Shanahan, F., & O’Toole, P. W. (2017). Tumour-associated and non-tumour-associated micro- biota in colorectal cancer. *Gut*, 66, 633–643.
- Gao, R., Kong, C., Li, H., Huang, L., Qu, X., Qin, N., & Qin, H. (2017). Dysbiosis signature of mycobiota in colon polyp and colorectal cancer. *European Journal of Clinical Microbiology & Infectious Diseases*, 36, 2457–2468.
- Gur, C., Ibrahim, Y., Isaacson, B., Yamin, R., Abed, J., Gamliel, M., Enk, J., Bar-On, Y., Staniet-ky-Kaynan, N., Copenhagen-Glazer, S., et al. (2015). Binding of the Fap2 protein of *Fusobacterium nucleatum* to human inhibitory receptor TIGIT protects tumors from immune cell attack. *Immunity*, 42, 344–355.
- Half, E., Bercovich, D., & Rozen, P. (2009). Familial adenomatous polyposis. *Orphanet Journal of Rare Diseases*, 4, 22.
- Helander, H. F., & Fandriks, L. (2014). Surface area of the digestive tract - revisited. *Scandinavian Journal of Gastroenterology*, 49, 681–689.
- Henderson, T. O., Oeffinger, K. C., Whitton, J., Leisenring, W., Neglia, J., Meadows, A., Crotty, C., Rubin, D. T., Diller, L., Inskip, P., et al. (2012). Secondary gastrointestinal cancer in childhood cancer survivors: a cohort study. *Annals of Internal Medicine*, 156, 757–766, W-260.
- Hibberd, A. A., Lyra, A., Ouwehand, A. C., Rolny, P., Lindegren, H., Cedgard, L., & Wettergren, Y. (2017). Intestinal microbiota is altered in patients with colon cancer and modified by probi- otic intervention. *BMJ Open Gastroenterology*, 4, e000145.
- Hugon, P., Dufour, J. C., Colson, P., Fournier, P. E., Sallah, K., & Raoult, D. (2015). A comprehensive repertoire of prokaryotic species identified in human beings. *The Lancet Infectious Diseases*, 15, 1211–1219.
- Jess, T., Loftus, E. V., Jr., Velayos, F. S., Harmsen, W. S., Zinsmeister, A. R., Smyrk, T. C., Schleck, C. D., Tremaine, W. J., Melton, L. J., 3rd, Munkholm, P., et al. (2006). Risk of intestinal cancer in inflammatory bowel disease: a population-based study from olmsted county, Minnesota. *Gastroenterology*, 130, 1039–1046.
- Jones, S., Chen, W. D., Parmigiani, G., Diehl, F., Beerenwinkel, N., Antal, T., Traulsen, A., Nowak, M. A., Siegel, C., Velculescu, V. E., et al. (2008). Comparative lesion sequencing provides insights into tumor evolution. *Proceedings of the National Academy of Sciences of the United States of America*, 105, 4283–4288.
- Karahalios, A., English, D. R., & Simpson, J. A. (2015). Weight change and risk of colorectal can- cer: a systematic review and meta-analysis. *American Journal of Epidemiology*, 181,

- 832–845. Khan, M. T., Duncan, S. H., Stams, A. J., van Dijk, J. M., Flint, H. J., & Harmsen, H. J. (2012). The gut anaerobe *Faecalibacterium prausnitzii* uses an extracellular electron shuttle to grow at oxic-anoxic interphases. *The ISME Journal*, 6, 1578–1585.
- Koliada, A., Syzenko, G., Moseiko, V., Budovska, L., Puchkov, K., Perederiy, V., Gavalko, Y., Dorofeyev, A., Romanenko, M., Tkach, S., et al. (2017). Association between body mass index and Firmicutes/Bacteroidetes ratio in an adult Ukrainian population. *BMC Microbiology*, 17, 120.
- Kostic, A. D., Gevers, D., Pedamallu, C. S., Michaud, M., Duke, F., Earl, A. M., Ojesina, A. I., Jung, J., Bass, A. J., Taberner, J., et al. (2012). Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma. *Genome Research*, 22, 292–298.
- Kostic, A. D., Chun, E., Robertson, L., Glickman, J. N., Gallini, C. A., Michaud, M., Clancy, T. E., Chung, D. C., Lochhead, P., Hold, G. L., et al. (2013). *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. *Cell Host & Microbe*, 14, 207–215.
- Kulaylat, M. N., & Dayton, M. T. (2010). Ulcerative colitis and cancer. *Journal of Surgical Oncology*, 101, 706–712.
- Leitch, E. C., Walker, A. W., Duncan, S. H., Holtrop, G., & Flint, H. J. (2007). Selective colonization of insoluble substrates by human faecal bacteria. *Environmental Microbiology*, 9, 667–679.
- Li, X. L., Zhou, J., Chen, Z. R., & Chng, W. J. (2015). P53 mutations in colorectal cancer - molecular pathogenesis and pharmacological reactivation. *World Journal of Gastroenterology*, 21, 84–93.
- Liu, L., Tabung, F. K., Zhang, X., Nowak, J. A., Qian, Z. R., Hamada, T., Nevo, D., Bullman, S., Mima, K., Kosumi, K., et al. (2018). Diets That Promote Colon Inflammation Associate With Risk of Colorectal Carcinomas That Contain *Fusobacterium nucleatum*. *Clinical Gastroenterology and Hepatology*, 16(1622–1631), e1623.
- Lopez-Siles, M., Martinez-Medina, M., Suris-Valls, R., Aldeguer, X., Sabat-Mir, M., Duncan, S. H., Flint, H. J., & Garcia-Gil, L. J. (2016). Changes in the Abundance of *Faecalibacterium prausnitzii* Phylogroups I and II in the Intestinal Mucosa of Inflammatory Bowel Disease and Patients with Colorectal Cancer. *Inflammatory Bowel Diseases*, 22, 28–41.
- Lynch, H. T., & de la Chapelle, A. (2003). Hereditary colorectal cancer. *The New England Journal of Medicine*, 348, 919–932.
- Lynch, H. T., & Krush, A. J. (1971). Cancer family “G” revisited: 1895-1970. *Cancer*, 27, 1505–1511.
- Machiels, K., Joossens, M., Sabino, J., De Preter, V., Arijs, I., Eeckhaut, V., Ballet, V., Claes, K., Van Immerseel, F., Verbeke, K., et al. (2014). A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. *Gut*, 63, 1275–1283.
- Mendez-Salazar, E. O., Ortiz-Lopez, M. G., Granados-Silvestre, M. L. A., Palacios-Gonzalez, B., & Menjivar, M. (2018). Altered Gut Microbiota and Compositional Changes in Firmicutes and Proteobacteria in Mexican Undernourished and Obese Children. *Frontiers in Microbiology*, 9, 2494.
- Mima, K., Nishihara, R., Qian, Z. R., Cao, Y., Sukawa, Y., Nowak, J. A., Yang, J., Dou, R., Masugi, Y., Song, M., et al. (2016). *Fusobacterium nucleatum* in colorectal carcinoma tissue and patient prognosis. *Gut*, 65, 1973–1980.
- Munkholm, P. (2003). Review article: the incidence and prevalence of colorectal cancer in inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*, 18(Suppl 2), 1–5.
- Rossi, O., van Berkel, L. A., Chain, F., Tanweer Khan, M., Taverne, N., Sokol, H., Duncan, S. H., Flint, H. J., Harmsen, H. J., Langella, P., et al. (2016). *Faecalibacterium prausnitzii* A2-165 has a high capacity to induce IL-10 in human and murine dendritic cells and modulates T cell responses. *Scientific Reports*, 6, 18507.

- Rubinstein, M. R., Wang, X., Liu, W., Hao, Y., Cai, G., & Han, Y. W. (2013). *Fusobacterium nucleatum* promotes colorectal carcinogenesis by modulating E-cadherin/beta-catenin signaling via its FadA adhesin. *Cell Host & Microbe*, 14, 195–206.
- Salyers, A. A., West, S. E., Vercellotti, J. R., & Wilkins, T. D. (1977). Fermentation of mucins and plant polysaccharides by anaerobic bacteria from the human colon. *Applied and Environmental Microbiology*, 34, 529–533.
- Sears, C. L. (2009). Enterotoxigenic *Bacteroides fragilis*: a rogue among symbiotes. *Clinical Microbiology Reviews*, 22, 349–369, Table of Contents.
- Siegel, R. L., Miller, K. D., & Jemal, A. (2019). Cancer statistics, 2019. *CA: a Cancer Journal for Clinicians*, 69, 7–34.
- Sun, X., & Jia, Z. (2018). Microbiome modulates intestinal homeostasis against inflammatory diseases. *Veterinary Immunology and Immunopathology*, 205, 97–105.
- Taylor, D. P., Burt, R. W., Williams, M. S., Haug, P. J., & Cannon-Albright, L. A. (2010). Population-based family history-specific risks for colorectal cancer: a constellation approach. *Gastroenterology*, 138, 877–885.
- Thiele Orberg, E., Fan, H., Tam, A. J., Dejea, C. M., Destefano Shields, C. E., Wu, S., Chung, L., Finard, B. B., Wu, X., Fathi, P., et al. (2017). The myeloid immune signature of enterotoxigenic *Bacteroides fragilis*-induced murine colon tumorigenesis. *Mucosal Immunology*, 10, 421–433.
- Thomas, A. M., Manghi, P., Asnicar, F., Pasolli, E., Armanini, F., Zolfo, M., Beghini, F., Manara, S., Karcher, N., Pozzi, C., et al. (2019). Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation. *Nature Medicine*, 25, 667–678.
- Toprak, N. U., Yagci, A., Gulluoglu, B. M., Akin, M. L., Demirkalem, P., Celenk, T., & Soyletir, G. (2006). A possible role of *Bacteroides fragilis* enterotoxin in the aetiology of colorectal cancer. *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases*, 12, 782–786.
- Tuohy, T. M., Rowe, K. G., Mineau, G. P., Pimentel, R., Burt, R. W., & Samadder, N. J. (2014). Risk of colorectal cancer and adenomas in the families of patients with adenomas: a population-based study in Utah. *Cancer*, 120, 35–42.
- Wedekind, K. J., Mansfield, H. R., & Montgomery, L. (1988). Enumeration and isolation of cellulolytic and hemicellulolytic bacteria from human feces. *Applied and Environmental Microbiology*, 54, 1530–1535.
- Weir, T. L., Manter, D. K., Sheflin, A. M., Barnett, B. A., Heuberger, A. L., & Ryan, E. P. (2013). Stool microbiome and metabolome differences between colorectal cancer patients and healthy adults. *PLoS One*, 8, e70803.
- Winther, K. V., Jess, T., Langholz, E., Munkholm, P., & Binder, V. (2004). Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. *Clinical Gastroenterology and Hepatology*, 2, 1088–1095.
- Wirbel, J., Pyl, P. T., Kartal, E., Zych, K., Kashani, A., Milanese, A., Fleck, J. S., Voigt, A. Y., Palreja, A., Ponnudurai, R., et al. (2019). Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. *Nature Medicine*, 25, 679–689.
- Wu, S., Morin, P. J., Maouyo, D., & Sears, C. L. (2003). *Bacteroides fragilis* enterotoxin induces c-Myc expression and cellular proliferation. *Gastroenterology*, 124, 392–400.
- Yang, Y., Weng, W., Peng, J., Hong, L., Yang, L., Toiyama, Y., Gao, R., Liu, M., Yin, M., Pan, C., et al. (2017). *Fusobacterium nucleatum* Increases Proliferation of Colorectal Cancer Cells and Tumor Development in Mice by Activating Toll-Like Receptor 4 Signaling to Nuclear Factor-kappaB, and Up-regulating Expression of MicroRNA-21. *Gastroenterology*, 152(851–866), e824.
- Yuhara, H., Steinmaus, C., Cohen, S. E., Corley, D. A., Tei, Y., & Buffler, P. A. (2011). Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? *The American Jour-*

- nal of Gastroenterology, 106, 1911–1921; quiz 1922.
- Yurgelun, M. B., Kulke, M. H., Fuchs, C. S., Allen, B. A., Uno, H., Hornick, J. L., Ukaegbu, C. I., Brais, L. K., McNamara, P. G., Mayer, R. J., et al. (2017). Cancer Susceptibility Gene Mutations in Individuals With Colorectal Cancer. *Journal of Clinical Oncology*, 35, 1086–1095.
- Ze, X., Duncan, S. H., Louis, P., & Flint, H. J. (2012). *Ruminococcus bromii* is a keystone species for the degradation of resistant starch in the human colon. *The ISME Journal*, 6, 1535–1543.
- Zeller, G., Tap, J., Voigt, A. Y., Sunagawa, S., Kultima, J. R., Costea, P. I., Amiot, A., Bohm, J., Brunetti, F., Habermann, N., et al. (2014). Potential of fecal microbiota for early-stage detection of colorectal cancer. *Molecular Systems Biology*, 10, 766.

# Bağırsak Mikrobiyotası ve Ateroskleroz Riski: Mekanizmalar ile ilgili Güncel Anlayış

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## 1. Giriş

İnsan bağırsağında, konağın normal işleyişi için gerekli olan çok sayıda komensal ve ortak yaşayan mikroorganizma bulunur (Aron-Wisnewsky ve diğerleri 2012; Bäckhed ve diğerleri. 2004; Cani ve diğerleri. 2012; Cox ve Blaser 2013; den Besten ve diğerleri. 2013; Le Chatelier ve diğerleri. 2013; Nicholson ve diğerleri. 2005; Tremaroli ve Bäckhed 2012 ). Bağırsak mikrobiyotası olarak adlandırılan bakteri, arke, mantar, virüs ve diğer protozoonlardan oluşan bağırsağın kolonizasyonu, milyonlarca yıl boyunca meydana gelen ortak evrimsel bir sürecin sonucudur (Aron-Wisnewsky ve diğerleri 2012; Bäckhed ve diğerleri. 2004; Cani ve diğerleri. 2012; Cox ve Blaser 2013; den Besten ve diğerleri. 2013; Le Chatelier ve diğerleri. 2013; Nicholson ve diğerleri. 2005; Tremaroli ve Bäckhed 2012 ). Bu organizmalar konaktan besin alırlar, kompleks karbonhidratların sindiriminde konakçıya yardımcı olurlar, bağışıklık sistemini hassas bir şekilde düzenlerler, metabolik ve enerji homeostazını korurlar, fırsatçı patojenlere karşı koruma sağlarlar ve hatta nörogelişime yardımcı olurlar (Aron-Wisnewsky ve diğerleri 2012; Bäckhed ve diğerleri. 2004; Cani ve diğerleri. 2012; Cox ve Blaser 2013; den Besten ve diğerleri. 2013; Le Chatelier ve diğerleri. 2013; Nicholson ve diğerleri. 2005; Tremaroli ve Bäckhed 2012 ). İlginç bir şekilde, doğumdan önce steril olan bağırsak, erken kolonize edicileri, doğum sırasında annenin fiziksel teması yoluyla edinir (Palmer ve ark. 2007; Dominguez-Bello ve ark. 2010). Bağırsağın barındırdığı trilyonlarca mikroorganizmanın çoğu, bileşimleri sindirim sistemi boyunca değişen zorunlu anaeroblardır (Aron-Wisnewsky ve ark. 2012; Fouhy ve ark. 2012). Yüksek verimli dizileme (HTS: high throughput sequencing) çalışmalarının ve biyoinformatik araçların geliştirilmesi; yaş, cinsiyet, genetik yapı ve çevresel etkilere dayalı olarak bağırsak mikrobiyotasının bileşiminde bireyler arası farklılıkları aydınlatmada devrim niteliğinde olmuştur (Fouhy ve diğerleri 2012; Li ve diğerleri 2014; Parkhill 2013; Santiago ve diğerleri 2014). Mikrobiyotadan elde edilen metabolitlerin taranması, metatranskriptomikler ve metaproteomikler gibi çeşitli modern yaklaşımlar; bağırsak mikrobiyomunu ve onun ateroskleroz ile ilişkisini daha iyi anlamak için büyük bir veri havuzundan yararlanmanın yollarını sağlar (Nicholson ve ark. 2005; Gosalbes ve

TMAO seviyelerini azaltarak ve hepatik safra asidi neo-sentezini artırarak TMAO'ya bağlı ateroskleroza zayıflattığını bulmuşlardır (Chen ve ark. 2016).

## 8 Sonuç

Ateroskleroz multifaktöriyel kronik inflamatuvar bir hastalıktır. Bu nedenle, kesin altta yatan mekanizmaları aydınlatmak zordur. Bununla birlikte, son bulgular, bağırsak mikrobiyotası ile ateroskleroz da dahil olmak üzere çok sayıda metabolik hastalığın patogenezi arasında bir bağlantı olduğunu göstermiştir. Çalışmalar, mikrobiyotanın; plak gelişimi, bağışıklık sistemini aktive etme, lipid ve kolesterol metabolizmasını değiştirme, arter duvarında iltihaplanmaya neden olma ve bakteriyel metabolitlerin üretimi gibi çoklu mekanizmalar yoluyla ateroskleroza etkileyebileceğini göstermektedir. Bağırsak mikrobiyota transplantasyonu ile ilgili deneysel çalışmalar ile insanlarda ve farelerde bağırsak mikrobiyotasının kompozisyonunun analizi, spesifik bağırsak mikrobiyal suşlarının bolluğunun değişmesinin ateroskleroz ile ilişkili olduğunu göstermektedir. Çeşitli hayvan modellerinde yapılan son araştırmalar; prebiyotikler, probiyotikler, antibiyotikler ve bağırsak mikrobiyotasını hedef alan küçük moleküller kullanılarak ateroskleroz gelişiminin başarılı terapötik manipülasyonunu bildirmiştir. Bununla birlikte, klinik ortamında kardiovasküler hastalıklar için bağırsak mikrobiyota hedefli tedavinin rutin uygulamasını görmeden önce, uzun bir yol katedilmesi gerekmektedir. Disbiyoz ve ateroskleroz arasında kesin ilişkiler kurmak için büyük prospektif klinik çalışmaların garanti edildiği bir aşamadayız. Ek olarak, bağırsak mikrobiyomunu hedef alan terapötikleri uygulamadan önce hastalıkla ilişkili temel bakteri taksonlarını ve metabolitleri belirlemek önemlidir.

## Kaynaklar

- Agerholm-Larsen, L., Raben, A., Haulrik, N., Hansen, A. S., Manders, M., & Astrup, A. (2000). Effect of 8-week intake of probiotic milk products on risk factors for cardiovascular diseases. *European Journal of Clinical Nutrition*, 54(4), 288–297.
- Aron-Wisniewsky, J., Doré, J., & Clement, K. (2012). The importance of the gut microbiota after bariatric surgery. *Nature Reviews. Gastroenterology & Hepatology*, 9(10), 590–598.
- Arpaia, N., Campbell, C., Fan, X., Dikiy, S., van der Veeken, J., de Roos, P., Liu, H., Cross, J. R., Pfeffer, K., Coffey, P. J., & Rudensky, A. Y. (2013). Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature*, 504(7480), 451–455.
- Bäckhed, F., Ding, H., Wang, T., Hooper, L. V., Koh, G. Y., Nagy, A., Semenkovich, C. F., & Gordon, J. I. (2004). The gut microbiota as an environmental factor that regulates fat storage. *Proceedings of the National Academy of Sciences of the United States of America*, 101(44), 15718–15723.
- Bellahcene, M., O'Dowd, J. F., Wargent, E. T., Zaibi, M. S., Hislop, D. C., Ngala, R. A., Smith, D. M., Cawthorne, M. A., Stocker, C. J., & Arch, J. R. (2013). Male mice that lack the G-protein-coupled receptor GPR41 have low energy expenditure and increased body fat content.

- The British Journal of Nutrition*, 109(10), 1755–1764.
- Bennett, B. J., de Aguiar Vallim, T. Q., Wang, Z., Shih, D. M., Meng, Y., Gregory, J., Allayee, H., Lee, R., Graham, M., Crooke, R., Edwards, P. A., Hazen, S. L., & Lusis, A. J. (2013). Trimethylamine-N-oxide, a metabolite associated with atherosclerosis, exhibits complex genetic and dietary regulation. *Cell Metabolism*, 17(1), 49–60.
- Bidulescu, A., Chambless, L. E., Siega-Riz, A. M., Zeisel, S. H., & Heiss, G. (2007). Usual choline and betaine dietary intake and incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. *BMC Cardiovascular Disorders*, 7, 20.
- Bjursell, M., Admyre, T., Göransson, M., Marley, A. E., Smith, D. M., Oscarsson, J., & Bohlooly-Y, M. (2011). Improved glucose control and reduced body fat mass in free fatty acid receptor 2-deficient mice fed a high-fat diet. *American Journal of Physiology. Endocrinology and Metabolism*, 300(1), E211–E220.
- Brown, J. M., & Hazen, S. L. (2018). Microbial modulation of cardiovascular disease. *Nature Reviews. Microbiology*, 16(3), 171–181.
- Canfora, E. E., Jocken, J. W., & Blaak, E. E. (2015). Short-chain fatty acids in control of body weight and insulin sensitivity. *Nature Reviews. Endocrinology*, 11(10), 577–591.
- Canfora, E. E., van der Beek, C. M., Jocken, J. W. E., Goossens, G. H., Holst, J. J., Olde Damink, S. W. M., Lenaerts, K., Dejong, C. H. C., & Blaak, E. E. (2017). Colonic infusions of short-chain fatty acid mixtures promote energy metabolism in overweight/obese men: a randomized crossover trial. *Scientific Reports*, 7(1), 2360.
- Cani, P. D., Amar, J., Iglesias, M. A., Poggi, M., Knauf, C., Bastelica, D., Neyrinck, A. M., Fava, F., Tuohy, K. M., Chabo, C., Waget, A., Delmée, E., Cousin, B., Sulpice, T., Chamontin, B., Ferrières, J., Tanti, J. F., Gibson, G. R., Casteilla, L., Delzenne, N. M., Alessi, M. C., & Burcelin, R. (2007). Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*, 56(7), 1761–1772.
- Cani, P. D., Bibiloni, R., Knauf, C., Waget, A., Neyrinck, A. M., Delzenne, N. M., & Burcelin, R. (2008). Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes*, 57(6), 1470–1481.
- Cani, P. D., Osto, M., Geurts, L., & Everard, A. (2012). Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity. *Gut Microbes*, 3(4), 279–288.
- Cashman, J. R., Camp, K., Fakharzadeh, S. S., Fennessey, P. V., Hines, R. N., Mamer, O. A., Mitchell, S. C., Nguyen, G. P., Schlenk, D., Smith, R. L., Tjoa, S. S., Williams, D. E., & Yannicelli, S. (2003). Biochemical and clinical aspects of the human flavin-containing monooxygenase form 3 (FMO3) related to trimethylaminuria. *Current Drug Metabolism*, 4(2), 151–170.
- Catry, E., Bindels, L. B., Tailleux, A., Lestavel, S., Neyrinck, A. M., Goossens, J. F., Lobysheva, I., Plovier, H., Essaghir, A., Demoulin, J. B., Bouzin, C., Pachikian, B. D., Cani, P. D., Staels, B., Dessy, C., & Delzenne, N. M. (2018). Targeting the gut microbiota with inulin-type fructans: preclinical demonstration of a novel approach in the management of endothelial dysfunction. *Gut*, 67(2), 271–283.
- Chaplin, A., Parra, P., Serra, F., & Palou, A. (2015). Conjugated linoleic acid supplementation under a high-fat diet modulates stomach protein expression and intestinal microbiota in adult mice. *PLoS One*, 10(4), e0125091.
- Chen, M. L., Yi, L., Zhang, Y., Zhou, X., Ran, L., Yang, J., Zhu, J. D., Zhang, Q. Y., & Mi, M. T. (2016). Resveratrol attenuates Trimethylamine-N-Oxide (TMAO)-induced atherosclerosis by regulating TMAO synthesis and bile acid metabolism via remodeling of the gut microbiota. *MBio*, 7(2), e02210–e02215.
- Colldahl, H. (1965). The intestinal flora in patients with bronchial asthma and rheumatoid arthritis. *Acta Allergol*, 20, 94–104.
- Collins, H. L., Drazul-Schrader, D., Sulpizio, A. C., Koster, P. D., Williamson, Y., Adelman, S. J., Owen, K., Sanli, T., & Bellamine, A. (2016). L-Carnitine intake and high trimethylamine

- N-oxide plasma levels correlate with low aortic lesions in ApoE(-/-) transgenic mice expressing CETP. *Atherosclerosis*, 244, 29–37.
- Collot-Teixeira, S., Martin, J., McDermott-Roe, C., Poston, R., & McGregor, J. L. (2007). CD36 and macrophages in atherosclerosis. *Cardiovascular Research*, 75, 468–477.
- Cox, L. M., & Blaser, M. J. (2013). Pathways in microbe-induced obesity. *Cell Metabolism*, 17(6), 883–894.
- Dalmeijer, G. W., Olthof, M. R., Verhoef, P., Bots, M. L., & van der Schouw, Y. T. (2008). Prospective study on dietary intakes of folate, betaine, and choline and cardiovascular disease risk in women. *European Journal of Clinical Nutrition*, 62(3), 386–394.
- Daugirdas, J. T., & Nawab, Z. M. (1987). Acetate relaxation of isolated vascular smooth muscle. *Kidney International*, 32(1), 39–46.
- De Vadder, F., Kovatcheva-Datchary, P., Zitoun, C., Duchamp, A., Bäckhed, F., & Mithieux, G. (2016). Microbiota-produced succinate improves glucose homeostasis via intestinal gluconeogenesis. *Cell Metabolism*, 24(1), 151–157.
- den Besten, G., van Eunen, K., Groen, A. K., Venema, K., Reijngoud, D. J., & Bakker, B. M. (2013). The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *Journal of Lipid Research*, 54(9), 2325–2340.
- Dominguez-Bello, M. G., Costello, E. K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., & Knight, R. (2010). Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proceedings of the National Academy of Sciences of the United States of America*, 107, 11971–11975.
- Durgan, D. J., Ganesh, B. P., Cope, J. L., Ajami, N. J., Phillips, S. C., Petrosino, J. F., Hollister, E. B., & Bryan, R. M., Jr. (2016). Role of the gut microbiome in obstructive sleep Apnea-induced hypertension. *Hypertension*, 67(2), 469–474.
- Eckburg, P. B., Bik, E. M., Bernstein, C. N., Purdom, E., Dethlefsen, L., Sargent, M., Gill, S. R., Nelson, K. E., & Relman, D. A. (2005). Diversity of the human intestinal microbial flora. *Science*, 308(5728), 1635–1638.
- El Kaoutari, A., Armougom, F., Gordon, J. I., Raoult, D., & Henrissat, B. (2013). The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. *Nature Reviews. Microbiology*, 11(7), 497–504.
- Ettinger, G., MacDonald, K., Reid, G., & Burton, J. P. (2014). The influence of the human microbiome and probiotics on cardiovascular health. *Gut Microbes*, 5(6), 719–728.
- Everard, A., Belzer, C., Geurts, L., Ouwerkerk, J. P., Druart, C., Bindels, L. B., Guiot, Y., Derrien, M., Muccioli, G. G., Delzenne, N. M., de Vos, W. M., & Cani, P. D. (2013). Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proceedings of the National Academy of Sciences of the United States of America*, 110(22), 9066–9071.
- Falk, E., Nakano, M., Bentzon, J. F., Finn, A. V., & Virmani, R. (2013). Update on acute coronary syndromes: The pathologists' view. *European Heart Journal*, 34, 719–728.
- Ferrier, K. E., Muhlmann, M. H., Baguet, J. P., Cameron, J. D., Jennings, G. L., Dart, A. M., & Kingwell, B. A. (2002). Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. *Journal of the American College of Cardiology*, 39(6), 1020–1005.
- Fouhy, F., Ross, R. P., Fitzgerald, G. F., Stanton, C., & Cotter, P. D. (2012). Composition of the early intestinal microbiota: knowledge, knowledge gaps and the use of high-throughput sequencing to address these gaps. *Gut Microbes*, 3(3), 203–220.
- Fry, L., & Baker, B. S. (2007). Triggering psoriasis: the role of infections and medications. *Clinics in Dermatology*, 25(6), 606–615.
- Fuentes, M. C., Lajo, T., Carrión, J. M., & Cuñé, J. (2013). Cholesterol-lowering efficacy of Lactobacillus plantarum CECT 7527, 7528 and 7529 in hypercholesterolaemic adults. *The British Journal of Nutrition*, 109(10), 1866–1872.

- Gaboriau-Routhiau, V., Rakotobe, S., Lécuyer, E., Mulder, I., Lan, A., Bridonneau, C., Rochet, V., Pisi, A., De Paepe, M., Brandi, G., Eberl, G., Snel, J., Kelly, D., & Cerf-Bensussan, N. (2009). The key role of segmented filamentous bacteria in the coordinated maturation of gut helper T cell responses. *Immunity*, 31(4), 677–689.
- Ghanim, H., Abuaysheh, S., Sia, C. L., Korzeniewski, K., Chaudhuri, A., Fernandez-Real, J. M., & Dandona, P. (2009). Increase in plasma endotoxin concentrations and the expression of Toll-like receptors and suppressor of cytokine signaling-3 in mononuclear cells after a high-fat, high-carbohydrate meal: implications for insulin resistance. *Diabetes Care*, 32(12), 2281–2287.
- Ghoshal, S., Witta, J., Zhong, J., de Villiers, W., & Eckhardt, E. (2009). Chylomicrons promote intestinal absorption of lipopolysaccharides. *Journal of Lipid Research*, 50(1), 90–97.
- Gómez-Ambrosi, J., Silva, C., Galofré, J. C., Escalada, J., Santos, S., Gil, M. J., Valentí, V., Rotellar, F., Ramírez, B., Salvador, J., & Frühbeck, G. (2011). Body adiposity and type 2 diabetes: increased risk with a high body fat percentage even having a normal BMI. *Obesity*, 19(7), 1439–1444.
- Gosalbes, M. J., Durbán, A., Pignatelli, M., Abellan, J. J., Jiménez-Hernández, N., Pérez-Cobas, A. E., Latorre, A., & Moya, A. (2011). Metatranscriptomic approach to analyze the functional human gut microbiota. *PLoS One*, 6(3), e17447.
- Gosalbes, M. J., Abellan, J. J., Durbán, A., Pérez-Cobas, A. E., Latorre, A., & Moya, A. (2012). Metagenomics of human microbiome: beyond 16s rDNA. *Clinical Microbiology and Infection*, 18(Suppl 4), 47–49.
- Gregor, M. F., & Hotamisligil, G. S. (2011). Inflammatory mechanisms in obesity. *Annual Review of Immunology*, 29, 415–445.
- Guarner, F. (2008). What is the role of the enteric commensal flora in IBD? *Inflammatory Bowel Diseases*, 14(Suppl 2), S83–S84.
- Hartman, H. B., Gardell, S. J., Petucci, C. J., Wang, S., Krueger, J. A., & Evans, M. J. (2009). Activation of farnesoid X receptor prevents atherosclerotic lesion formation in LDLR<sup>-/-</sup> and apoE<sup>-/-</sup> mice. *Journal of Lipid Research*, 50(6), 1090–1100.
- Hoving, L. R., Katiraei, S., Heijink, M., Pronk, A., van der Wee-Pals, L., Streefland, T., Giera, M., Willems van Dijk, K., & van Harmelen, V. (2018). Dietary Mannan oligosaccharides modulate gut microbiota, increase fecal bile acid excretion, and decrease plasma cholesterol and athero-sclerosis development. *Molecular Nutrition & Food Research*, 62(10), e1700942.
- Kallus, S. J., & Brandt, L. J. (2012). The intestinal microbiota and obesity. *Journal of Clinical Gastroenterology*, 46(1), 16–24.
- Kapil, V., Haydar, S. M., Pearl, V., Lundberg, J. O., Weitzberg, E., & Ahluwalia, A. (2013). Physiological role for nitrate-reducing oral bacteria in blood pressure control. *Free Radical Biology & Medicine*, 55, 93–100.
- Karbach, S. H., Schönfelder, T., Brandão, I., Wilms, E., Hörmann, N., Jäckel, S., Schüler, R., Finger, S., Knorr, M., Lagrange, J., Brandt, M., Waisman, A., Kossmann, S., Schäfer, K., Münzel, T., Reinhardt, C., & Wenzel, P. (2016). Gut microbiota promote Angiotensin II-induced arterial hypertension and vascular dysfunction. *Journal of the American Heart Association*, 5(9), e003698.
- Karlsson, F. H., Fåk, F., Nookaew, I., Tremaroli, V., Fagerberg, B., Petranovic, D., Bäckhed, F., & Nielsen, J. (2012). Symptomatic atherosclerosis is associated with an altered gut metagenome. *Nature Communications*, 3, 1245.
- Karlsson, F. H., Tremaroli, V., Nookaew, I., Bergström, G., Behre, C. J., Fagerberg, B., Nielsen, J., & Bäckhed, F. (2013). Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature*, 498(7452), 99–103.
- Kaska, L., Sledzinski, T., Chomiczewska, A., Dettlaff-Pokora, A., & Swierczynski, J. (2016). Improved glucose metabolism following bariatric surgery is associated with increased circulating bile acid concentrations and remodeling of the gut microbiome. *World Journal of*

- Gastroenterology*, 22(39), 8698–8719.
- Koeth, R. A., Wang, Z., Levison, B. S., Buffa, J. A., Org, E., Sheehy, B. T., Britt, E. B., Fu, X., Wu, Y., Li, L., Smith, J. D., DiDonato, J. A., Chen, J., Li, H., Wu, G. D., Lewis, J. D., Warrier, M., Brown, J. M., Krauss, R. M., Tang, W. H., Bushman, F. D., Lusis, A. J., & Hazen, S. L. (2013). Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nature Medicine*, 19(5), 576–585.
- Koh, A., De Vadder, F., Kovatcheva-Datchary, P., & Bäckhed, F. (2016). From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell*, 165(6), 1332–1345.
- Kohashi, O., Kuwata, J., Umehara, K., Uemura, F., Takahashi, T., & Ozawa, A. (1979). Susceptibility to adjuvant-induced arthritis among germfree, specific-pathogen-free, and conventional rats. *Infection and Immunity*, 26(3), 791–794.
- Kolmeder, C. A., de Been, M., Nikkilä, J., Ritamo, I., Mättö, J., Valmu, L., Salojärvi, J., Palva, A., Salonen, A., & de Vos, W. M. (2012). Comparative metaproteomics and diversity analysis of human intestinal microbiota testifies for its temporal stability and expression of core functions. *PLoS One*, 7(1), e29913.
- Koppe, L., Pillon, N. J., Vella, R. E., Croze, M. L., Pelletier, C. C., Chambert, S., Massy, Z., Glorieux, G., Vanholder, R., Dugenet, Y., Soula, H. A., Fouque, D., & Soulage, C. O. (2013). p-Cresyl sulfate promotes insulin resistance associated with CKD. *Journal of the American Society of Nephrology*, 24(1), 88–99.
- Koyama, M., Hattori, S., Amano, Y., Watanabe, M., & Nakamura, K. (2014). Blood pressure-lowering peptides from neo-fermented buckwheat sprouts: a new approach to estimating ACE-inhibitory activity. *PLoS One*, 9(9), e105802.
- Kugelberg, E. (2013). Surgery: Altered gut microbiota trigger weight loss. *Nature Reviews. Endocrinology*, 9(6), 314.
- Lairon, D., Arnault, N., Bertrais, S., Planells, R., Clero, E., Hercberg, S., & Boutron-Ruault, M. C. (2005). Dietary fiber intake and risk factors for cardiovascular disease in French adults. *The American Journal of Clinical Nutrition*, 82(6), 1185–1194.
- Lang, D. H., Yeung, C. K., Peter, R. M., Ibarra, C., Gasser, R., Itagaki, K., Philpot, R. M., & Rettie, E. (1998). Isoform specificity of trimethylamine N-oxygenation by human flavin-containing monooxygenase (FMO) and P450 enzymes: selective catalysis by FMO3. *Biochemical Pharmacology*, 56(8), 1005–1012.
- Le Chatelier, E., Nielsen, T., Qin, J., Prifti, E., Hildebrand, F., Falony, G., Almeida, M., Arumugam, M., Batto, J. M., Kennedy, S., Leonard, P., Li, J., Burgdorf, K., Grarup, N., Jørgensen, T., Brandslund, I., Nielsen, H. B., Juncker, A. S., Bertalan, M., Levenez, F., Pons, N., Rasmussen, S., Sunagawa, S., Tap, J., Tims, S., Zoetendal, E. G., Brunak, S., Clément, K., Doré, J., Kleerebezem, M., Kristiansen, K., Renault, P., Sicheritz-Ponten, T., de Vos, W. M., Zucker, J. D., Raes, J., Hansen, T., MetaHIT consortium, Bork, P., Wang, J., Ehrlich, S. D., & Pedersen, O. (2013). Richness of human gut microbiome correlates with metabolic markers. *Nature*, 500(7464), 541–546.
- Ley, R. E., Bäckhed, F., Turnbaugh, P., Lozupone, C. A., Knight, R. D., & Gordon, J. I. (2005). Obesity alters gut microbial ecology. *Proceedings of the National Academy of Sciences of the United States of America*, 102(31), 11070–11075.
- Li, X., & Shimizu, Y. (2017). Kimura I Gut microbial metabolite short-chain fatty acids and obesity. *Bioscience of Microbiota, Food and Health*, 36(4), 135–140.
- Li, J., Jia, H., Cai, X., Zhong, H., Feng, Q., Sunagawa, S., Arumugam, M., Kultima, J. R., Prifti, E., Nielsen, T., Juncker, A. S., Manichanh, C., Chen, B., Zhang, W., Levenez, F., Wang, J., Xu, X., Xiao, L., Liang, S., Zhang, D., Zhang, Z., Chen, W., Zhao, H., Al-Aama, J. Y., Edris, S., Yang, H., Wang, J., Hansen, T., Nielsen, H. B., Brunak, S., Kristiansen, K., Guarner, F., Pedersen, O., Doré, J., Ehrlich, S. D., MetaHIT Consortium, Bork, P., & Wang, J. (2014). An integrated catalog of reference genes in the human gut microbiome. *Nature Biotechnology*, 32(8), 834–841.

- Li, J., Zhao, F., Wang, Y., Chen, J., Tao, J., Tian, G., Wu, S., Liu, W., Cui, Q., Geng, B., Zhang, W., Weldon, R., Auguste, K., Yang, L., Liu, X., Chen, L., Yang, X., Zhu, B., & Cai, J. (2017). Gut microbiota dysbiosis contributes to the development of hypertension. *Microbiome*, 5(1), 14.
- Lundberg, J. O., & Govoni, M. (2004). Inorganic nitrate is a possible source for systemic generation of nitric oxide. *Free Radical Biology & Medicine*, 37(3), 395–400.
- Lusis, A. J. (2000). Atherosclerosis. *Nature*, 407, 233–241.
- Lutz, T. A., & Bueter, M. (2014). Physiological mechanisms behind Roux-en-Y gastric bypass surgery. *Digestive Surgery*, 31(1), 13–24.
- Ma, G., Pan, B., Chen, Y., Guo, C., Zhao, M., Zheng, L., & Chen, B. (2017). Trimethylamine N-oxide in atherogenesis: impairing endothelial self-repair capacity and enhancing monocyte adhesion. *Bioscience Reports*, 37(2), BSR20160244.
- Marques, F. Z., Nelson, E., Chu, P. Y., Horlock, D., Fiedler, A., Ziemann, M., Tan, J. K., Kuruppu, S., Rajapakse, N. W., El-Osta, A., Mackay, C. R., & Kaye, D. M. (2017). High-fiber diet and acetate supplementation change the gut microbiota and prevent the development of hypertension and heart failure in hypertensive mice. *Circulation*, 135(10), 964–977.
- McLaren, J. E., Michael, D. R., Ashlin, T. G., & Ramji, D. P. (2011). Cytokines, macrophage lipid metabolism and foam cells: Implications for cardiovascular disease therapy. *Progress in Lipid Research*, 50, 331–347.
- McNelis, J. C., Lee, Y. S., Mayoral, R., van der Kant, R., Johnson, A. M., Wollam, J., & Olefsky, M. (2015). GPR43 potentiates  $\beta$ -Cell function in obesity. *Diabetes*, 64(9), 3203–3217.
- Miao, J., Ling, A. V., Manthana, P. V., Gearing, M. E., Graham, M. J., Crooke, R. M., Croce, J., Esquejo, R. M., Clish, C. B., Morbid Obesity Study Group, Vicent, D., & Biddinger, S. B. (2015). Flavin-containing monooxygenase 3 as a potential player in diabetes-associated atherosclerosis. *Nature Communications*, 6, 6498.
- Miyamoto, J., Kasubuchi, M., Nakajima, A., Irie, J., Itoh, H., & Kimura, I. (2016). The role of short-chain fatty acid on blood pressure regulation. *Current Opinion in Nephrology and Hypertension*, 25(5), 379–383.
- Miyazaki-Anzai, S., Masuda, M., Levi, M., Keenan, A. L., & Miyazaki, M. (2014). Dual activation of the bile acid nuclear receptor FXR and G-protein-coupled receptor TGR5 protects mice against atherosclerosis. *PLoS One*, 9(9), e108270.
- Moore, K. J., & Tabas, I. (2011). The cellular biology of macrophages in atherosclerosis. *Cell*, 145, 341–355.
- Moore, K. J., Sheedy, F. J., & Fisher, E. A. (2013). Macrophages in atherosclerosis: a dynamic balance. *Nature Reviews. Immunology*, 13(10), 709–721.
- Nagata, C., Wada, K., Tamura, T., Konishi, K., Kawachi, T., Tsuji, M., & Nakamura, K. (2015). Choline and Betaine intakes are not associated with cardiovascular disease mortality risk in Japanese men and women. *The Journal of Nutrition*, 145(8), 1787–1792.
- Neal, M. D., Leaphart, C., Levy, R., Prince, J., Billiar, T. R., Watkins, S., Li, J., Cetin, S., Ford, H., Schreiber, A., & Hackam, D. J. (2006). Enterocyte TLR4 mediates phagocytosis and translocation of bacteria across the intestinal barrier. *Journal of Immunology*, 176(5), 3070–3079.
- Nguyen, T. D., Kang, J. H., & Lee, M. S. (2007). Characterization of *Lactobacillus plantarum* PH04, a potential probiotic bacterium with cholesterol-lowering effects. *International Journal of Food Microbiology*, 113(3), 358–361.
- Nicholson, J. K., Holmes, E., & Wilson, I. D. (2005). Gut microorganisms, mammalian metabolism and personalized health care. *Nature Reviews. Microbiology*, 3(5), 431–438.
- Nutting, C. W., Islam, S., & Daugirdas, J. T. (1991). Vasorelaxant effects of short chain fatty acid salts in rat caudal artery. *The American Journal of Physiology*, 261(2 Pt 2), H561–H567.
- Ochoa-Repáraz, J., Mielcarz, D. W., Ditrio, L. E., Burroughs, A. R., Foureau, D. M., Haque-Begum, S., & Kasper, L. H. (2009). Role of gut commensal microflora in the development of experimental autoimmune encephalomyelitis. *Journal of Immunology*, 183(10), 6041–6050.
- Ortega, F. B., Lavie, C. J., & Blair, S. N. (2016). Obesity and cardiovascular disease. *Circulation*

- Research*, 118(11), 1752–1770.
- Osto, M., Abegg, K., Bueter, M., le Roux, C. W., Cani, P. D., & Lutz, T. A. (2013). Roux-en-Y gastric bypass surgery in rats alters gut microbiota profile along the intestine. *Physiology & Behavior*, 119, 92–96.
- Ottman, N., Reunanen, J., Meijerink, M., Pietilä, T. E., Kainulainen, V., Klievink, J., Huuskonen, L., Aalvink, S., Skurnik, M., Boeren, S., Satokari, R., Mercenier, A., Palva, A., Smidt, H., de Vos, W. M., & Belzer, C. (2017). Pili-like proteins of Akkermansia muciniphila modulate host immune responses and gut barrier function. *PLoS One*, 12(3), e0173004.
- Palmer, C., Bik, E. M., DiGiulio, D. B., Relman, D. A., & Brown, P. O. (2007). Development of the Human infant intestinal microbiota. *PLoS Biology*, 5, e177.
- Parkhill, J. (2013). What has high-throughput sequencing ever done for us? *Nature Reviews. Microbiology*, 11(10), 664–665.
- Pedersen, H. K., Gudmundsdottir, V., Nielsen, H. B., Hyötyläinen, T., Nielsen, T., Jensen, B. A., Forslund, K., Hildebrand, F., Pridfti, E., Falony, G., Le Chatelier, E., Levenez, F., Doré, J., Mattila, I., Plichta, D. R., Pöhö, P., Hellgren, L. I., Arumugam, M., Sunagawa, S., Vieira-Silva, S., Jørgensen, T., Holm, J. B., Trošt, K., MetaHIT Consortium, Kristiansen, K., Brix, S., Raes, J., Wang, J., Hansen, T., Bork, P., Brunak, S., Oresic, M., Ehrlich, S. D., & Pedersen, O. (2016). Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature*, 535(7612), 376–381.
- Petersson, J., Carlström, M., Schreiber, O., Phillipson, M., Christoffersson, G., Jägare, A., Roos, S., Jansson, E. A., Persson, A. E., Lundberg, J. O., & Holm, L. (2009). Gastroprotective and blood pressure lowering effects of dietary nitrate are abolished by an antiseptic mouthwash. *Free Radical Biology & Medicine*, 46(8), 1068–1075.
- Piya, M. K., McTernan, P. G., & Kumar, S. (2013). Adipokine inflammation and insulin resistance: the role of glucose, lipids and endotoxin. *The Journal of Endocrinology*, 216(1), T1–T15.
- Plovier, H., Everard, A., Druart, C., Depommier, C., Van Hul, M., Geurts, L., Chilloux, J., Ottman, N., Duparc, T., Lichtenstein, L., Myridakis, A., Delzenne, N. M., Klievink, J., Bhattacharjee, A., van der Ark, K. C., Aalvink, S., Martinez, L. O., Dumas, M. E., Maiter, D., Loumaye, A., Hermans, M. P., Thissen, J. P., Belzer, C., de Vos, W. M., & Cani, P. D. (2017). A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nature Medicine*, 23(1), 107–113.
- Pluznick, J. L., Protzko, R. J., Gevorgyan, H., Peterlin, Z., Sipos, A., Han, J., Brunet, I., Wan, L. X., Rey, F., Wang, T., Firestein, S. J., Yanagisawa, M., Gordon, J. I., Eichmann, A., Peti-Peterdi, J., & Caplan, M. J. (2013). Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation. *Proceedings of the National Academy of Sciences of the United States of America*, 110(11), 4410–4415.
- Qin, J., Li, Y., Cai, Z., Li, S., Zhu, J., Zhang, F., Liang, S., Zhang, W., Guan, Y., Shen, D., Peng, Y., Zhang, D., Jie, Z., Wu, W., Qin, Y., Xue, W., Li, J., Han, L., Lu, D., Wu, P., Dai, Y., Sun, X., Li, Z., Tang, A., Zhong, S., Li, X., Chen, W., Xu, R., Wang, M., Feng, Q., Gong, M., Yu, J., Zhang, Y., Zhang, M., Hansen, T., Sanchez, G., Raes, J., Falony, G., Okuda, S., Almeida, M., LeChatelier, E., Renault, P., Pons, N., Batto, J. M., Zhang, Z., Chen, H., Yang, R., Zheng, W., Li, S., Yang, H., Wang, J., Ehrlich, S. D., Nielsen, R., Pedersen, O., Kristiansen, K., & Wang, J. (2012). A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature*, 490(7418), 55–60.
- Ramadoss, P., Marcus, C., & Perdew, G. H. (2005). Role of the aryl hydrocarbon receptor in drug metabolism. *Expert Opinion on Drug Metabolism & Toxicology*, 1(1), 9–21.
- Rault-Nania, M. H., Gueux, E., Demougeot, C., Demigné, C., Rock, E., & Mazur, A. (2006). Inulin attenuates atherosclerosis in apolipoprotein E-deficient mice. *The British Journal of Nutrition*, 96(5), 840–844.
- Ridaura, V. K., Faith, J. J., Rey, F. E., Cheng, J., Duncan, A. E., Kau, A. L., Griffin, N. W., Lombard, V., Henrissat, B., Bain, J. R., Muehlbauer, M. J., Ilkayeva, O., Semenkovich, C. F., Funai, K.,

- Hayashi, D. K., Lyle, B. J., Martini, M. C., Ursell, L. K., Clemente, J. C., Van Treuren, W., Walters, W. A., Knight, R., Newgard, C. B., Heath, A. C., & Gordon, J. I. (2013). Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science*, *341*(6150), 1241214.
- Roberfroid, M., Gibson, G. R., Hoyles, L., McCartney, A. L., Rastall, R., Rowland, I., Wolvers, D., Watzl, B., Szajewska, H., Stahl, B., Guarner, F., Respondek, F., Whelan, K., Coxam, V., Davicco, M. J., Léotoing, L., Wittrant, Y., Delzenne, N. M., Cani, P. D., Neyrinck, A. M., & Meheust, A. (2010). Prebiotic effects: metabolic and health benefits. *The British Journal of Nutrition*, *104*(Suppl 2), S1–63.
- Ryan, K. K., Tremaroli, V., Clemmensen, C., Kovatcheva-Datchary, P., Myronovych, A., Karns, R., Wilson-Pérez, H. E., Sandoval, D. A., Kohli, R., Bäckhed, F., & Seeley, R. J. (2014). FXR is a molecular target for the effects of vertical sleeve gastrectomy. *Nature*, *509*(7499), 183–188.
- Samuel, B. S., Shaito, A., Motoike, T., Rey, F. E., Backhed, F., Manchester, J. K., Hammer, R. E., Williams, S. C., Crowley, J., Yanagisawa, M., & Gordon, J. I. (2008). Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(43), 16767–16772.
- Sanders, M. E. (2008). Probiotics: definition, sources, selection, and uses. *Clinical Infectious Diseases*, *46*(Suppl 2), S58–61; discussion S144–51.
- Santiago, A., Panda, S., Mengels, G., Martinez, X., Azpiroz, F., Dore, J., Guarner, F., & Manichanh, C. (2014). Processing faecal samples: a step forward for standards in microbial community analysis. *BMC Microbiology*, *14*, 112.
- Sartor, R. B. (2008). Microbial influences in inflammatory bowel diseases. *Gastroenterology*, *134*(2), 577–594.
- Sartor, R. B., & Wu, G. D. (2017). Roles for intestinal bacteria, viruses, and fungi in pathogenesis of inflammatory bowel diseases and therapeutic approaches. *Gastroenterology*, *152*(2), 327–339.
- Senthong, V., Li, X. S., Hudc, T., Coughlin, J., Wu, Y., Levison, B., Wang, Z., Hazen, S. L., & Tang, W. H. (2016). Plasma Trimethylamine N-Oxide, a Gut Microbe-Generated Phosphatidylcholine Metabolite, Is Associated With Atherosclerotic Burden. *Journal of the American College of Cardiology*, *67*(22), 2620–2628.
- Shi, H., Kokoeva, M. V., Inouye, K., Tzamei, I., Yin, H., & Flier, J. S. (2006). TLR4 links innate immunity and fatty acid-induced insulin resistance. *The Journal of Clinical Investigation*, *116*(11), 3015–3025.
- Shih, D. M., Wang, Z., Lee, R., Meng, Y., Che, N., Charugundla, S., Qi, H., Wu, J., Pan, C., Brown, J. M., Vallim, T., Bennett, B. J., Graham, M., Hazen, S. L., & Lusis, A. J. (2015). Flavin containing monooxygenase 3 exerts broad effects on glucose and lipid metabolism and atherosclerosis. *Journal of Lipid Research*, *56*(1), 22–37.
- Sparacino-Watkins, C., Stolz, J. F., & Basu, P. (2014). Nitrate and periplasmic nitrate reductases. *Chemical Society Reviews*, *43*(2), 676–706.
- Tan, J. K., McKenzie, C., Mariño, E., Macia, L., & Mackay, C. R. (2017). Metabolite-sensing G protein-coupled receptors-facilitators of diet-related immune regulation. *Annual Review of Immunology*, *35*, 371–402.
- Tang, W. H., Wang, Z., Levison, B. S., Koeth, R. A., Britt, E. B., Fu, X., Wu, Y., & Hazen, S. L. (2013). Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *The New England Journal of Medicine*, *368*(17), 1575–1584.
- Tang, W. H., Wang, Z., Shrestha, K., Borowski, A. G., Wu, Y., Troughton, R. W., Klein, A. L., & Hazen, S. L. (2015). Intestinal microbiota-dependent phosphatidylcholine metabolites, diastolic dysfunction, and adverse clinical outcomes in chronic systolic heart failure. *Journal of Cardiac Failure*, *21*(2), 91–96.
- Thomas, C., Gioiello, A., Noriega, L., Strehle, A., Oury, J., Rizzo, G., Macchiarulo, A., Yamamoto,

- H., Matakı, C., Pruzanski, M., Pellicciari, R., Auwerx, J., & Schoonjans, K. (2009). TGR5-mediated bile acid sensing controls glucose homeostasis. *Cell Metabolism*, 10(3), 167–177.
- Tremaroli, V., & Bäckhed, F. (2012). Functional interactions between the gut microbiota and host metabolism. *Nature*, 489(7415), 242–249.
- Tremaroli, V., Karlsson, E., Werling, M., Ståhlman, M., Kovatcheva-Datchary, P., Olbers, T., Fändriks, L., le Roux, C. W., Nielsen, J., & Bäckhed, F. (2015). Roux-en-Y gastric bypass and vertical banded gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. *Cell Metabolism*, 22(2), 228–238.
- Turnbaugh, P. J., Ley, R. E., Mahowald, M. A., Magrini, V., Mardis, E. R., & Gordon, J. I. (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*, 444(7122), 1027–1031.
- Turnbaugh, P. J., Hamady, M., Yatsunenko, T., Cantarel, B. L., Duncan, A., Ley, R. E., Sogin, M. L., Jones, W. J., Roe, B. A., Affourtit, J. P., Egholm, M., Henrissat, B., Heath, A. C., Knight, R., & Gordon, J. I. (2009). A core gut microbiome in obese and lean twins. *Nature*, 457(7228), 480–484.
- Ufnal, M., Jazwiec, R., Dadlez, M., Drapala, A., Sikora, M., & Skrzypecki, J. (2014). Trimethylamine-N-oxide: a carnitine-derived metabolite that prolongs the hypertensive effect of angiotensin II in rats. *The Canadian Journal of Cardiology*, 30(12), 1700–1705.
- Valdimarsson, H., Baker, B. S., Jónsdóttir, I., Powles, A., & Fry, L. (1995). Psoriasis: a T-cell-mediated autoimmune disease induced by streptococcal superantigens? *Immunology Today*, 16(3), 145–149.
- Venkatesh, M., Mukherjee, S., Wang, H., Li, H., Sun, K., Benechet, A. P., Qiu, Z., Maher, L., Redinbo, M. R., Phillips, R. S., Fleet, J. C., Kortagere, S., Mukherjee, P., Fasano, A., Le Ven, J., Nicholson, J. K., Dumas, M. E., Khanna, K. M., & Mani, S. (2014). Symbiotic bacterial metabolites regulate gastrointestinal barrier function via the xenobiotic sensor PXR and Toll-like receptor 4. *Immunity*, 41(2), 296–310.
- Veprik, A., Laufer, D., Weiss, S., Rubins, N., & Walker, M. D. (2016). GPR41 modulates insulin secretion and gene expression in pancreatic  $\beta$ -cells and modifies metabolic homeostasis in fed and fasting states. *The FASEB Journal*, 30(11), 3860–3869.
- Vijay-Kumar, M., Aitken, J. D., Carvalho, F. A., Cullender, T. C., Mwangi, S., Srinivasan, S., Sitaraman, S. V., Knight, R., Ley, R. E., & Gewirtz, A. T. (2010). Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science*, 328(5975), 228–231.
- Vreugdenhil, A. C., Rousseau, C. H., Hartung, T., Greve, J. W., van 't Veer, C., & Buurman, W. A. (2003). Lipopolysaccharide (LPS)-binding protein mediates LPS detoxification by chylomicrons. *Journal of Immunology*, 170(3), 1399–1405.
- Wander, P. L., Boyko, E. J., Leonetti, D. L., McNeely, M. J., Kahn, S. E., & Fujimoto, W. Y. (2013). Change in visceral adiposity independently predicts a greater risk of developing type 2 diabetes over 10 years in Japanese Americans. *Diabetes Care*, 36(2), 289–293.
- Wang, Y., & Kasper, L. H. (2014). The role of microbiome in central nervous system disorders. *Brain, Behavior, and Immunity*, 38, 1–12.
- Wang, Z., Klipfell, E., Bennett, B. J., Koeth, R., Levison, B. S., Dugar, B., Feldstein, A. E., Britt, E. B., Fu, X., Chung, Y. M., Wu, Y., Schauer, P., Smith, J. D., Allayee, H., Tang, W. H., DiDonato, J. A., Lusis, A. J., & Hazen, S. L. (2011). Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature*, 472(7341), 57–63.
- Warrier, M., Shih, D. M., Burrows, A. C., Ferguson, D., Gromovsky, A. D., Brown, A. L., Marshall, S., McDaniel, A., Schugar, R. C., Wang, Z., Sacks, J., Rong, X., Vallim, T. A., Chou, J., Ivanova, P. T., Myers, D. S., Brown, H. A., Lee, R. G., Crooke, R. M., Graham, M. J., Liu, X., Parini, P., Tontonoz, P., Lusis, A. J., Hazen, S. L., Temel, R. E., & Brown, J. M. (2015). The TMAO-generating enzyme flavin monooxygenase 3 is a central regulator of cholesterol balance. *Cell Reports*. pii: S2211-1247(14)01065-1.
- Watzl, B., Girrbaach, S., & Roller, M. (2005). Inulin, oligofructose and immunomodulation. *The*

- British Journal of Nutrition*, 93(Suppl 1), S49–S55.
- Wu, X., Ma, C., Han, L., Nawaz, M., Gao, F., Zhang, X., Yu, P., Zhao, C., Li, L., Zhou, A., Wang, J., Moore, J. E., Millar, B. C., & Xu, J. (2010). Molecular characterisation of the faecal microbiota in patients with type II diabetes. *Current Microbiology*, 61(1), 69–78.
- Yadav, H., Jain, S., & Sinha, P. R. (2007). Antidiabetic effect of probiotic dahi containing *Lactobacillus acidophilus* and *Lactobacillus casei* in high fructose fed rats. *Nutrition*, 23(1), 62–68.
- Yamashiro, K., Tanaka, R., Urabe, T., Ueno, Y., Yamashiro, Y., Nomoto, K., Takahashi, T., Tsuji, H., Asahara, T., & Hattori, N. (2017). Gut dysbiosis is associated with metabolism and systemic inflammation in patients with ischemic stroke. *PLoS One*, 12(2), e0171521.
- Yang, T., Santisteban, M. M., Rodriguez, V., Li, E., Ahmari, N., Carvajal, J. M., Zadeh, M., Gong, M., Qi, Y., Zubcevic, J., Sahay, B., Pepine, C. J., Raizada, M. K., & Mohamadzadeh, M. (2015). Gut dysbiosis is linked to hypertension. *Hypertension*, 65(6), 1331–1340.
- Zhang, H., DiBaise, J. K., Zuccolo, A., Kudrna, D., Braidotti, M., Yu, Y., Parameswaran, P., Crowell, M. D., Wing, R., Rittmann, B. E., & Krajmalnik-Brown, R. (2009). Human gut microbiota in obesity and after gastric bypass. *Proceedings of the National Academy of Sciences of the United States of America*, 106(7), 2365–2370.
- Zhu, W., Gregory, J. C., Org, E., Buffa, J. A., Gupta, N., Wang, Z., Li, L., Fu, X., Wu, Y., Mehrabian, M., Sartor, R. B., McIntyre, T. M., Silverstein, R. L., Tang, W. H. W., DiDonato, J. A., Brown, J. M., Luscis, A. J., & Hazen, S. L. (2016). Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. *Cell*, 165(1), 111–124.
- Zhu, L., Zhang, D., Zhu, H., Zhu, J., Weng, S., Dong, L., Liu, T., Hu, Y., & Shen, X. (2018). Berberine treatment increases *Akkermansia* in the gut and improves high-fat diet-induced atherosclerosis in *Apoe*<sup>-/-</sup> mice. *Atherosclerosis*, 268, 117–126.

# Bağırsak Mikrobiyomu ve Mikrobiyal Patojenlerle Enterik Enfeksiyonlarda Rolü

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## 1. Giriş

Enterik enfeksiyonlara tipik olarak enterik bakteriler neden olur. Bakteriler insan veya hayvan vücuduna girer ve akut enterik hastalıklara neden olmak için bağırsaklara gider. Enterik bakterilerin bazı yaygın örnekleri *Escherichia coli*, *Vibrio cholerae*, *Shigella* ve *Salmonella enterica*'dır. Ana giriş yolu ağızdır, çünkü bu organizmalar en yaygın olarak kontamine yiyecek veya suda bulunur. Kontamine gıda tüketildiğinde patojen organizmalar anında vücuda girer ve istila süreci başlar. Kontamine gıda mideye ulaştığında, sindirimin bir sonucu olarak midenin pH'ı yükselir. Midedeki pH yükseldiğinde, bazı bakteriler hayatta kalabilir ve sindirim sisteminin bir sonraki kısmı olan ince bağırsağa geçebilir. Neyse ki, mide suyu, patojenik organizmaların kolonize olmak için aşması gereken tek engel değildir. Vücudun bağışıklık hücrelerinin %70 kadarı ince bağırsağın içinde, özellikle ileumda (ince bağırsağın son kısmı) bulunur. Bu bağışıklık hücreleri, Peyer yamaları adı verilen kitleler halinde kümelenir. Kitleler lenfoid foliküllerdir ve bağırsakların bağışıklık sensörleri olarak kabul edilirler (Jung ve ark. 2010). Luminal antijenleri ve bakterileri taşıma yetenekleriyle tanınırlar. Peyer yama hücreleri, kommensaller ve patojenler arasındaki karmaşık etkileşimler, vücutta doğuştan gelen ve adaptif bağışıklığın oluşmasını sağlar.

Ayrıca, patojenik organizmaların mikrobiyal bariyer olarak adlandırılabilir bir engeli aşması gerekir. Patojenik organizmaların kolonize olmaya başlamak için bağırsakta kendilerine yer açmaları gerekir. Bağırsaklar normalde patojenik organizmaların rekabet etmek zorunda olduğu kommensal bakteriler tarafından kolonize edilir. Rolhion ve Chassaing'e (2016) göre, mikrobiyal bariyer "bağırsak bakterilerinin, diğer türlerin yeni bakterilerinin veya aynı türün diğer suşlarının istilasını önlemek için bir bariyer oluşturduğu mekanizmadır. Bu düşünce, *Clostridium difficile* enfeksiyonu gibi antibiyotik kullanımından kaynaklanan çeşitli enfeksiyonlarla ve ayrıca birçok enterik patojenin mikropsuz koşullar altında (bağırsak mikrobiyotasının yokluğunda) veya antibiyotik tedavilerini takiben farelerde daha güçlü hastalığa neden olduğu gözlemlenilen iyi bir şekilde örneklenir. Rolhion ve Chassaing (2016) tarafından gözlemlendiği üzere bu, alt bağırsak yolunun etkili bir koruma mekanizmasıdır. Bu bariyer, bağır-

## 12 Sonuç

Bağırsak mikrobiyomu, simbiyotik bir ilişki sürdürmek için birbirleriyle ve konakçılarıyla etkileşime giren bir organizmalar topluluğudur. Bakteriler, virüsler, mantarlar ve diğer mikroskopik organizmalar, insanların ve diğer hayvanların bağırsaklarındaki kaynaklar için sürekli olarak işbirliği yapmakta ve rekabet etmektedir. Bu etkileşimler simbiyotik olabilir ve konakçı için faydalı olabilir ve hatta insan konakçı için zararlı olabilir. Mikrobiyom, yalnızca bağırsak sağlığına değil, insan sağlığına da tüm yönleriyle katkı sağlayarak bu alanda araştırma yapılmasının önemini ortaya koymaktadır. Bu mikropların insan yaşamının çeşitli yönleri üzerinde sahip olabileceği sağlık ve zindelik etkilerini daha iyi anlamak için araştırmalara ihtiyaç vardır. Dünyadaki tüm mikropları yok edecek bir felaket, insanlar üzerinde geniş kapsamlı etkilere sahip olacaktır. Bakterisitlerin, mantar öldürücülerin ve virüs öldürücülerin insan uygulamaları üzerinde, olumlu etkileri var gibi görünse de, zararlı yan etkileri de olabilir. Artan antibiyotik direnci uzun vadeli araştırmaların önemini göstermektedir. Uzun vadeli araştırmalar, antibiyotik direncini azaltmanın ve antibiyotik gerektiren hastalıkları tedavi etmenin daha iyi yollarını aydınlatılabilir.

## Kaynaklar

- Bäckhed, F., Roswall, J., Peng, Y., Feng, Q., Jia, H., Kovatcheva-Datchary, P., et al. (2015). Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host & Microbe*, 17, 690–703.
- Baeshen, M. N., Al-Hejin, A. M., Bora, R. S., Ahmed, M. M. M., Ramadan, H. A. I., Saini, K. S., Baeshen, N. A., & Redwan, E. M. (2015). Production of biopharmaceuticals in *E. coli*: Current scenario and future perspectives. *Journal of Microbiology and Biotechnology*, 25, 953–962.
- Barka, E. A., Vatsa, P., Sanchez, L., Gaveau-Vaillant, N., Jacquard, C., Klenk, H. P., et al. (2016). Taxonomy, physiology, and natural products of Actinobacteria. *Microbiology and Molecular Biology Reviews*, 80, 1–43.
- Belkaid, Y., & Hand, T. W. (2014). Role of the microbiota in immunity and inflammation. *Cell*, 157, 121–141.
- Britton, R. A., & Versalovic, J. (2008). Probiotics and gastrointestinal infections. *Interdisciplinary Perspectives on Infectious Diseases*, 2008.
- Carrió, M. M., & Villaverde, A. (2003). Role of molecular chaperones in inclusion body formation. *FEBS Letters*, 537, 215–221.
- Cash, H. L., Whitham, C. V., Behrendt, C. L., & Hooper, L. V. (2006). Symbiotic bacteria direct expression of an intestinal bactericidal lectin. *Science*, 313, 1126–1130.
- Christa, L., Carnot, F., Simon, M. T., Levavasseur, F., Stinnakre, M. G., Lasserre, C., et al. (1996). HIP/PAP is an adhesive protein expressed in hepatocarcinoma, normal Paneth, and pancreatic cells. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, 271, G993–G1002.
- Claesson, M. J., Cusack, S., O'Sullivan, O., Greene-Diniz, R., de Weerd, H., Flannery, E., et al. (2011). Composition, variability, and temporal stability of the intestinal microbiota of the elderly. *Proceedings of the National Academy of Sciences*, 108, 4586–4591.

- Cole, K., Farnell, M. B., Donoghue, A. M., Stern, N. J., Svetoch, E. A., Eruslanov, B. N., et al. (2006). Bacteriocins reduce *Campylobacter* colonization and alter gut morphology in Turkey poults. *Poultry Science*, *85*, 1570–1575.
- Conlon, M., & Bird, A. (2015). The impact of diet and lifestyle on gut microbiota and human health. *Nutrients*, *7*, 17–44.
- Cornejo-Pareja, I., Muñoz-Garach, A., Clemente-Postigo, M., & Tinahones, F. J. (2018). Importance of gut microbiota in obesity. *European Journal of Clinical Nutrition*, *1*.
- Coyte, K. Z., Schluter, J., & Foster, K. R. (2015). The ecology of the microbiome: Networks, competition, and stability. *Science*, *350*, 663–666.
- De Filippo, C., Cavalieri, D., Di Paola, M., Ramazzotti, M., Poullet, J. B., Massart, S., et al. (2010). Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proceedings of the National Academy of Sciences*, *107*, 14691–14696.
- Deriu, E., Liu, J. Z., Pezeshki, M., Edwards, R. A., Ochoa, R. J., Contreras, H., et al. (2013). Probiotic bacteria reduce salmonella typhimurium intestinal colonization by competing for iron. *Cell Host & Microbe*, *14*, 26–37.
- Dubos, J. R. (1965). *Man Adapting*. New Haven: Yale University Press.
- Flores, G. E., Caporaso, J. G., Henley, J. B., Rideout, J. R., Domogala, D., Chase, J., et al. (2014). Temporal variability is a personalized feature of the human microbiome. *Genome Biology*, *15*, 531.
- Foster, J. A., Rinaman, L., & Cryan, J. F. (2017). Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiology of Stress*, *7*, 124–136.
- Goodrich, J. K., Waters, J. L., Poole, A. C., Sutter, J. L., Koren, O., Blekhan, R., et al. (2014). Human genetics shape the gut microbiome. *Cell*, *159*, 789–799.
- Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, *30*, 1181–1197.
- Jin, Y., Wu, S., Zeng, Z., & Fu, Z. (2017). Effects of environmental pollutants on gut microbiota. *Environmental Pollution*, *222*, 1–9.
- Johnson, E. L., Heaver, S. L., Walters, W. A., & Ley, R. E. (2017). Microbiome and metabolic disease: Revisiting the bacterial phylum Bacteroidetes. *Journal of Molecular Medicine*, *95*, 1–8.
- Juge, N. (2012). Microbial adhesins to gastrointestinal mucus. *Trends in Microbiology*, *20*, 30–39.
- Jung, C., Hugot, J. P., & Barreau, F. (2010). Peyer's patches: The immune sensors of the intestine. *International Journal of Inflammation*, *2010*.
- Kamada, N., Chen, G. Y., Inohara, N., & Núñez, G. (2013). Control of pathogens and pathobionts by the gut microbiota. *Nature Immunology*, *14*, 685.
- Kane, J. F. (1995). Effects of rare codon clusters on high-level expression of heterologous proteins in *Escherichia coli*. *Current Opinion in Biotechnology*, *6*, 494–500.
- Kang, S. S., Jeraldo, P. R., Kurti, A., Miller, M. E. B., Cook, M. D., Whitlock, K., et al. (2014). Diet and exercise orthogonally alter the gut microbiome and reveal independent associations with anxiety and cognition. *Molecular Neurodegeneration*, *9*, 36.
- Kelly, J. R., Kennedy, P. J., Cryan, J. F., Dinan, T. G., Clarke, G., & Hyland, N. P. (2015). Breaking down the barriers: The gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Frontiers in Cellular Neuroscience*, *9*, 392.
- Khan, W. I., & Ghia, J. E. (2010). Gut hormones: Emerging role in immune activation and inflammation. *Clinical and Experimental Immunology*, *161*(1), 19–27.
- Koenig, J. E., Spor, A., Scalfone, N., Fricker, A. D., Stombaugh, J., Knight, R., et al. (2011). Succession of microbial consortia in the developing infant gut microbiome. *Proceedings of the National Academy of Sciences*, *108*, 4578–4585.
- Koh, J. H., & Kim, W. U. (2017). Dysregulation of gut microbiota and chronic inflammatory disease: From epithelial defense to host immunity. *Experimental & Molecular Medicine*,

- 49, e337. Lee, Y. K., Lim, C. Y., Teng, W. L., Ouwehand, A. C., Tuomola, E. M., & Salminen, S. (2000). Quantitative approach in the study of adhesion of lactic acid bacteria to intestinal cells and their competition with enterobacteria. *Applied and Environmental Microbiology*, 66, 3692–3697.
- Li, Z., Quan, G., Jiang, X., Yang, Y., Ding, X., Zhang, D., et al. (2018). Effects of metabolites derived from gut microbiota and hosts on pathogens. *Frontiers in Cellular and Infection Microbiology*, 8.
- Lobanovska, M., & Pilla, G. (2017). Penicillin's discovery and antibiotic resistance: Lessons for the future? *The Yale Journal of Biology and Medicine*, 90, 135–145.
- Lozupone, C. A., Stombaugh, J. I., Gordon, J. I., Jansson, J. K., & Knight, R. (2012). Diversity, stability and resilience of the human gut microbiota. *Nature*, 489, 220.
- Matsuoka, K., & Kanai, T. (2015). The gut microbiota and inflammatory bowel disease. *Seminars in Immunopathology*, 37, 47–55.
- Mawdsley, J. E., & Rampton, D. S. (2005). Psychological stress in IBD: New insights into pathogenic and therapeutic implications. *Gut*, 54, 1481–1491.
- Monda, V., Villano, I., Messina, A., Valenzano, A., Esposito, T., Moscatelli, F., et al. (2017). Exercise modifies the gut microbiota with positive health effects. *Oxidative Medicine and Cellular Longevity*, 2017.
- Nagpal, R., Mainali, R., Ahmadi, S., Wang, S., Singh, R., Kavanagh, K., et al. (2018). Gut microbiome and aging: Physiological and mechanistic insights. *Nutrition and Healthy Aging*, 4, 267–285.
- Odamaki, T., Kato, K., Sugahara, H., Hashikura, N., Takahashi, S., Xiao, J. Z., et al. (2016). Age-related changes in gut microbiota composition from newborn to centenarian: A cross-sectional study. *BMC Microbiology*, 16, 90.
- Ogawa, H., Fukushima, K., Naito, H., Funayama, Y., Unno, M., Takahashi, K. I., et al. (2003). Increased expression of HIP/PAP and regenerating gene III in human inflammatory bowel disease and a murine bacterial reconstitution model. *Inflammatory Bowel Diseases*, 9, 162–170.
- Okumura, R., & Takeda, K. (2017). Roles of intestinal epithelial cells in the maintenance of gut homeostasis. *Experimental & Molecular Medicine*, 49, e338.
- Olle, B. (2013). Medicines from microbiota. *Nature Biotechnology*, 309–315.
- Pacheco, A. R., & Sperandio, V. (2015). Enteric pathogens exploit the microbiota-generated nutritional environment of the gut. *Microbiology Spectrum*, 3.
- Padungtod, P., & Kaneene, J. B. (2005). Campylobacter in food animals and humans in northern Thailand. *Journal of Food Protection*, 68, 2519–2526.
- Petritz, B. A., Castro, A. P., Almeida, J. A., Gomes, C. P., Fernandes, G. R., Kruger, R. H., et al. (2014). Exercise induction of gut microbiota modifications in obese, non-obese and hypertensive rats. *BMC Genomics*, 15, 511.
- Putignani, L., Del Chierico, F., Petrucca, A., Vernocchi, P., & Dallapiccola, B. (2014). The human gut microbiota: A dynamic interplay with the host from birth to senescence settled during childhood. *Pediatric Research*, 76, 2.
- Quianzon, C. C., & Cheikh, I. (2012). History of insulin. *Journal of Community Hospital Internal Medicine Perspectives*, 2.
- Raetz, C. R., & Whitfield, C. (2002). Lipopolysaccharide endotoxins. *Annual Review of Biochemistry*, 71, 635–700.
- Rodríguez, J. M., Murphy, K., Stanton, C., Ross, R. P., Kober, O. I., Juge, N., et al. (2015). The composition of the gut microbiota throughout life, with an emphasis on early life. *Microbial Ecology in Health and Disease*, 26, 26050.
- Rolhion, N., & Chassaing, B. (2016). When pathogenic bacteria meet the intestinal microbiota. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 371.
- Rothschild, D., Weissbrod, O., Barkan, E., Kurilshikov, A., Korem, T., Zeevi, D., et al. (2018).

- Environment dominates over host genetics in shaping human gut microbiota. *Nature*, 555, 210. Salonen, A., & de Vos, W. (2014). Impact of diet on human intestinal microbiota and health. *Annual Review of Food Science and Technology*, 5, 239–262.
- Segev, G., Sykes, J. E., Klumpp, D. J., Schaeffer, A. J., Antaki, E. M., Byrne, B. A., Yaggie, R. E., & Westropp, J. L. (2018). Evaluation of the live biotherapeutic product, asymptomatic bacteriuria *Escherichia coli* 2-12, in healthy dogs and dogs with clinical recurrent UTI. *Journal of Veterinary Internal Medicine*, 32, 267–273.
- Sharon, N. (1987). Bacterial lectins, cell-cell recognition and infectious disease. *FEBS Letters*, 217, 145–157.
- Shin, N. R., Whon, T. W., & Bae, J. W. (2015). Proteobacteria: Microbial signature of dysbiosis in gut microbiota. *Trends in Biotechnology*, 33, 496–503.
- Shreiner, A. B., Kao, J. Y., & Young, V. B. (2015). The gut microbiome in health and in disease. *Current Opinion in Gastroenterology*, 31, 69.
- Singh, P., Teal, T. K., Marsh, T. L., Tiedje, J. M., Mosci, R., Jernigan, K., Zell, A., Newton, D. W., Salimnia, H., Lephart, P., Sundin, D., Khalife, W., Britton, R. A., Rudrik, J. T., et al. (2015). Intestinal microbial communities associated with acute enteric infections and disease recovery. *Microbiome*, 3, 45.
- Singh, R. K., Chang, H. W., Yan, D., Lee, K. M., Ucmak, D., Wong, K., et al. (2017). Influence of diet on the gut microbiome and implications for human health. *Journal of Translational Medicine*, 15, 73.
- Stecher, B. (2015). The roles of inflammation, nutrient availability and the commensal microbiota in enteric pathogen infection. *Metabolism and Bacterial Pathogenesis*, 297–320.
- Takeda, K., & Akira, S. (2005). Toll-like receptors in innate immunity. *International Immunology*, 17, 1–14.
- Tasnim, N., Abulizi, N., Pither, J., Hart, M. M., & Gibson, D. L. (2017). Linking the gut microbial ecosystem with the environment: Does gut health depend on where we live? *Frontiers in Microbiology*, 8, 1935.
- Vinolo, M. A., Rodrigues, H. G., Nachbar, R. T., & Curi, R. (2011). Regulation of inflammation by short chain fatty acids. *Nutrients*, 3, 858–876.
- Xu, Z. R., et al. (2003). Effects of dietary fructooligosaccharide on digestive enzyme activities, intestinal microflora and morphology of male broilers. *Poultry Science*, 82(6), 1030–1036.
- Yatsunenko, T., Rey, F. E., Manary, M. J., Trehan, I., Dominguez-Bello, M. G., Contreras, M., et al. (2012). Human gut microbiome viewed across age and geography. *Nature*, 486, 222.
- Zhou, D., Pan, Q., Shen, F., Cao, H. X., Ding, W. J., Chen, Y. W., & Fan, J. G. (2017). Total fecal microbiota transplantation alleviates high-fat diet-induced steatohepatitis in mice via beneficial regulation of gut microbiota. *Scientific Reports*, 7, 1529.

# Obezite ve Kilo Kaybında Antibiyotik Tedavisi ve Bağırsak Mikrobiyomu Üzerine Etkisi

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## 1. Giriş

Gastrointestinal hastalıkların sayısındaki artış, Amerika Birleşik Devletleri'nde ciddi bir sorun haline gelmiştir. Milyonlarca insana Crohn hastalığı, inflamatuvar bağırsak sendromu (IBS), ülseratif kolit ve diğer gastrointestinal sorunlar teşhisi konmaktadır (Kappelman ve ark. 2012; Locke III ve ark. 2004). Bu bozuklukların tümü, gastrointestinal sistemde bulunan mikropların dengesizliği ile ilişkilendirilmiştir. Bağırsak disbiyozu diğer olumsuz etkilere neden olabilir ve obezite de dahil olmak üzere çeşitli sağlık sorunlarına neden olabilir. Çocuklarda ve yetişkinlerde obezite son yıllarda önemli ölçüde artmıştır. Aşırı antibiyotik kullanımı ve Batı tarzı diyet, Amerika Birleşik Devletleri'nde obezite artışının temel nedenleri arasında görülmektedir. Sentetik antibiyotiklerin keşfi tıpta bir dönüm noktası olarak kabul edilebilir. İnsanlar için ölümcül olduğu düşünülen enfeksiyonlar ve salgınlarla savaşarak yaşam beklentisini büyük ölçüde arttırmıştır. Belirli hastalıkları tedavi etmek veya hastalarda birçok hastalığın kontrolüne yardımcı olmak için farklı kategorilerdeki antibiyotikler kullanılır. Enfeksiyonu tedavi etmedeki etkinlikleri nedeniyle, dünya çapındaki popülasyonlar birçok tıbbi komplikasyon için antibiyotiklere güvenmiştir. Hastalara her yıl artan bir oranda antibiyotik reçete edilmektedir, Hastalık Kontrol ve Önleme Merkezleri (CDC), 2016 yılında yalnızca Amerika Birleşik Devletleri'nde 270,2 milyon antibiyotiğin satıldığını belirtmiştir (CDC 2017; Durkin ve ark. 2018). Bununla birlikte, bu uzun süreli antibiyotik kullanımının antibiyotik direncini ve bağırsak mikrobiyotasının dengesizliğini de içeren bazı sonuçları vardır. Gelişmiş ülkelerdeki çoğu insan, enfeksiyonları tedavi etmek için antibiyotiklere baş vurarak daha fazla bağımlı hale gelmektedir. Bu durum, bazı bakteriyel enfeksiyonlarda başarılı olabilese de, antibiyotiklerin kısa ve uzun vadeli aşırı ve yanlış kullanımı kronik sonuçlara yol açabilir (Pichichero 1999; McGowan Jr 1983). Bu inceleme, antibiyotik tedavisi kavramını ve antibiyotik direncinin yanı sıra bağırsak mikrobiyomu üzerindeki etkisini açıklamayı amaçlamaktadır. Bu bölümde; bağırsak disbiyozu, obezite ve diğer mide-bağırsak hastalıkları tanımlanacak ve aynı zamanda enfeksiyonların sentetik antibiyotikler kullanılmadan tedavi edilmesi için alternatif yöntemler de gösterilecektir.

## Kaynaklar

- Adedeji, W. A. (2016). The treasure called antibiotics. *Annals of Ibadan Postgraduate Medicine*, 14(2), 56.
- Allen, N. E., & Nicas, T. I. (2003). Mechanism of action of oritavancin and related glyco-peptide antibiotics. *FEMS Microbiology Reviews*, 26(5), 511–532. <https://doi.org/10.1111/j.1574-6976.2003.tb00628.x>.
- Andrade, M. J., Jayaprakash, C., Bhat, S., Evangelatos, N., Brand, A., & Satyamoorthy, K. (2017). Antibiotics-induced obesity: A mitochondrial perspective. *Public Health Genomics*, 20(5), 257–273. <https://doi.org/10.1159/000485095>.
- Arslan, E., Atılğan, H., & Yavaşoğlu, İ. (2009). The prevalence of *Helicobacter pylori* in obese subjects. *European Journal of Internal Medicine*, 20(7), 695–697.
- Azad, M. B., Bridgman, S. L., Becker, A. B., & Kozyrskyj, A. L. (2014). Infant antibiotic exposure and the development of childhood overweight and central adiposity. *International Journal of Obesity*, 38(10), 1290.
- Azuma, T., Suto, H., Ito, Y., Ohtani, M., Dojo, M., Kuriyama, M., & Kato, T. (2001). Gastric leptin and *Helicobacter pylori*infection. *Gut*, 49(3), 324–329.
- Bäckhed, F., Ding, H., Wang, T., Hooper, L. V., Koh, G. Y., Nagy, A., et al. (2004). The gut microbiota as an environmental factor that regulates fat storage. *Proceedings of the National Academy of Sciences*, 101(44), 15718–15723. <https://doi.org/10.1073/pnas.0407076101>.
- Bäckhed, F., Ley, R. E., Sonnenburg, J. L., Peterson, D. A., & Gordon, J. I. (2005). Host bacterial mutualism in the human intestine. *Science*, 307(5717), 1915–1920. <https://doi.org/10.1126/science.1104816>.
- Belizário, J. E., & Faintuch, J. (2018). Microbiome and gut dysbiosis. *Experientia Supplementum Metabolic Interaction in Infection*, 459–476. [https://doi.org/10.1007/978-3-319-74932-7\\_13](https://doi.org/10.1007/978-3-319-74932-7_13).
- Belkaid, Y., & Hand, T. W. (2014). Role of the microbiota in immunity and inflammation. *Cell*, 157(1), 121–141.
- Blair, J. M., Richmond, G. E., & Piddock, L. J. (2014). Multidrug efflux pumps in Gram-negative bacteria and their role in antibiotic resistance. *Future Microbiology*, 9(10), 1165–1117. <https://doi.org/10.2217/fmb.14.66>.
- Blaser, M. J. (1997). Ecology of *Helicobacter pylori* in the human stomach. *The Journal of Clinical Investigation*, 100(4), 759–762.
- Block, J. P., Bailey, L. C., Gillman, M. W., Lunsford, D., Daley, M. F., Eneli, I., et al. (2018). Early antibiotic exposure and weight outcomes in young children. *Pediatrics*, 142(6). Retrieved from: <http://pediatrics.aappublications.org/content/142/6/e20180290.long#ref-3>.
- Bodinhm, C. L., Smith, L., Wright, J., Frost, G. S., & Robertson, M. D. (2012). Dietary fibre improves first-phase insulin secretion in overweight individuals. *PLoS One*, 7(7), e40834. <https://doi.org/10.1371/journal.pone.0040834>.
- Bonder, M. J., Kurilshikov, A., Tigchelaar, E. F., Mujagic, Z., Imhann, F., Vila, A. V., et al. (2016). The effect of host genetics on the gut microbiome. *Nature Genetics*, 48(11), 1407–1412.
- Bozdogan, B., & Appelbaum, P. C. (2004). Oxazolidinones: activity, mode of action, and mechanism of resistance. *International Journal of Antimicrobial Agents*, 23(2), 113–119. <https://doi.org/10.1016/j.ijantimicag.2003.11.003>.
- Champney, W. S., & Miller, M. (2002). Linezolid is a specific inhibitor of 50S ribosomal sub-unit formation in *Staphylococcus aureus* cells. *Current Microbiology*, 44, 350–356. <https://doi.org/10.1007/s00284-001-0023-7>.
- Cherayil, B. J. (2011). The role of iron in the immune response to bacterial infection. *Immunologic Research*, 50(1), 1–9. <https://doi.org/10.1007/s12026-010-8199-1>.
- Chopra, I., Hawkey, P. M., & Hinton, M. (1992). Tetracyclines, molecular and clinical aspects. *Journal of Antimicrobial Chemotherapy*, 29(3), 245–277. <https://doi.org/10.1093/>

- jac/29.3.245.
- Conlon, M. A., & Bird, A. R. (2015). The impact of diet and lifestyle on gut microbiota and human health. *Nutrients*, 7, 17–44.
- Centers for Disease Control and Prevention and Centers for Disease Control and Prevention (2017). Outpatient antibiotic prescriptions—United States, 2014. *Dentistry*, 24, p. 203.
- Davies, J., & Davies, D. (2010). Origins and evolution of antibiotic resistance. *American Society for Microbiology Journals*, 74(3), 417–433. <https://doi.org/10.1128/MMBR.00016-10>.
- Dinos, G. P., Athanassopoulos, C. M., Missiri, D. A., Giannopoulou, P. C., Vlachogiannis, I. A., Papadopoulos, G. E., & Papaioannou, D. (2016). Chloramphenicol derivatives as antibacterial and anticancer agents: Historic problems and current solutions. *Antibiotics*, 5(2), 20. <https://doi.org/10.3390/antibiotics5020020>.
- Durkin, M. J., Jafarzadeh, S. R., Hsueh, K., Sallah, Y. H., Munshi, K. D., Henderson, R. R., & Fraser, V. J. (2018). Outpatient antibiotic prescription trends in the United States: A national cohort study. *Infection Control & Hospital Epidemiology*, 39(5), 584–589.
- Fabrega, A., Madurga, S., Giralt, E., & Vila, J. (2008). Mechanism of action of and resistance to quinolones. *Microbial Technology*, 2(1), 40–61. <https://doi.org/10.1111/j.1751-7915.2008.00063.x>.
- Foti, J. J., Devadoss, B., Winkler, J. A., Collins, J. J., & Walker, G. C. (2012). Oxidation of the guanine nucleotide pool underlies cell death by bactericidal antibiotics. *Science*, 336(6079), 315–319. <https://doi.org/10.1126/science.1219192>.
- Francino, M. P. (2016). Antibiotics and the human gut microbiome: Dysbioses and accumulation of resistances. *Frontiers Microbiology*. <https://doi.org/10.3389/fmicb.2015.01543>.
- Fyfe, C., Grossman, T. H., Kerstein, K., & Sutcliffe, J. (2016). Resistance to macrolide antibiotics in public health pathogens. *Cold Spring Harbor Perspective in Medicine*, 6(10). <https://doi.org/10.1101/cshperspect.a025395>.
- Gad El-Hak, H. N., Moustafa, A. A., & Mansour, S. R. (2018). The gut microbiome - implications for human disease. *Advanced Research in Gastroenterology and Hepatology*, 10(3). <https://doi.org/10.5772/61423>.
- Gagliardi, A., Totino, V., Cacciotti, F., Iebba, V., Neroni, B., Bonfiglio, G., et al. (2018). Rebuilding the gut microbiota ecosystem. *International Journal of Environmental Research and Public Health*, 15(8), 1679.
- Garneau-Tsodikova, S., & Labby, K. (2015). Mechanisms of resistance to aminoglycoside antibiotics: Overview and perspectives. *Medchemcomm*, 7(1), 11–27. <https://doi.org/10.1039/C5MD00344J>.
- Hancock, R. E. (2005). Mechanisms of action of newer antibiotics for Gram-positive pathogens. *The Lancet Infectious Diseases*, 5(4), 209–218. [https://doi.org/10.1016/S1473-3099\(05\)70051-7](https://doi.org/10.1016/S1473-3099(05)70051-7).
- Hayashi, M., Bizerra, F., & Da Silva, P. (2013). Antimicrobial compounds from natural sources. *Frontiers in Microbiology*, 4, 195. <https://doi.org/10.3389/fmicb.2013.00195>.
- Heesemann, J. (1993). Mechanisms of resistance to beta-lactam antibiotics. *Infection*, 21(1), 4–9. <https://doi.org/10.1007/BF01710336>.
- Henson, M. A., & Phalak, P. (2017). Microbiota dysbiosis in inflammatory bowel diseases: in silico investigation of the oxygen hypothesis. *BMC Systems Biology*, 11(1), 145. <https://doi.org/10.1186/s12918-017-0522-1>.
- Iwu, M. M., Duncan, A. R., Okunji, C. O. (1999). New antimicrobials of plant origin. Perspectives on new crops and new uses. 457–462. <https://hort.purdue.edu/newcrop/proceedings1999/pdf/v4-457.pdf>.
- Jacoby, G. A. (2005). Mechanisms of resistance to quinolones. *Clinical Infectious Diseases*, 41(2), S120–S126. <https://doi.org/10.1086/428052>.
- Jakobsson, H. E., Jernberg, C., Andersson, A. F., Sjölund-Karlsson, M., Jansson, J. K., & Engstrand,

- L. (2010). Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. *PLoS One*, 5(3), e9836.
- Jenkinson, H. F., & Douglas, L. J. (2002). Interactions between *Candida* species and bacteria in mixed infections. <https://www.ncbi.nlm.nih.gov/books/NBK2486/>.
- Jernberg, C., Lofmark, S., Edlund, C., & Jansson, J. K. (2007). Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. *The ISME Journal*, 1(1), 56–66. <https://doi.org/10.1038/ismej.2007.3>.
- Kanoh, S., & Rubin, B. (2010a). The mechanism of action of aminoglycosides. *Clinical Microbial Reviews*, 23(3), 590–615. <https://doi.org/10.1128/CMR.00078-09>.
- Kanoh, S., & Rubin, B. K. (2010b). Mechanisms of action and clinical application of macrolides as immunomodulatory medications. *Clinical Microbiology Reviews*, 23(3), 590–615. <https://doi.org/10.1128/CMR.00078-09>.
- Kappelman, M. D., Moore, K. R., Allen, J. K., & Cook, S. F. (2012). Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. *Digestive Diseases and Sciences*, 58(2), 519–525. <https://doi.org/10.1007/s10620-012-2371-5>.
- Kohanski, M. A., Dawyer, D. J., Hayete, B., Lawrence, C. A., & Collins, J. J. (2007). A common mechanism of cellular death induced by bactericidal antibiotics. *Cell*, 130(5), 797–810. <https://doi.org/10.1016/j.cell.2007.06.049>.
- Kohanski, M. A., Dawyer, D. J., & Collins, J. J. (2010a). How antibiotics kill bacteria: from targets to networks. *Nature Reviews Microbiology*, 8(6), 423–435. <https://doi.org/10.1038/nrmicro2333>.
- Kohanski, M. A., DePristo, M. A., & Collins, J. J. (2010b). Sublethal antibiotic treatment leads to multidrug resistance via radical-induced mutagenesis. *Molecular Cell*, 37(2), 311–320. <https://doi.org/10.1016/j.molcel.2010.01.003>.
- Koskinen, K., Pausan, M. R., Perras, A. K., Beck, M., Bang, C., Mora, M., et al. (2017). First insights into the diverse human archaeome: specific detection of archaea in the gastrointestinal tract, lung, and nose and on skin. *MBio*, 8(6), e00824–e00817.
- Kotra, L., Haddad, J., & Mobashery, S. (2000). Aminoglycosides: Perspectives on mechanisms of action and resistance and strategies to counter resistance. *Antimicrobial Agents and Chemotherapy*, 44(12), 3249–3256. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC90188/>.
- Kourkouta, L., Kotsifopoulos, C. H., Papageorgiou, M., Iliadis, C. D., & Monios, A. (2017). The rational use of antibiotic medicine. *Journal of Healthcare Communications*. <https://doi.org/10.4172/2472-1654.100076>.
- Krulwich, T. A., Sachs, G., & Padan, E. (2011). Molecular aspects of bacterial pH sensing and homeostasis. *Nature Reviews Microbiology*, 9(5), 330–343. <https://doi.org/10.1038/nrmicro2549>.
- Kümmerer, K. (2009). Antibiotics in the aquatic environment – A review – Part I. *Chemosphere*, 75(4), 417–434. <https://doi.org/10.1016/j.chemosphere.2008.11.086>.
- Langdon, A., Crook, N., & Dantas, G. (2016). The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Genome Medicine*, 8(1), 39. Retrieved from: <https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-016-0294-z>.
- Lange, K., Buerger, M., Stallmach, A., & Bruns, T. (2016). Effects of antibiotics on gut microbiota. *Digestive Diseases*, 34(3), 260–268.
- Leclercq, R., & Courvalin, P. (1998). Streptogramins: An answer to antibiotic resistance in gram-positive bacteria. *The Lancet*, 352(9128), 591–592. [https://doi.org/10.1016/S0140-6736\(05\)79570-2](https://doi.org/10.1016/S0140-6736(05)79570-2).
- Leekha, S., Terrell, C. L., & Edson, R. S. (2011). General principles of antimicrobial therapy. *Mayo Clinic Proceedings*, 86(2), 156–167. <https://doi.org/10.4065/mcp.2010.0639>.
- Ley, R. E., Bäckhard, F., Lozupone, C. A., Knight, R. D., & Gordon, J. I. (2005). Obesity alters gut

- microbial ecology. *PNAS*, 102(31), 11070–11075. <https://doi.org/10.1073/pnas.0504978102>.
- Locke, G. R., III, Yawn, B. P., Wollan, P. C., Melton, L. J., III, Lydick, E., & Talley, N. J. (2004). Incidence of a clinical diagnosis of the irritable bowel syndrome in a United States population. *Alimentary Pharmacology & Therapeutics*, 19(9), 1025–1031.
- Manichanh, C., Rigottier-Gois, L., Bonnaud, E., Gloux, K., Pelletier, E., Frangeul, L., et al. (2006). Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. *Gut*, 55(2), 205–211. <https://gut.bmj.com/content/55/2/205.short>.
- Marnila, P., & Korhonen, H. (2009). Lactoferrin for human health. Dairy-derived ingredients. *Food and Nutraceutical Uses*, 290–307. <https://doi.org/10.1533/9781845697198.2.290>.
- Martin, A. M., Sun, E. W., Rogers, G. B., & Keating, D. J. (2019). The influence of the gut microbiome on host metabolism through the regulation of gut hormone release. *Frontiers in Physiology*, 10, 428.
- Masson, P. L., Heremans, J. F., & Schonke, E. (1969). Lactoferrin, an iron-binding protein in neutrophilic leukocyte. *Journal of Experimental Medicine*, 130(3), 643–658. <https://doi.org/10.1084/jem.130.3.643>.
- McGowan, J. E., Jr. (1983). Antimicrobial resistance in hospital organisms and its relation to anti-biotic use. *Reviews of Infectious Diseases*, 5(6), 1033–1048.
- Mishra, S. (2013). Is *Helicobacter pylori* good or bad? *European Journal of Clinical Microbiology & Infectious Diseases*, 32(3), 301–304. <https://doi.org/10.1007/s10096-012-1773-9>.
- Monteagudo-chu, M. O., & Shaeshaa, N. (2017). Duration of antibiotic therapy: General principles. <https://www.pharmacytimes.com/publications/health-system-edition/2017/july2017/duration-of-antibiotic-therapy-general-principles>
- Munita, J. M., & Arias, C. A. (2016). Mechanisms of antibiotic resistance. *Microbiology Spectrum*, 4(2). <https://doi.org/10.1128/microbiolspec.VMBF-0016-2015>.
- Ni Lochlainn, M., Bowyer, R. C., & Steves, C. J. (2018). Dietary protein and muscle in aging people: the potential role of the gut microbiome. *Nutrients*, 10(7), 929.
- Panda, S., El khader, I., Casellas, F., López Vivancos, J., García Cors, M., Santiago, A., et al. (2014). Short-term effect of antibiotics on human gut microbiota. *PLoS One*, 9, e95476.
- Pankey, G. A., & Sabath, L. D. (2004). Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of gram-positive bacterial infections. *Clinical Infectious Diseases*, 38(6), 870–864. <https://doi.org/10.1086/381972>.
- Parrow, N. L., Fleming, R. E., & Minnick, M. F. (2013). Sequestration and scavenging of iron in infection. *Infection and Immunity*, 81(10), 3503–3514. <https://doi.org/10.1128/IAI.00602-13>.
- Pecheré, J. C. (2001). Patients' interviews and misuse of antibiotics. *Clinical Infectious Diseases*, 33(3), 5170–5173.
- Petersen, C., & Round, J. L. (2014). Defining dysbiosis and its influence on host immunity and disease. *Cellular Microbiology*, 16(7), 1024–1033. <https://doi.org/10.1111/cmi.12308>.
- Pew. (2019). Tracking the global pipeline of antibiotics in development. The Pew Charitable Trust.
- Pichichero, M. E. (1999). Understanding antibiotic overuse for respiratory tract infections in children. *Pediatrics*, 104(6), 1384–1388.
- Rigottier-Gois, L. (2013). Dysbiosis in inflammatory bowel diseases: the oxygen hypothesis. *The ISME Journal*, 7(7), 1256–1261. <https://doi.org/10.1038/ismej.2013.80>.
- Rosa, L., Cutone, A., Lepanto, M. S., Paesano, R., & Valenti, P. (2017). Lactoferrin: A natural glycoprotein involved in iron and inflammatory homeostasis. *International Journal of Molecular Sciences*, 18(9), 1985. <https://doi.org/10.3390/ijms18091985>.
- Shao, X., Ding, X., Wang, B., Li, L., An, X., Yao, Q., Song, R., & Zhang, J. (2018). Antibiotic exposure in early life increases risk of childhood obesity: A systematic review and meta-analysis. In *Yearbook of pediatric endocrinology*. <https://doi.org/10.1530/ey.15.15.4>.
- Speer, B. S., Shoemaker, N. B., & Salyers, A. A. (1992). Bacterial resistance to tetracycline: mechanisms, transfer, and clinical significance. *Clinical Microbiology Reviews*, 5(4), 387–399.

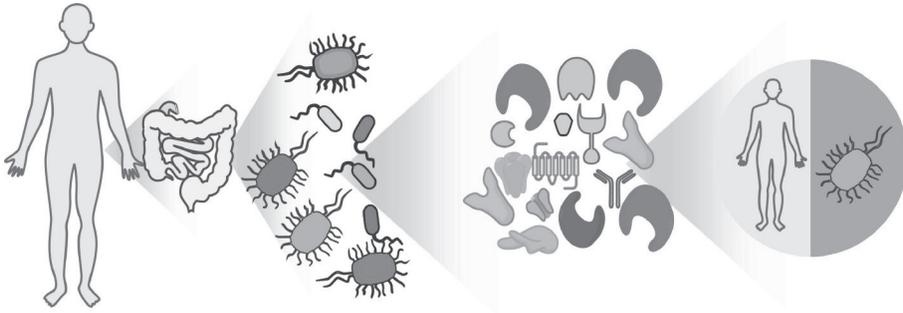
- Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC358256/?page=1>.
- Steenbergen, J. N., Alder, J., Thorne, G. M., & Tally, F. P. (2005). Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections. *Journal of Antimicrobial Chemotherapy*, 55(3), 283–288. <https://doi.org/10.1093/jac/dkh546>.
- Tačić, A., Nikolić, V., Nikolić, L., & Savić, I. (2017). Antimicrobial sulfonamides drugs. *Advanced Technologies*, 6(1), 58–71. Retrieved from <http://www.tf.ni.ac.rs/casopis-arhiva/sveska6vol1/c8.pdf>.
- Theriot, C. M., Koenigsnecht, M. J., Carlson, P. E., Jr., Hatton, G. E., Nelson, A. M., Li, B., et al. (2014). Antibiotic-induced shifts in the mouse gut microbiome and metabolome increase susceptibility to *Clostridium difficile* infection. *Nature Communications*, 5, 3114.
- Thorne, G. M., & Alder, J. (2002). Daptomycin: A novel lipopeptide antibiotic. *Clinical Microbiology Newsletter*, 24(5), 33–40. [https://doi.org/10.1016/S0196-4399\(02\)80007-1](https://doi.org/10.1016/S0196-4399(02)80007-1).
- Turnbaugh, P. J., Ley, R., Mahowald, M. A., Magrini, V., Mardis, E. R., & Gordon, J. I. (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*, 444, 1027–1031. <https://www.nature.com/articles/nature05414>.
- Turnbaugh, P. J., Hamady, M., Yatsunencko, T., Cantarel, B. L., Duncan, A., Ley, R. E., et al. (2009). A core gut microbiome in obese and lean twins. *Nature*, 457(7228), 480.
- Turta, O., & Rautava, S. (2016). Antibiotics, obesity and the link to microbes - what are we doing to our children? *BMC Medicine*, 14, 57. <https://doi.org/10.1186/s12916-016-0605-7>.
- Vael, C., Verhulst, S. L., Nelen, V., Goossens, H., & Desager, K. N. (2011). Intestinal microflora and body mass index during the first three years of life: an observational study. *Gut Pathogens*, 3(1), 8.
- Valenti, P., & Antonini, G. (2005). Lactoferrin. *Cellular and Molecular Life Sciences*, 62(22), 2576. <https://doi.org/10.1007/s00018-005-5372-0>.
- Van Boeckel, T. P., Gandra, S., Ashok, A., Caudron, Q., Grenfell, B. T., Levin, S. A., & Laxminarayan, R. (2014). Global antibiotic consumption 2000 to 2010: An analysis of national pharmaceutical sales data. *The Lancet Infectious Diseases*, 14(8), 742–750. [https://doi.org/10.1016/S1473-3099\(14\)70780-7](https://doi.org/10.1016/S1473-3099(14)70780-7).
- Vangay, P., Ward, T., Gerber, J. S., & Knights, D. (2015). Antibiotics, pediatric dysbiosis, and disease. *Cell Host & Microbe*, 17(5), 553–564.
- Wehril, W. (1983). Rifampin: mechanisms of action and resistance. *Reviews of Infectious Diseases*, 5(3), 407–411. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/6356275>.
- Williamson, R., Collatz, E., & Gutmann, L. (1986). Mechanisms of action of beta-lactam antibiotics and mechanisms of non-enzymatic resistance. *Presse Médicale*, 15(46). Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/2949269>.
- Windey, K., De Preter, V., & Verbeke, K. (2012). Relevance of protein fermentation to gut health. *Molecular Nutrition & Food Research*, 56(1), 184–196. <https://doi.org/10.1002/mnfr.201100542>.
- Xiong, W., Abraham, P. E., Li, Z., Pan, C., & Hettich, R. L. (2015). Microbial metaproteomics for characterizing the range of metabolic functions and activities of human gut microbiota. *Proteomics*, 15(20), 3424–3438.
- Yeung, E., Yong, E., & Wong, F. (2004). Renal dysfunction in cirrhosis: Diagnosis, treatment, and prevention. *Medscape General Medicine*, 6(4), 9. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1480573/>.

# Proteomik Arařtırmalarının Konak Baęırsak Mikrobiyotasına Etkisi

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## 1. Giriř

Mikroplar tm ekosistemlerde bulunur ve biyojeokimyasal dng ile insan saęlıęında nemli roller oynarlar. İnsan vcudu, vcudun farklı kısımlarını kolonize eden trilyonlarca mikrobun varlıęında iřlev grr. Ortalama bir insan vcudunda tahmini 37 trilyon hcre vardır ve mikrobiyomun biraz daha fazla hcreden oluřtuęu ve ortalama sayının 39 trilyon olduęu tahmin edilmektedir (Sender ve ark. 2016). İnsan baęırsaęının mikroplar tarafından kolonizasyonu, insan ve baęırsak mikrobiyotası arasındaki iliřkinin birlikte evriminin bir sonucudur (řekil 1). İnsan baęırsaęında bulunan mikroplar "baęırsak mikrobiyotası" ve bunlar tarafından ifade edilen genler veya proteinler "baęırsak mikrobiyomu" olarak adlandırılır (Turnbaugh ve ark.2006,2007). Genel olarak, bu tr iliřkiler simbiyotiktir ve baęırsak, mikrobiyal hcreler ile konakçı hcreler arasında dinamik bir etkileřim iin karmařık bir ortam saęlar (Moeller ve ark. 2016). Bu etkileřim, normal doęum sonrası geliřimden yetiřkin saęlıęına kadar insan fizyolojisinin birok ynn modle eder (Moeller ve dięerleri 2016; Gordo 2019).



**řekil 1.** İnsan baęırsaęı mikrobiyomu analizi tipik olarak, baęırsaktan izolatların (Tablo 1'de mukozal lmen ara yznn dıřkı malzemeleri) rneklenmesi yoluyla gerekleřtirilir. Ortaya ıkan protein izolatları, insan hcrelerinin yanı sıra karmařık bir bakteri topluluęundan elde edilir.

İnsan saęlıęı, baęırsakta yařayan mikropların bileřiminden olumlu veya olumsuz etkilenebilir (Mohajeri ve ark. 2018). Deęiřen baęırsak mikrobiyomları obezite, diya-

belirlemek için kritik adımlardır. Bu, doldurulması zor bir alandır ve büyük işbirlikçi çabalar gerektirecektir. Peptitlerin tandem MS spektral kütüphanelerini oluşturmak ve kullanmak için çabalara ihtiyaç vardır. Ayrıca protein ekstraksiyonu, LC-MS numune hazırlama, depolama ve LC-MS verilerinin biyoinformatik analizi de dahil olmak üzere bağırsak mikrobiyolojik analizi için proteomik iş akışını standartlaştırmaya ihtiyaç vardır. Mikrobiyom alanında proteomik uygulamaların çoğaldığına dair şüphe yoktur, ancak bu tekniğin potansiyel faydalarını tam olarak gerçekleştirmek için ele alınması gereken birçok zorluk vardır. Yüksek kaliteli ve kapsamlı bir spektral kütüphane veritabanı oluşturmak ve mevcut iş akışlarına tutarlı spektral kütüphane arama araçlarını eklemek, bu alanı ilerletmek için kritik öneme sahiptir. Bağırsak mikrobiyotası ve insan sağlığı arasındaki bağlantıya dair artan kanıtlarla birlikte, gelecekteki çalışmalar, bağırsak mikrobiyotası ve mikrobiyom temelli terapötiklerin geliştirilmesi hakkında işlevsel bilgiler sağlamak için sıralı genomların ve spektral kütüphane veritabanlarının artan kullanılabilirliği ile birlikte gelişmiş analitik ve hesaplama araçlarından tam olarak yararlanacaktır.

## Kaynaklar

- Altelaar, A. F., Munoz, J., & Heck, A. J. (2013). Next-generation proteomics: Towards an integrative view of proteome dynamics. *Nature Reviews Genetics*, *14*(1), 35–48.
- Anderson, N. L. (2018). Dynamics of clinically important proteins: Measuring turnover of drug targets and biomarkers. *Clinical Chemistry*, *64*(2), 247–248.
- Anderson, N. L., Ptolemy, A. S., & Rifai, N. (2013). The riddle of protein diagnostics: Future bleak or bright? *Clinical Chemistry*, *59*(1), 194–197.
- Angel, T. E., Luft, B. J., Yang, X., Nicora, C. D., Camp, D. G., 2nd, Jacobs, J. M., & Smith, R. D. (2010). Proteome analysis of *Borrelia burgdorferi* response to environmental change. *PLoS One*, *5*(11), e13800.
- Angel, T. E., Aryal, U. K., Hengel, S. M., Baker, E. S., Kelly, R. T., Robinson, E. W., & Smith, R. D. (2012a). Mass spectrometry-based proteomics: Existing capabilities and future directions. *Chemical Society Reviews*, *41*(10), 3912–3928.
- Angel, T. E., Jacobs, J. M., Smith, R. P., Pasternack, M. S., Elias, S., Gritsenko, M. A., Shukla, A., Gilmore, E. C., McCarthy, C., Camp, D. G., 2nd, Smith, R. D., & Warren, H. S. (2012b). Cerebrospinal fluid proteome of patients with acute Lyme disease. *Journal of Proteome Research*, *11*(10), 4814–4822.
- Impact of Gut Microbiota on Host by Exploring Proteomics Angel, T. E., Jacobs, J. M., Spudich, S. S., Gritsenko, M. A., Fuchs, D., Liegler, T., Zetterberg, H., Camp, D. G., 2nd, Price, R. W., & Smith, R. D. (2012c). The cerebrospinal fluid proteome in HIV infection: Change associated with disease severity. *Clinical Proteomics*, *9*(1), 3.
- Aryal, U. K., & Ross, A. R. (2010). Enrichment and analysis of phosphopeptides under different experimental conditions using titanium dioxide affinity chromatography and mass spectrometry. *Rapid Communications in Mass Spectrometry*, *24*(2), 219–231.
- Aryal, U. K., Olson, D. J., & Ross, A. R. (2008). Optimization of immobilized gallium (III) ion affinity chromatography for selective binding and recovery of phosphopeptides from protein digests. *Journal of Biomolecular Techniques*, *19*(5), 296–310.
- Aryal, U. K., Stockel, J., Krovvidi, R. K., Gritsenko, M. A., Monroe, M. E., Moore, R. J., Koppena-

- al, D. W., Smith, R. D., Pakrasi, H. B., & Jacobs, J. M. (2011). Dynamic proteomic profiling of a unicellular cyanobacterium *Cyanothece* ATCC51142 across light-dark diurnal cycles. *BMC Systems Biology*, 5, 194.
- Aryal, U. K., Stockel, J., Welsh, E. A., Gritsenko, M. A., Nicora, C. D., Koppelaar, D. W., Smith, R. D., Pakrasi, H. B., & Jacobs, J. M. (2012). Dynamic proteome analysis of *Cyanothece* sp. ATCC 51142 under constant light. *Journal of Proteome Research*, 11(2), 609–619.
- Aryal, U. K., Callister, S. J., Mishra, S., Zhang, X., Shutthanandan, J. I., Angel, T. E., Shukla, A. K., Monroe, M. E., Moore, R. J., Koppelaar, D. W., Smith, R. D., & Sherman, L. (2013). Proteome analyses of strains ATCC 51142 and PCC 7822 of the diazotrophic cyanobacterium *Cyanothece* sp. under culture conditions resulting in enhanced H<sub>2</sub> production. *Applied and Environmental Microbiology*, 79(4), 1070–1077.
- Aryal, U. K., Callister, S. J., McMahon, B. H., McCue, L. A., Brown, J., Stockel, J., Liberton, M., Mishra, S., Zhang, X., Nicora, C. D., Angel, T. E., Koppelaar, D. W., Smith, R. D., Pakrasi, H. B., & Sherman, L. A. (2014). Proteomic profiles of five strains of oxygenic photosynthetic cyanobacteria of the genus *Cyanothece*. *Journal of Proteome Research*, 13(7), 3262–3276.
- Aryal, U. K., McBride, Z., Chen, D., Xie, J., & Szymanski, D. B. (2017). Analysis of protein complexes in *Arabidopsis* leaves using size exclusion chromatography and label-free protein correlation profiling. *Journal of Proteomics*, 166, 8–18.
- Bache, N., Geyer, P. E., Bekker-Jensen, D. B., Hoerning, O., Falkenby, L., Treit, P. V., Doll, S., Paron, I., Muller, J. B., Meier, F., Olsen, J. V., Vorm, O., & Mann, M. (2018). A novel LC system embeds analytes in pre-formed gradients for rapid, ultra-robust proteomics. *Molecular & Cellular Proteomics*, 17(11), 2284–2296.
- Bantscheff, M., Eberhard, D., Abraham, Y., Bastuck, S., Boesche, M., Hobson, S., Mathieson, T., Perrin, J., Raida, M., Rau, C., Reader, V., Sweetman, G., Bauer, A., Bouwmeester, T., Hopf, C., Kruse, U., Neubauer, G., Ramsden, N., Rick, J., Kuster, B., & Drewes, G. (2007). Quantitative chemical proteomics reveals mechanisms of action of clinical ABL kinase inhibitors. *Nature Biotechnology*, 25(9), 1035–1044.
- Bercik, P., Denou, E., Collins, J., Jackson, W., Lu, J., Jury, J., Deng, Y., Blennerhassett, P., Macri, J., McCoy, K. D., Verdu, E. F., & Collins, S. M. (2011). The intestinal microbiota affect central levels of brain-derived neurotrophic factor and behavior in mice. *Gastroenterology*, 141(2), 599–609. e591–593.
- Berry, D., & Loy, A. (2018). Stable-isotope probing of human and animal microbiome function. *Trends in Microbiology*, 26(12), 999–1007.
- Blackburn, J. M., & Martens, L. (2016). The challenge of metaproteomic analysis in human samples. *Expert Review of Proteomics*, 13(2), 135–138.
- Blakeley-Ruiz, J. A., Erickson, A. R., Cantarel, B. L., Xiong, W., Adams, R., Jansson, J. K., Fraser, C. M., & Hettich, R. L. (2019). Metaproteomics reveals persistent and phylum-redundant metabolic functional stability in adult human gut microbiomes of Crohn's remission patients despite temporal variations in microbial taxa, genomes, and proteomes. *Microbiome*, 7(1), 18.
- Boersema, P. J., Raijmakers, R., Lemeer, S., Mohammed, S., & Heck, A. J. (2009). Multiplex peptide stable isotope dimethyl labeling for quantitative proteomics. *Nature Protocols*, 4(4), 484–494.
- Brooks, B., Mueller, R. S., Young, J. C., Morowitz, M. J., Hettich, R. L., & Banfield, J. F. (2015). Strain-resolved microbial community proteomics reveals simultaneous aerobic and anaerobic function during gastrointestinal tract colonization of a preterm infant. *Frontiers in Microbiology*, 6, 654.
- Brown, J. N., Ortiz, G. M., Angel, T. E., Jacobs, J. M., Gritsenko, M., Chan, E. Y., Purdy, D. E., Murnane, R. D., Larsen, K., Palermo, R. E., Shukla, A. K., Clauss, T. R., Katze, M. G., McCune, J. M., & Smith, R. D. (2012). Morphine produces immunosuppressive effects in nonhuman primates at the proteomic and cellular levels. *Molecular & Cellular Proteomics*,

- 11(9), 605–618.
- Buchanan, J. M. (2002). Biochemistry during the life and times of Hans Krebs and Fritz Lipmann. *The Journal of Biological Chemistry*, 277(37), 33531–33536.
- Busch, R., Neese, R. A., Awada, M., Hayes, G. M., & Hellerstein, M. K. (2007). Measurement of cell proliferation by heavy water labeling. *Nature Protocols*, 2(12), 3045–3057.
- Cantarel, B. L., Erickson, A. R., VerBerkmoes, N. C., Erickson, B. K., Carey, P. A., Pan, C., Shah, M., Mongodin, E. F., Jansson, J. K., Fraser-Liggett, C. M., & Hettich, R. L. (2011). Strategies for metagenomic-guided whole-community proteomics of complex microbial environments. *PLoS One*, 6(11), e27173.
- Carson, R. H., Lewis, C. R., Erickson, M. N., Zagieboylo, A. P., Naylor, B. C., Li, K. W., Farnsworth, P. B., & Price, J. C. (2017). Imaging regiospecific lipid turnover in mouse brain with desorption electrospray ionization mass spectrometry. *Journal of Lipid Research*, 58(9), 1884–1892.
- Clarke, G., Grenham, S., Scully, P., Fitzgerald, P., Moloney, R. D., Shanahan, F., Dinan, T. G., & Cryan, J. F. (2013). The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Molecular Psychiatry*, 18(6), 666–673.
- Claydon, A. J., & Beynon, R. (2012). Proteome dynamics: Revisiting turnover with a global perspective. *Molecular & Cellular Proteomics*, 11(12), 1551–1565.
- Crumeyrolle-Arias, M., Jaglin, M., Bruneau, A., Vancassel, S., Cardona, A., Dauge, V., Naudon, L., & Rabot, S. (2014). Absence of the gut microbiota enhances anxiety-like behavior and neuroendocrine response to acute stress in rats. *Psychoneuroendocrinology*, 42, 207–217.
- David, L. A., Maurice, C. F., Carmody, R. N., Gootenberg, D. B., Button, J. E., Wolfe, B. E., Ling, A. V., Devlin, A. S., Varma, Y., Fischbach, M. A., Biddinger, S. B., Dutton, R. J., & Turnbaugh, P. J. (2014). Diet rapidly and reproducibly alters the human gut microbiome. *Nature*, 505(7484), 559–563.
- Debyser, G., Mesuere, B., Clement, L., Van de Weygaert, J., Van Hecke, P., Duytschaever, G., Aerts, M., Dawyndt, P., De Boeck, K., Vandamme, P., & Devreese, B. (2016). Faecal proteomics: A tool to investigate dysbiosis and inflammation in patients with cystic fibrosis. *Journal of Cystic Fibrosis*, 15(2), 242–250.
- Decaris, M. L., Emson, C. L., Li, K., Gatmaitan, M., Luo, F., Cattin, J., Nakamura, C., Holmes, W. E., Angel, T. E., Peters, M. G., Turner, S. M., & Hellerstein, M. K. (2015). Turnover rates of hepatic collagen and circulating collagen-associated proteins in humans with chronic liver disease. *PLoS One*, 10(4), e0123311.
- Decaris, M. L., Li, K. W., Emson, C. L., Gatmaitan, M., Liu, S., Wang, Y., Nyangau, E., Colangelo, M., Angel, T. E., Beysen, C., Cui, J., Hernandez, C., Lazaro, L., Brenner, D. A., Turner, S. M., Hellerstein, M. K., & Loomba, R. (2017). Identifying nonalcoholic fatty liver disease patients with active fibrosis by measuring extracellular matrix remodeling rates in tissue and blood. *Hepatology*, 65(1), 78–88.
- Desbonnet, L., Clarke, G., Shanahan, F., Dinan, T. G., & Cryan, J. F. (2014). Microbiota is essential for social development in the mouse. *Molecular Psychiatry*, 19(2), 146–148.
- Diamandis, E. P. (2012). The failure of protein cancer biomarkers to reach the clinic: Why, and what can be done to address the problem? *BMC Medicine*, 10, 87. Eckburg, P. B., Bik, E. M., Bernstein, C. N., Purdom, E., Dethlefsen, L., Sargent, M., Gill, S. R., Nelson, K. E., & Relman, D. A. (2005). Diversity of the human intestinal microbial flora. *Science*, 308(5728), 1635–1638.
- Erickson, A. R., Cantarel, B. L., Lamendella, R., Darzi, Y., Mongodin, E. F., Pan, C., Shah, M., Halfvarson, J., Tysk, C., Henrissat, B., Raes, J., Verberkmoes, N. C., Fraser, C. M., Hettich, R. L., & Jansson, J. K. (2012). Integrated metagenomics/metaproteomics reveals human host-microbiota signatures of Crohn's disease. *PLoS One*, 7(11), e49138.
- Ferrer, M., Ruiz, A., Lanza, F., Haange, S. B., Oberbach, A., Till, H., Bargiela, R., Campoy, C., Segura, M. T., Richter, M., von Bergen, M., Seifert, J., & Suarez, A. (2013). Microbiota from

- the distal guts of lean and obese adolescents exhibit partial functional redundancy besides clear differences in community structure. *Environmental Microbiology*, 15(1), 211–226.
- Forslund, K., Sunagawa, S., Kultima, J. R., Mende, D. R., Arumugam, M., Typas, A., & Bork, P. (2013). Country-specific antibiotic use practices impact the human gut resistome. *Genome Research*, 23(7), 1163–1169.
- Foster, J. A., Rinaman, L., & Cryan, J. F. (2017). Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiol Stress*, 7, 124–136.
- Garud, N. R., Good, B. H., Hallatschek, O., & Pollard, K. S. (2019). Evolutionary dynamics of bacteria in the gut microbiome within and across hosts. *PLoS Biology*, 17(1), e3000102.
- Gavin, P. G., Mullaney, J. A., Loo, D., Cao, K. L., Gottlieb, P. A., Hill, M. M., Zipris, D., & Hamilton-Williams, E. E. (2018). Intestinal Metaproteomics reveals host-microbiota interactions in subjects at risk for type 1 diabetes. *Diabetes Care*, 41(10), 2178–2186.
- Gerard, P. (2016). Gut microbiota and obesity. *Cellular and Molecular Life Sciences*, 73(1), 147–162.
- Goodrich, D. W., Wang, N. P., Qian, Y. W., Lee, E. Y., & Lee, W. H. (1991). The retinoblastoma gene product regulates progression through the G1 phase of the cell cycle. *Cell*, 67(2), 293–302.
- Goodrich, J. K., Waters, J. L., Poole, A. C., Sutter, J. L., Koren, O., Blekhman, R., Beaumont, M., Van Treuren, W., Knight, R., Bell, J. T., Spector, T. D., Clark, A. G., & Ley, R. E. (2014). Human genetics shape the gut microbiome. *Cell*, 159(4), 789–799.
- Gordo, I. (2019). Evolutionary change in the human gut microbiome: From a static to a dynamic view. *PLoS Biology*, 17(2), e3000126.
- Haange, S. B., Oberbach, A., Schlichting, N., Hugenholz, F., Smidt, H., von Bergen, M., Till, H., & Seifert, J. (2012). Metaproteome analysis and molecular genetics of rat intestinal microbiota reveals section and localization resolved species distribution and enzymatic functionalities. *Journal of Proteome Research*, 11(11), 5406–5417.
- Hartman, A. L., Lough, D. M., Barupal, D. K., Fiehn, O., Fishbein, T., Zasloff, M., & Eisen, J. A. (2009). Human gut microbiome adopts an alternative state following small bowel transplantation. *Proceedings of the National Academy of Sciences of the United States of America*, 106(40), 17187–17192.
- Hebert, A. S., Merrill, A. E., Bailey, D. J., Still, A. J., Westphall, M. S., Strieter, E. R., Pagliarini, D. J., & Coon, J. J. (2013). Neutron-encoded mass signatures for multiplexed proteome quantification. *Nature Methods*, 10(4), 332–334.
- Heintz-Buschart, A., May, P., Laczny, C. C., Lebrun, L. A., Bellora, C., Krishna, A., Wampach, L., Schneider, J. G., Hogan, A., de Beaufort, C., & Wilmes, P. (2016). Integrated multiomics of the human gut microbiome in a case study of familial type 1 diabetes. *Nature Microbiology*, 2, 16180.
- Hellerstein, M. K. (2003). In vivo measurement of fluxes through metabolic pathways: The missing link in functional genomics and pharmaceutical research. *Annual Review of Nutrition*, 23, 379–402.
- Hellerstein, M. K., & Neese, R. A. (1992). Mass isotopomer distribution analysis: A technique for measuring biosynthesis and turnover of polymers. *The American Journal of Physiology*, 263(5 Pt 1), E988–E1001.
- Hellerstein, M. K., & Neese, R. A. (1999). Mass isotopomer distribution analysis at eight years: Theoretical, analytic, and experimental considerations. *The American Journal of Physiology*, 276(6 Pt 1), E1146–E1170.
- Hellerstein, M. K., Christiansen, M., Kaempfer, S., Kletke, C., Wu, K., Reid, J. S., Mulligan, K., Hellerstein, N. S., & Shackleton, C. H. (1991). Measurement of de novo hepatic lipogenesis in humans using stable isotopes. *The Journal of Clinical Investigation*, 87(5), 1841–1852.
- Hernandez, E., Bargiela, R., Diez, M. S., Friedrichs, A., Perez-Cobas, A. E., Gosalbes, M. J., Knecht, H., Martinez-Martinez, M., Seifert, J., von Bergen, M., Artacho, A., Ruiz, A., Cam-

- poy, C., Latorre, A., Ott, S. J., Moya, A., Suarez, A., Martins dos Santos, V. A., & Ferrer, M. (2013). Functional consequences of microbial shifts in the human gastrointestinal tract linked to antibiotic treatment and obesity. *Gut Microbes*, 4(4), 306–315.
- Holmes, W. E., Angel, T. E., Li, K. W., & Hellerstein, M. K. (2015). Dynamic proteomics: In vivo proteome-wide measurement of protein kinetics using metabolic labeling. *Methods in Enzymology*, 561, 219–276.
- Human Microbiome Project Consortium. (2012). Structure, function and diversity of the healthy human microbiome. *Nature*, 486(7402), 207–214.
- Jones, P. J., & Leatherdale, S. T. (1991). Stable isotopes in clinical research: Safety reaffirmed. *Clinical Science (London, England)*, 80(4), 277–280.
- Juste, C., Kreil, D. P., Beauvallet, C., Guillot, A., Vaca, S., Carapito, C., Mondot, S., Sykacek, P., Sokol, H., Blon, F., Lepercq, P., Levenez, F., Valot, B., Carre, W., Loux, V., Pons, N., David, O., Schaeffer, B., Lepage, P., Martin, P., Monnet, V., Seksik, P., Beaugerie, L., Ehrlich, S. D., Gibrat, J. F., Van Dorsselaer, A., & Dore, J. (2014). Bacterial protein signals are associated with Crohn's disease. *Gut*, 63(10), 1566–1577.
- Karlsson, E., Tremaroli, V., Nielsen, J., & Backhed, F. (2013). Assessing the human gut microbiota in metabolic diseases. *Diabetes*, 62(10), 3341–3349.
- Keshishian, H., Burgess, M. W., Specht, H., Wallace, L., Clauser, K. R., Gillette, M. A., & Carr, S. A. (2017). Quantitative, multiplexed workflow for deep analysis of human blood plasma and biomarker discovery by mass spectrometry. *Nature Protocols*, 12(8), 1683–1701.
- Klaassens, E. S., de Vos, W. M., & Vaughan, E. E. (2007). Metaproteomics approach to study the functionality of the microbiota in the human infant gastrointestinal tract. *Applied and Environmental Microbiology*, 73(4), 1388–1392.
- Klimmeck, D., Hansson, J., Raffel, S., Vakhrushev, S. Y., Trumpp, A., & Krijgsveld, J. (2012). Proteomic cornerstones of hematopoietic stem cell differentiation: Distinct signatures of multipotent progenitors and myeloid committed cells. *Molecular & Cellular Proteomics*, 11(8), 286–302.
- Kolmeder, C. A., & de Vos, W. M. (2014). Metaproteomics of our microbiome – developing insight in function and activity in man and model systems. *Journal of Proteomics*, 97, 3–16.
- Kolmeder, C. A., de Been, M., Nikkila, J., Ritamo, I., Matto, J., Valmu, L., Salojarvi, J., Palva, A., Salonen, A., & de Vos, W. M. (2012). Comparative metaproteomics and diversity analysis of human intestinal microbiota testifies for its temporal stability and expression of core functions. *PLoS One*, 7(1), e29913.
- Kolmeder, C. A., Salojarvi, J., Ritari, J., de Been, M., Raes, J., Falony, G., Vieira-Silva, S., Kekkonen, R. A., Corthals, G. L., Palva, A., Salonen, A., & de Vos, W. M. (2016). Faecal metaproteomic analysis reveals a personalized and stable functional microbiome and limited effects of a probiotic intervention in adults. *PLoS One*, 11(4), e0153294.
- Kristensen, N. B., Bryrup, T., Allin, K. H., Nielsen, T., Hansen, T. H., & Pedersen, O. (2016). Alterations in fecal microbiota composition by probiotic supplementation in healthy adults: A systematic review of randomized controlled trials. *Genome Medicine*, 8(1), 52.
- Lam, M. P., Wang, D., Lau, E., Liem, D. A., Kim, A. K., Ng, D. C., Liang, X., Bleakley, B. J., Liu, C., Tabaraki, J. D., Cadeiras, M., Wang, Y., Deng, M. C., & Ping, P. (2014). Protein kinetic signatures of the remodeling heart following isoproterenol stimulation. *The Journal of Clinical Investigation*, 124(4), 1734–1744.
- Lee, P. Y., Chin, S. F., Neoh, H. M., & Jamal, R. (2017). Metaproteomic analysis of human gut microbiota: Where are we heading? *Journal of Biomedical Science*, 24(1), 36.
- Lehmann, T., Schallert, K., Vilchez-Vargas, R., Benndorf, D., Puttker, S., Sydor, S., Schulz, C., Bechmann, L., Canbay, A., Heidrich, B., Reichl, U., Link, A., & Heyer, R. (2019). Metaproteomics of fecal samples of Crohn's disease and ulcerative colitis. *Journal of Proteomics*, 201, 93–103.

- Ley, R. E., Backhed, F., Turnbaugh, P., Lozupone, C. A., Knight, R. D., & Gordon, J. I. (2005). Obesity alters gut microbial ecology. *Proceedings of the National Academy of Sciences of the United States of America*, 102(31), 11070–11075.
- Impact of Gut Microbiota on Host by Exploring Proteomics Ley, R. E., Turnbaugh, P. J., Klein, S., & Gordon, J. I. (2006). Microbial ecology: Human gut microbes associated with obesity. *Nature*, 444(7122), 1022–1023.
- Li, X., LeBlanc, J., Truong, A., Vuthoori, R., Chen, S. S., Lustgarten, J. L., Roth, B., Allard, J., Ippoliti, A., Presley, L. L., Borneman, J., Bigbee, W. L., Gopalakrishnan, V., Graeber, T. G., Elashoff, D., Braun, J., & Goodglick, L. (2011). A metaproteomic approach to study human-microbial ecosystems at the mucosal luminal interface. *PLoS One*, 6(11), e26542.
- Li, L., Zhang, X., Ning, Z., Mayne, J., Moore, J. I., Butcher, J., Chiang, C. K., Mack, D., Stintzi, A., & Figeys, D. (2018). Evaluating in vitro culture medium of gut microbiome with orthogonal experimental design and a metaproteomics approach. *Journal of Proteome Research*, 17(1), 154–163.
- Liu, C. W., Chi, L., Tu, P., Xue, J., Ru, H., & Lu, K. (2019). Isobaric labeling quantitative metaproteomics for the study of gut microbiome response to arsenic. *Journal of Proteome Research*, 18(3), 970–981.
- Lloyd-Price, J., Mahurkar, A., Rahnavard, G., Crabtree, J., Orvis, J., Hall, A. B., Brady, A., Creasy, H. H., McCracken, C., Giglio, M. G., McDonald, D., Franzosa, E. A., Knight, R., White, O., & Huttenhower, C. (2017). Strains, functions and dynamics in the expanded Human Microbiome Project. *Nature*, 550(7674), 61–66.
- Lundberg, E., & Borner, G. H. H. (2019). Spatial proteomics: A powerful discovery tool for cell biology. *Nature Reviews. Molecular Cell Biology*, 20(5), 285–302.
- Lynch, S. V., Ng, S. C., Shanahan, F., & Tilg, H. (2019). Translating the gut microbiome: Ready for the clinic? *Nature Reviews. Gastroenterology & Hepatology*, 16(11), 656–661.
- Matsuoka, K., & Kanai, T. (2015). The gut microbiota and inflammatory bowel disease. *Seminars in Immunopathology*, 37(1), 47–55.
- McBride, Z., Chen, D., Lee, Y., Aryal, U. K., Xie, J., & Szymanski, D. B. (2019). A label-free mass spectrometry method to predict endogenous protein complex composition. *Molecular & Cellular Proteomics*, 18, 1588–1606.
- Meier, F., Brunner, A. D., Koch, S., Koch, H., Lubeck, M., Krause, M., Goedecke, N., Decker, J., Kosinski, T., Park, M. A., Bache, N., Hoerning, O., Cox, J., Rather, O., & Mann, M. (2018). Online parallel accumulation-serial fragmentation (PASEF) with a novel trapped ion mobility mass spectrometer. *Molecular & Cellular Proteomics*, 17(12), 2533–2545.
- Merrill, A. E., Hebert, A. S., MacGilvray, M. E., Rose, C. M., Bailey, D. J., Bradley, J. C., Wood, W. W., El Masri, M., Westphall, M. S., Gasch, A. P., & Coon, J. J. (2014). NeuCode labels for relative protein quantification. *Molecular & Cellular Proteomics*, 13(9), 2503–2512.
- Mertins, P., Udeshi, N. D., Clauser, K. R., Mani, D. R., Patel, J., Ong, S. E., Jaffe, J. D., & Carr, S. A. (2012). iTRAQ labeling is superior to mTRAQ for quantitative global proteomics and phosphoproteomics. *Molecular & Cellular Proteomics*, 11(6), M111 014423.
- Moeller, A. H., Li, Y., Mpoudi Ngole, E., Ahuka-Mundeke, S., Lonsdorf, E. V., Pusey, A. E., Peeters, M., Hahn, B. H., & Ochman, H. (2014). Rapid changes in the gut microbiome during human evolution. *Proceedings of the National Academy of Sciences of the United States of America*, 111(46), 16431–16435.
- Moeller, A. H., Caro-Quintero, A., Mjungu, D., Georgiev, A. V., Lonsdorf, E. V., Muller, M. N., Pusey, A. E., Peeters, M., Hahn, B. H., & Ochman, H. (2016). Cospeciation of gut microbiota with hominids. *Science*, 353(6297), 380–382.
- Mohajeri, M. H., La Fata, G., Steinert, R. E., & Weber, P. (2018). Relationship between the gut microbiome and brain function. *Nutrition Reviews*, 76(7), 481–496.
- Moulder, R., Bhosale, S. D., Goodlett, D. R., & Laheesmaa, R. (2018). Analysis of the plasma proteome using iTRAQ and TMT-based isobaric labeling. *Mass Spectrometry Reviews*, 37(5),

- 583–606.
- Munoz, J., Stange, D. E., Schepers, A. G., van de Wetering, M., Koo, B. K., Itzkovitz, S., Volckmann, R., Kung, K. S., Koster, J., Radulescu, S., Myant, K., Versteeg, R., Sansom, O. J., van Es, J. H., Barker, N., van Oudenaarden, A., Mohammed, S., Heck, A. J., & Clevers, H. (2012). The Lgr5 intestinal stem cell signature: Robust expression of proposed quiescent '+4' cell markers. *The EMBO Journal*, *31*(14), 3079–3091.
- Munson, M. A., Baumann, P., Clark, M. A., Baumann, L., Moran, N. A., Voegtlin, D. J., & Campbell, B. C. (1991). Evidence for the establishment of aphid-eubacterium endosymbiosis in an ancestor of four aphid families. *Journal of Bacteriology*, *173*(20), 6321–6324.
- Muth, T., Behne, A., Heyer, R., Kohrs, F., Benndorf, D., Hoffmann, M., Lehteva, M., Reichl, U., Martens, L., & Rapp, E. (2015). The MetaProteomeAnalyzer: A powerful open-source software suite for metaproteomics data analysis and interpretation. *Journal of Proteome Research*, *14*(3), 1557–1565.
- Muth, T., Renard, B. Y., & Martens, L. (2016). Metaproteomic data analysis at a glance: Advances in computational microbial community proteomics. *Expert Review of Proteomics*, *13*(8), 757–769.
- Naylor, B. C., Porter, M. T., Wilson, E., Herring, A., Lofthouse, S., Hannemann, A., Piccolo, S. R., Rockwood, A. L., & Price, J. C. (2017). Deuterater: A tool for quantifying peptide isotope precision and kinetic proteomics. *Bioinformatics*, *33*(10), 1514–1520.
- Neese, R. A., Schwarz, J. M., Faix, D., Turner, S., Letscher, A., Vu, D., & Hellerstein, M. K. (1995). Gluconeogenesis and intrahepatic triose phosphate flux in response to fasting or substrate loads. Application of the mass isotopomer distribution analysis technique with testing of assumptions and potential problems. *The Journal of Biological Chemistry*, *270*(24), 14452–14466.
- Nolting, D., Malek, R., & Makarov, A. (2017). Ion traps in modern mass spectrometry. *Mass Spectrometry Reviews*, *38*, 150–168.
- Ochman, H., Worobey, M., Kuo, C. H., Ndjanga, J. B., Peeters, M., Hahn, B. H., & Hugenholtz, P. (2010). Evolutionary relationships of wild hominids recapitulated by gut microbial communities. *PLoS Biology*, *8*(11), e1000546.
- O'Farrell, P. H. (1975). High resolution two-dimensional electrophoresis of proteins. *The Journal of Biological Chemistry*, *250*(10), 4007–4021.
- Ogbonnaya, E. S., Clarke, G., Shanahan, F., Dinan, T. G., Cryan, J. F., & O'Leary, O. F. (2015). Adult hippocampal neurogenesis is regulated by the microbiome. *Biological Psychiatry*, *78*(4), e7–e9.
- Ong, S. E., Blagoev, B., Kratchmarova, I., Kristensen, D. B., Steen, H., Pandey, A., & Mann, M. (2002). Stable isotope labeling by amino acids in cell culture, SILAC, as a simple and accurate approach to expression proteomics. *Molecular & Cellular Proteomics*, *1*(5), 376–386.
- Overmyer, K. A., Tyanova, S., Hebert, A. S., Westphall, M. S., Cox, J., & Coon, J. J. (2018). Multiplexed proteome analysis with neutron-encoded stable isotope labeling in cells and mice. *Nature Protocols*, *13*(1), 293–306.
- Paulovich, A. G., Whiteaker, J. R., Hoofnagle, A. N., & Wang, P. (2008). The interface between biomarker discovery and clinical validation: The tar pit of the protein biomarker pipeline. *Proteomics. Clinical Applications*, *2*(10–11), 1386–1402.
- Percy, A. J., Byrns, S., Pennington, S. R., Holmes, D. T., Anderson, N. L., Agreste, T. M., & Duffly, M. A. (2016). Clinical translation of MS-based, quantitative plasma proteomics: Status, challenges, requirements, and potential. *Expert Review of Proteomics*, *13*(7), 673–684.
- Perez-Cobas, A. E., Artacho, A., Knecht, H., Ferrus, M. L., Friedrichs, A., Ott, S. J., Moya, A., Latorre, A., & Gosalbes, M. J. (2013a). Differential effects of antibiotic therapy on the structure and function of human gut microbiota. *PLoS One*, *8*(11), e80201.
- Perez-Cobas, A. E., Gosalbes, M. J., Friedrichs, A., Knecht, H., Artacho, A., Eismann, K., Otto, W., Rojo, D., Bargiela, R., von Bergen, M., Neulinger, S. C., Daumer, C., Heinsen, F. A., La-

- torre, A., Barbas, C., Seifert, J., dos Santos, V. M., Ott, S. J., Ferrer, M., & Moya, A. (2013b). Gut microbiota disturbance during antibiotic therapy: A multi-omic approach. *Gut*, *62*(11), 1591–1601.
- Pfamatter, S., Bonneil, E., McManus, F. P., Prasad, S., Bailey, D. J., Belford, M., Dunyach, J.-J., & Thibault, P. (2018). A novel differential ion mobility device expands the depth of proteome coverage and the sensitivity of multiplex proteomic measurements. *Molecular & Cellular Proteomics*, *17*(10), 2051–2067.
- Impact of Gut Microbiota on Host by Exploring Proteomics Presley, L. L., Ye, J., Li, X., Leblanc, J., Zhang, Z., Ruegger, P. M., Allard, J., McGovern, D., Ippoliti, A., Roth, B., Cui, X., Jeske, D. R., Elashoff, D., Goodglick, L., Braun, J., & Borneman, J. (2012). Host-microbe relationships in inflammatory bowel disease detected by bacterial and metaproteomic analysis of the mucosal-luminal interface. *Inflammatory Bowel Diseases*, *18*(3), 409–417.
- Price, J. C., Guan, S., Burlingame, A., Prusiner, S. B., & Ghaemmaghani, S. (2010). Analysis of proteome dynamics in the mouse brain. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(32), 14508–14513.
- Price, J. C., Holmes, W. E., Li, K. W., Floreani, N. A., Neese, R. A., Turner, S. M., & Hellerstein, M. K. (2012a). Measurement of human plasma proteome dynamics with (2)H(2)O and liquid chromatography tandem mass spectrometry. *Analytical Biochemistry*, *420*(1), 73–83.
- Price, J. C., Khambatta, C. F., Li, K. W., Bruss, M. D., Shankaran, M., Dalidd, M., Floreani, N. A., Roberts, L. S., Turner, S. M., Holmes, W. E., & Hellerstein, M. K. (2012b). The effect of long term calorie restriction on in vivo hepatic proteostasis: A novel combination of dynamic and quantitative proteomics. *Molecular & Cellular Proteomics*, *11*(12), 1801–1814.
- Price, R. W., Peterson, J., Fuchs, D., Angel, T. E., Zetterberg, H., Hagberg, L., Spudich, S., Smith, R. D., Jacobs, J. M., Brown, J. N., & Gisslen, M. (2013). Approach to cerebrospinal fluid (CSF) biomarker discovery and evaluation in HIV infection. *Journal of Neuroimmune Pharmacology*, *8*(5), 1147–1158.
- Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K. S., Manichanh, C., Nielsen, T., Pons, N., Levenez, F., Yamada, T., Mende, D. R., Li, J., Xu, J., Li, S., Li, D., Cao, J., Wang, B., Liang, H., Zheng, H., Xie, Y., Tap, J., Lepage, P., Bertalan, M., Batto, J. M., Hansen, T., Le Paslier, D., Linneberg, A., Nielsen, H. B., Pelletier, E., Renault, P., Sicheritz-Ponten, T., Turner, K., Zhu, H., Yu, C., Li, S., Jian, M., Zhou, Y., Li, Y., Zhang, X., Li, S., Qin, N., Yang, H., Wang, J., Brunak, S., Dore, J., Guarner, F., Kristiansen, K., Pedersen, O., Parkhill, J., Weissenbach, J., Meta, H. I. T. C., Bork, P., Ehrlich, S. D., & Wang, J. (2010). A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*, *464*(7285), 59–65.
- Rhoads, T. W., Rose, C. M., Bailey, D. J., Riley, N. M., Molden, R. C., Nestler, A. J., Merrill, A. E., Smith, L. M., Hebert, A. S., Westphall, M. S., Pagliarini, D. J., Garcia, B. A., & Coon, J. J. (2014). Neutron-encoded mass signatures for quantitative top-down proteomics. *Analytical Chemistry*, *86*(5), 2314–2319.
- Richards, A. L., Vincent, C. E., Guthals, A., Rose, C. M., Westphall, M. S., Bandeira, N., & Coon, J. J. (2013). Neutron-encoded signatures enable product ion annotation from tandem mass spectra. *Molecular & Cellular Proteomics*, *12*(12), 3812–3823.
- Saji, N., Niida, S., Murotani, K., Hisada, T., Tsuduki, T., Sugimoto, T., Kimura, A., Toba, K., & Sakurai, T. (2019). Analysis of the relationship between the gut microbiome and dementia: A cross-sectional study conducted in Japan. *Scientific Reports*, *9*(1), 1008.
- Savitski, M. M., Zinn, N., Faeltz-Savitski, M., Poeckel, D., Gade, S., Becher, I., Muelbaier, M., Wagner, A. J., Strohmmer, K., Werner, T., Melchert, S., Petretich, M., Rutkowska, A., Vappiani, J., Franken, H., Steidel, M., Sweetman, G. M., Gilan, O., Lam, E. Y. N., Dawson, M. A., Prinjha, R. K., Grandi, P., Bergamini, G., & Bantscheff, M. (2018). Multiplexed proteome dynamics profiling reveals mechanisms controlling protein homeostasis. *Cell*, *173*(1), 260–274 e225.

- Schloss, P. D., Iverson, K. D., Petrosino, J. F., & Schloss, S. J. (2014). The dynamics of a family's gut microbiota reveal variations on a theme. *Microbiome*, 2, 25.
- Schoenheimer, R., & Rittenberg, D. (1936). Deuterium as an indicator in the study of intermediary metabolism: VI. Synthesis and destruction of fatty acids in the organism. *Journal of Biological Chemistry*, 114(2), 381–396.
- Schutzer, S. E., Liu, T., Natelson, B. H., Angel, T. E., Schepmoes, A. A., Purvine, S. O., Hixson, K. K., Lipton, M. S., Camp, D. G., Coyle, P. K., Smith, R. D., & Bergquist, J. (2010). Establishing the proteome of normal human cerebrospinal fluid. *PLoS One*, 5(6), e10980.
- Schutzer, S. E., Angel, T. E., Liu, T., Schepmoes, A. A., Clauss, T. R., Adkins, J. N., Camp, D. G., Holland, B. K., Bergquist, J., Coyle, P. K., Smith, R. D., Fallon, B. A., & Natelson, B. H. (2011). Distinct cerebrospinal fluid proteomes differentiate post-treatment Lyme disease from chronic fatigue syndrome. *PLoS One*, 6(2), e17287. T. E. Angel and U. K. Aryal
- Schutzer, S. E., Angel, T. E., Liu, T., Schepmoes, A. A., Xie, F., Bergquist, J., Vecsei, L., Zadori, D., Camp, D. G., 2nd, Holland, B. K., Smith, R. D., & Coyle, P. K. (2013). Gray matter is targeted in first-attack multiple sclerosis. *PLoS One*, 8(9), e66117.
- Schwanhaussner, B., Busse, D., Li, N., Dittmar, G., Schuchhardt, J., Wolf, J., Chen, W., & Selbach, M. (2011). Global quantification of mammalian gene expression control. *Nature*, 473(7347), 337–342.
- Sender, R., Fuchs, S., & Milo, R. (2016). Revised estimates for the number of human and bacteria cells in the body. *PLoS Biology*, 14(8), e1002533.
- Shankaran, M., King, C. L., Angel, T. E., Holmes, W. E., Li, K. W., Colangelo, M., Price, J. C., Turner, S. M., Bell, C., Hamilton, K. L., Miller, B. F., & Hellerstein, M. K. (2016). Circulating protein synthesis rates reveal skeletal muscle proteome dynamics. *The Journal of Clinical Investigation*, 126(1), 288–302.
- Sharon, G., Sampson, T. R., Geschwind, D. H., & Mazmanian, S. K. (2016). The central nervous system and the gut microbiome. *Cell*, 167(4), 915–932.
- Slebos, R. J., Brock, J. W., Winters, N. F., Stuart, S. R., Martinez, M. A., Li, M., Chambers, M. C., Zimmerman, L. J., Ham, A. J., & Tabb, D. L. (2008). Evaluation of strong cation exchange versus isoelectric focusing of peptides for multidimensional liquid chromatography-tandem mass spectrometry. *Journal of Proteome Research*, 7(12), 5286–5294.
- Smith, L. M., Kelleher, N. L., & Consortium for Top Down Proteomics. (2013). Proteoform: A single term describing protein complexity. *Nature Methods*, 10(3), 186–187.
- Smith, J. S., Angel, T. E., Chavkin, C., Orton, D. J., Moore, R. J., & Smith, R. D. (2014). Characterization of individual mouse cerebrospinal fluid proteomes. *Proteomics*, 14(9), 1102–1106.
- Song, S. J., Lauber, C., Costello, E. K., Lozupone, C. A., Humphrey, G., Berg-Lyons, D., Caporaso, J. G., Knights, D., Clemente, J. C., Nakielny, S., Gordon, J. I., Fierer, N., & Knight, R. (2013). Cohabiting family members share microbiota with one another and with their dogs. *eLife*, 2, e00458.
- Tanca, A., Palomba, A., Pisanu, S., Addis, M. F., & Uzzau, S. (2015). Enrichment or depletion? The impact of stool pretreatment on metaproteomic characterization of the human gut microbiota. *Proteomics*, 15(20), 3474–3485.
- Timmins-Schiffman, E., May, D. H., Mikan, M., Riffle, M., Frazar, C., Harvey, H. R., Noble, W. S., & Nunn, B. L. (2017). Critical decisions in metaproteomics: Achieving high confidence protein annotations in a sea of unknowns. *The ISME Journal*, 11(2), 309–314.
- Turnbaugh, P. J., Ley, R. E., Mahowald, M. A., Magrini, V., Mardis, E. R., & Gordon, J. I. (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*, 444(7122), 1027–1031.
- Turnbaugh, P. J., Ley, R. E., Hamady, M., Fraser-Liggett, C. M., Knight, R., & Gordon, J. I. (2007). The human microbiome project. *Nature*, 449(7164), 804–810.
- Turnbaugh, P. J., Ridaura, V. K., Faith, J. J., Rey, F. E., Knight, R., & Gordon, J. I. (2009). The effect of diet on the human gut microbiome: A metagenomic analysis in humanized gnotobiotic

- mice. *Science Translational Medicine*, 1(6), 6ra14.
- Turner, S. M., & Hellerstein, M. K. (2005). Emerging applications of kinetic biomarkers in pre-clinical and clinical drug development. *Current Opinion in Drug Discovery & Development*, 8(1), 115–126.
- Verberkmoes, N. C., Russell, A. L., Shah, M., Godzik, A., Rosenquist, M., Halfvarson, J., Lefsrud, M. G., Apajalahti, J., Tysk, C., Hettich, R. L., & Jansson, J. K. (2009). Shotgun metaproteomics of the human distal gut microbiota. *The ISME Journal*, 3(2), 179–189.
- Voogt, J. N., Awada, M., Murphy, E. J., Hayes, G. M., Busch, R., & Hellerstein, M. K. (2007). Measurement of very low rates of cell proliferation by heavy water labeling of DNA and gas chromatography/pyrolysis/isotope ratio-mass spectrometric analysis. *Nature Protocols*, 2(12), 3058–3062.
- Wei, X., Jiang, S., Chen, Y., Zhao, X., Li, H., Lin, W., Li, B., Wang, X., Yuan, J., & Sun, Y. (2016). Cirrhosis related functionality characteristic of the fecal microbiota as revealed by a metaproteomic approach. *BMC Gastroenterology*, 16(1), 121.
- Impact of Gut Microbiota on Host by Exploring Proteomics Welle, K. A., Zhang, T., Hryhorenko, J. R., Shen, S., Qu, J., & Ghaemmaghani, S. (2016). Time-resolved analysis of proteome dynamics by tandem mass tags and stable isotope labeling in cell culture (TMT-SILAC) hyperplexing. *Molecular & Cellular Proteomics*, 15(12), 3551–3563.
- Wong, M. L., Insera, A., Lewis, M. D., Mastronardi, C. A., Leong, L., Choo, J., Kentish, S., Xie, P., Morrison, M., Wesselingh, S. L., Rogers, G. B., & Licinio, J. (2016). Inflammasome signaling affects anxiety- and depressive-like behavior and gut microbiome composition. *Molecular Psychiatry*, 21(6), 797–805.
- Xiong, W., Abraham, P. E., Li, Z., Pan, C., & Hettich, R. L. (2015). Microbial metaproteomics for characterizing the range of metabolic functions and activities of human gut microbiota. *Proteomics*, 15(20), 3424–3438.
- Yang, F., Shen, Y., Camp, D. G., & Smith, R. D. (2012). High-pH reversed-phase chromatography with fraction concatenation for 2D proteomic analysis. *Expert Review of Proteomics*, 9(2), 129–134.
- Yatsunenkov, T., Rey, F. E., Manary, M. J., Trehan, I., Dominguez-Bello, M. G., Contreras, M., Magris, M., Hidalgo, G., Baldassano, R. N., Anokhin, A. P., Heath, A. C., Warner, B., Reeder, J., Kuczynski, J., Caporaso, J. G., Lozupone, C. A., Lauber, C., Clemente, J. C., Knights, D., Knight, R., & Gordon, J. I. (2012). Human gut microbiome viewed across age and geography. *Nature*, 486(7402), 222–227.
- Young, J. C., Pan, C., Adams, R. M., Brooks, B., Banfield, J. F., Morowitz, M. J., & Hettich, R. L. (2015). Metaproteomics reveals functional shifts in microbial and human proteins during a preterm infant gut colonization case. *Proteomics*, 15(20), 3463–3473.
- Young, P. A., Leonard, S., Martin, D. S., & Findlay, J. B. (2016). Analysis of the effect of a novel therapeutic for type 2 diabetes on the proteome of a muscle cell line. *Proteomics*, 16(1), 70–79.
- Zecha, J., Meng, C., Zolg, D. P., Samaras, P., Wilhelm, M., & Kuster, B. (2018). Peptide level turnover measurements enable the study of proteoform dynamics. *Molecular & Cellular Proteomics*, 17(5), 974–992.
- Zhang, X., Ning, Z., Mayne, J., Moore, J. I., Li, J., Butcher, J., Deeke, S. A., Chen, R., Chiang, C. K., Wen, M., Mack, D., Stintzi, A., & Figeys, D. (2016). MetaPro-IQ: A universal metaproteomic approach to studying human and mouse gut microbiota. *Microbiome*, 4(1), 31.
- Zhang, X., Deeke, S. A., Ning, Z., Starr, A. E., Butcher, J., Li, J., Mayne, J., Cheng, K., Liao, B., Li, L., Singleton, R., Mack, D., Stintzi, A., & Figeys, D. (2018a). Metaproteomics reveals associations between microbiome and intestinal extracellular vesicle proteins in pediatric inflammatory bowel disease. *Nature Communications*, 9(1), 2873.
- Zhang, X., Li, L., Mayne, J., Ning, Z., Stintzi, A., & Figeys, D. (2018b). Assessing the impact of protein extraction methods for human gut metaproteomics. *Journal of Proteomics*, 180,

120–127.

- Zheng, X., Wojcik, R., Zhang, X., Ibrahim, Y. M., Burnum-Johnson, K. E., Orton, D. J., Monroe, M. E., Moore, R. J., Smith, R. D., & Baker, E. S. (2017). Coupling front-end separations, ion mobility spectrometry, and mass spectrometry for enhanced multidimensional biological and environmental analyses. *Annual Review of Analytical Chemistry (Palo Alto, California)*, 10(1), 71–92.
- Zou, Y., Xue, W., Luo, G., Deng, Z., Qin, P., Guo, R., Sun, H., Xia, Y., Liang, S., Dai, Y., Wan, D., Jiang, R., Su, L., Feng, Q., Jie, Z., Guo, T., Xia, Z., Liu, C., Yu, J., Lin, Y., Tang, S., Huo, G., Xu, X., Hou, Y., Liu, X., Wang, J., Yang, H., Kristiansen, K., Li, J., Jia, H., & Xiao, L. (2019). 1,520 reference genomes from cultivated human gut bacteria enable functional microbiome analyses. *Nature Biotechnology*, 37(2), 179–185.
- Zwittink, R. D., van Zoeren-Grobbe, D., Martin, R., van Lingen, R. A., Groot Jebbink, L. J., Boreen, S., Renes, I. B., van Elburg, R. M., Belzer, C., & Knol, J. (2017). Metaproteomics reveals functional differences in intestinal microbiota development of preterm infants. *Molecular & Cellular Proteomics*, 16(9), 1610–1620.

# Bağırsak Florasının Modülasyonu ve Hayvansal Gıda Ürünlerinde Uygulanması

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## 1. Giriş

Bağırsak mikrobiyotası, hayvan sağlığını etkileyen en önemli faktörlerden biri haline gelmiştir. Dengeli bağırsak mikrobiyotası enfeksiyona karşı direnci artırır. Öte yandan, bağırsak mikrobiyotası bozulduğunda dirençteki azalma fark edilir; bu nedenle bağırsak mikrobiyotasının dengelenmesi konak sağlığı için önemlidir (Belkaid ve Hand 2014). Dengeli ve bozulmuş bağırsak popülasyonlarının kompozisyonları net olmasa da, Lactobacilli ve Bifidobacteria türleri strese duyarlı görünmektedir ve bu popülasyonlar bir hayvan stres altındayken azalma eğilimindedir (Conlon ve Bird 2014).

Bitki yan ürünleri, prebiyotikler ve/veya probiyotikler ve hayvan kaynaklı ürünler de dahil olmak üzere biyoaktif bileşikler; diğer faydalı özelliklerinin yanı sıra anti-inflamatuar, antimikrobiyal, antikanserojenik, antioksidan ve vazodilatör özellikleri ile sağlığın iyileştirilmesinde rol oynar (Boivin ve ark. 2007; Tzounis ve diğerleri 2011; Salaheen ve diğerleri 2014a, 2015, 2017). Bu fayda verici aktivitelerin mekanizmaları henüz açıklığa kavuşturulmamıştır, ancak olasılıklardan biri bağırsak/bağırsak mikrobiyotasının modülasyonudur (Hernández ve ark. 2004). Yine, gözlemsel ve epidemiyolojik çalışmalar, konvansiyonel hayvanların çekumlarının mikrobiyal topluluklarında organik benzerlerine göre farklılıklar olduğunu göstermiştir (Torok ve ark. 2011; Mancabelli ve ark. 2016). Antibiyotik büyüme arttırıcıların (AGP) mikropsuz hayvanlar üzerindeki nötr etkileri, hayvanlarda büyümenin desteklenmesinde AGP'ye bağlı bağırsak mikrobiyota modülasyonunun önemini göstermiştir (Turnbaugh ve ark. 2006). İki baskın bakteri filumunun, Bacteroidetes ve Firmicutes'in kilo alımı ile ilişkisi, daha sonraki diğer çalışmalarla desteklenmiştir (Mancabelli ve diğerleri 2016; Singh ve diğerleri. 2013). Diğer bir çalışmada, AGP ile beslenen tavukların bağırsağında *Lactobacillus* türleri, Clostridiales ve Enterobacteriaceae bolluğunun arttığı görülmüştür (Gong ve ark. 2008). Ayrıca *Firmicutes/Bacteroidetes* (F/B) oranı, çiftlik hayvanlarının kilo alımı ve çeşitli ürünlerin terapötik rolü arasında bir ilişki olduğu bildirilmiştir (Singh ve ark. 2013).

Fruktooligosakarit (FOS) ürünleri (oligofruktoz ve inülin), transgalaktooligosakaritler, glukoligosakaritler, glikooligosakaritler, laktuloz, laktitol, maltooligosakka-

ve/veya probiyotiklerin hayvan beslenmesinde destek olarak kullanılması, hayvan sağlığı ve performansını iyileştirmede bağırsak mikrobiyotasını modüle etmek için umut verici bir yaklaşım olabilir, çünkü takviyeler ayrıca yararlı bakteri türlerinin büyümesini teşvik ederek ve spesifik patojenik bakteri suşlarını azaltarak bizi daha güvenli gıda ürünlerine yönlendirebilir. Doğal bitki yan ürünlerinin, prebiyotiklerin ve/veya probiyotiklerin hayvan beslenmesinde takviye olarak kullanılması, hayvan sağlığını ve performansını iyileştirmek için bağırsak mikrobiyotasını modüle etmekte umut verici bir yaklaşım olabilir. Takviyeler ayrıca yararlı bakteri türlerinin büyümesini teşvik ederek ve spesifik patojenik bakteri türlerini azaltarak bizi daha güvenli gıda ürünlerine yönlendirebilir. Çeşitli çalışmalar, bu ürünlerin hayvan yemine eklenmesinin sadece büyümeyi artırmakla kalmayıp aynı zamanda et kalitesini de büyük ölçüde iyileştirdiğini göstermiştir. Bu nedenle, artık bağırsak florasının gıda hayvanlarının büyümesi ve genel kalitesi üzerindeki etkisini belirlemek için laboratuvar/alan denemelerini teşvik etmek gerekmektedir. Ayrıca, bağırsak mikrobiyal popülasyonunu modüle etmede bağırsak mikrobiyotası ve çeşitli yem takviyeleri arasındaki etkileşimleri daha iyi anlamak için gelecekteki deneyler metagenomik, transkriptomik ve proteomik yaklaşımlara odaklanmalıdır. Yakın gelecekte, daha fazla araştırma, yem takviyelerinin bağırsak bakteri popülasyonlarını nasıl modüle ettiğini ve besi hayvanları üretimi ve güvenliğinde nasıl daha etkili olabileceklerini açıklayacaktır.

## Kaynaklar

- Abnous, K., Brooks, S. P., Kwan, J., Matias, F., Green-Johnson, J., Selinger, L. B., Thomas, M., & Kalmokoff, M. (2009). Diets enriched in oat bran or wheat bran temporally and differentially alter the composition of the fecal community of rats. *The Journal of Nutrition*, 139, 2024–2031.
- Ahmed, S. T., Hossain, M. E., Kim, G. M., Hwang, J. A., Ji, H., & Yang, C. J. (2013). Effects of resveratrol and essential oils on growth performance, immunity and microbial shedding in challenged piglets. *Asian-Australasian Journal of Animal Sciences*, 26, 683–690.
- Ahn, Y. J., Sakanaka, S., Kawamura, T., Kim, M., Yamamoto, T., & Mitsuoka, T. (1990). Effect of green tea extract on growth of intestinal bacteria. *Microbial Ecology in Health and Disease*, 3, 335–338.
- Antonopoulos, D. A., Huse, S. M., Morrison, H. G., Schmidt, T. M., Sogin, M. L., & Young, V. B. (2009). Reproducible community dynamics of the gastrointestinal microbiota following antibiotic perturbation. *Infection and Immunity*, 77, 2367–2375.
- Apajalahti, J., & Vienola, K. (2016). Interaction between chicken intestinal microbiota and protein digestion. *Animal Feed Science and Technology*, 22, 323–330.
- Arumugam, M., Raes, J., Pelletier, E., Le Paslier, D., Yamada, T., Mende, D. R., Fernandes, G. R., Tap, J., Bruls, T., Batto, J. M., et al. (2011). Enterotypes of the human gut microbiome. *Nature*, 473, 174–180.
- Bäckhed, F., Ley, R. E., Sonnenburg, J. L., Peterson, D. A., & Gordon, J. I. (2005). Host-bacterial mutualism in the human intestine. *Science*, 307, 1915–1920.
- Belkaid, Y., & Hand, T. W. (2014). Role of the microbiota in immunity and inflammation. *Cell*, 157(1), 121–141.

- Benson, A. K., Kelly, S. A., Legge, R., Ma, F., Low, S. J., Kim, J., et al. (2010). Individuality in gut microbiota composition is a complex polygenic trait shaped by multiple environmental and host genetic factors. *Proceedings of the National Academy of Sciences*, *107*, 18933–18938.
- Bialonska, D., Ramnani, P., Kasimsetty, S. G., Muntha, K. R., Gibson, G. R., & Ferreira, D. (2010). The influence of pomegranate by-product and punicalagins on selected groups of human intestinal microbiota. *International Journal of Food Microbiology*, *140*, 175–182.
- Biswas, D., Wideman, N. E., O'Bryan, C. A., Muthaiyan, A., Lingbeck, J. M., Crandall, P. G., & Steven, C. R. (2012). Pasteurized blueberry (*Vaccinium corymbosum*) juice inhibits growth of bacterial pathogens in milk but allows survival of probiotic bacteria. *Journal of Food Safety*, *32*, 204–209.
- Boivin, J., Bunting, L., Collins, J. A., & Nygren, K. G. (2007). International estimates of infertility prevalence and treatment-seeking: Potential need and demand for infertility medical care. *Human Reproduction*, *22*, 1506–1512.
- Brunet, S., de Montellano, C. M., Torres-Acosta, J. F., Sandoval-Castro, C. A., Aguilar-Caballero, A. J., Capetillo-Leal, C., & Hoste, H. (2008). Effect of the consumption of *Lysiloma latisiliquum* on the larval establishment of gastrointestinal nematodes in goats. *Veterinary Parasitology*, *157*, 81–88.
- Chambers, J. R., & Gong, J. (2011). The intestinal microbiota and its modulation for Salmonella control in chickens. *Food Research International*, *44*, 3149–3159.
- Cho, I., Yamanishi, S., Cox, L., Methé, B. A., Zavadil, J., Li, K., Gao, Z., Mahana, D., Raju, K., Teitler, I., Li, H., Alekseyenko, A. V., & Blaser, M. J. (2012). Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature*, *488*, 621–626.
- Choy, Y. Y., Quifer-Rada, P., Holstege, D. M., Frese, S. A., Calvert, C. C., Mills, D. A., Lamuela-Raventos, R. M., & Waterhouse, A. L. (2014). Phenolic metabolites and substantial Modulation of Gut Flora and Its Application in Food Animal Products microbiome changes in pig feces by ingesting grape seed proanthocyanidins. *Food & Function*, *5*, 2298–2308.
- Clarke, S. F., Murphy, E. F., Nilaweera, K., Ross, P. R., Shanahan, F., O'Toole, P. W., & Cotter, P. D. (2012). The gut microbiota and its relationship to diet and obesity: New insights. *Gut Microbes*, *3*, 186–202.
- Coddens, A., Loos, M., Vanrompay, D., Remon, J. P., & Cox, E. (2017). Cranberry extract inhibits in vitro adhesion of F4 and F18+ *Escherichia coli* to pig intestinal epithelium and reduces in vivo excretion of pigs orally challenged with F18+ verotoxigenic *E. coli*. *Veterinary Microbiology*, *202*, 64–71.
- Collins, M. D., & Gibson, G. R. (1999). Probiotics, prebiotics, and synbiotics: Approaches for modulating the microbial ecology of the gut. *The American Journal of Clinical Nutrition*, *69*(Suppl. 1), 1042S–1057S.
- Cotter, P. D., Hill, C., & Ross, R. P. (2005). Bacteriocins: Developing innate immunity for food. *Nature Reviews. Microbiology*, *3*, 777–788.
- Cotter, P. D., Stanton, C., Ross, R. P., & Hill, C. (2012). The impact of antibiotics on the gut microbiota as revealed by high throughput DNA sequencing. *Discovery Medicine*, *13*, 193.
- Conlon, M. A., & Bird, A. R. (2014). The impact of diet and lifestyle on gut microbiota and human health. *Nutrients*, *7*(1), 17–44.
- Dąbrowska, K., & Witkiewicz, W. (2016). Correlations of host genetics and gut microbiome composition. *Frontiers in Microbiology*, *7*, 1357.
- Del Chierico, F., Vernocchi, P., Bonizzi, L., Carsetti, R., Castellazzi, A. M., Dallapiccola, B., de Vos, W., Guerzoni, M. E., Manco, M., Marseglia, G. L., Muraca, M., Roncada, P., Salvatori, G., Signore, F., Urbani, A., & Putignani, L. (2012). Early-life gut microbiota under physiological and pathological conditions: The central role of combined meta-omics-based approaches. *Journal of Proteomics*, *75*, 4580–4587.
- Desrues, O., Pena-Espinoza, M., Hansen, T. V., Enemark, H. L., & Thamsborg, S. M. (2016). Anti-parasitic activity of pelleted sainfoin (*Onobrychis viciifolia*) against *Ostertagia ostertagi*

- and *Cooperia oncophora* in calves. *Parasites & Vectors*, 9, 329.
- Dicksved, J., Halfvarson, J., Rosenquist, M., Järnerot, G., Tysk, C., Apajalahti, J., Engstrand, L., & Jansson, J. K. (2008). Molecular analysis of the gut microbiota of identical twins with Crohn's disease. *The ISME Journal*, 2, 716–727.
- Dolara, P., Luceri, C., De Filippo, C., Femia, A. P., Giovannelli, L., Caderni, G., Cecchini, C., Silvi, S., Orpianesi, C., & Creci, A. (2005). Red wine polyphenols influence carcinogenesis, intestinal microflora, oxidative damage and gene expression profiles of colonic mucosa in F344 rats. *Mutation Research*, 591, 237–246.
- Duncan, S. H., Belenguer, A., Holtrop, G., Johnstone, A. M., Flint, H. J., & Lobley, G. E. (2007). Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. *Applied and Environmental Microbiology*, 73, 1073–1078.
- Dunne, C., O'Mahony, L., Murphy, L., Thornton, G., Morrissey, D., O'Halloran, S., Feeney, M., Flynn, S., Fitzgerald, G., Daly, C., Kiely, B., O'Sullivan, G. C., Shanahan, F., & Collins, J. K. (2001). In vitro selection criteria for probiotic bacteria of human origin: Correlation with in vivo findings. *The American Journal of Clinical Nutrition*, 73, 386S–392S.
- Ellis, R. J., Bruce, K. D., Jenkins, C., Stothard, J. R., Ajarova, L., Mugisha, L., & Viney, M. E. (2013). Comparison of the distal gut microbiota from people and animals in Africa. *PLoS One*, 8, e54783.
- Fiesel, A., Gessner, D., Most, E., & Eder, K. (2014). Effects of dietary polyphenol-rich plant products from grape or hop on pro-inflammatory gene expression in the intestine, nutrient digestibility and faecal microbiota of weaned pigs. *BMC Veterinary Research*, 10, 196.
- Forester, S. C., & Waterhouse, A. L. (2008). Identification of Cabernet Sauvignon anthocyanin gut microflora metabolites. *Journal of Agricultural and Food Chemistry*, 56, 9299–9304.
- Freter, R. (1992). Factors affecting the microecology of the gut. In *Probiotics* (pp. 111–144). Dordrecht: Springer. Z. Tabashsum et al.
- Gabert, L., Vors, C., Louche-Péllissier, C., Sauvinet, V., Lambert-Porcheron, S., Draï, J., Laville, M., Désage, M., & Michalski, M. C. (2011). <sup>13</sup>C tracer recovery in human stools after digestion of a fat-rich meal labelled with [1, 1, 1-<sup>13</sup>C<sub>3</sub>] tripalmitin and [1, 1, 1-<sup>13</sup>C<sub>3</sub>] triolein. *Rapid Communications in Mass Spectrometry*, 25, 2697–2703.
- Gaggia, F., Mattarelli, P., & Biavati, B. (2010). Probiotics and prebiotics in animal feeding for safe food production. *International Journal of Food Microbiology*, 141, S15–S28.
- Ganan, M., Martinez-Rodriguez, A. J., & Carrascosa, A. V. (2009). Antimicrobial activity of phenolic compounds of wine against *Campylobacter jejuni*. *Food Control*, 20, 739–742.
- Gibson, G. R., Probert, H. M., Loo, J. V., Rastall, R. A., & Roberfroid, M. B. (2004). Dietary modulation of the human colonic microbiota: Updating the concept of prebiotics. *Nutrition Research Reviews*, 17, 259–275.
- Golder, H. M., Geier, M. S., Forder, R. E. A., Hynd, P. I., & Hughes, R. J. (2011). Effects of necrotic enteritis challenge on intestinal micro-architecture and mucin profile. *British Poultry Science*, 52(4), 500–506.
- Gong, J., Yu, H., Liu, T., Gill, J. J., Chambers, J. R., Wheatcroft, R., & Sabour, P. M. (2008). Effects of zinc bacitracin, bird age and access to range on bacterial microbiota in the ileum and caeca of broiler chickens. *Journal of Applied Microbiology*, 104, 1372–1382.
- Guo, X., Li, D., Lu, W., Piao, X., & Chen, X. (2006). Screening of *Bacillus* strains as potential probiotics and subsequent confirmation of the in vivo effectiveness of *Bacillus subtilis* MA139 in pigs. *Antonie Van Leeuwenhoek*, 90, 139–146.
- Hara, H., Orita, N., Hatano, S., Ichikawa, H., Hara, Y., Matsumoto, N., Kimura, Y., Terada, A., & Mitsuoka, T. (1995). Effect of tea polyphenols on fecal flora and fecal metabolic products of pigs. *The Journal of Veterinary Medical Science*, 57, 45–49.
- Hernández, F., Madrid, J., García, V., Orengo, J., & Megías, M. D. (2004). Influence of two plant extracts on broilers performance, digestibility, and digestive organ size. *Poultry Science*, 83,

- 169–174.
- Hervert-Hernandez, D., Pintado, C., Rotger, R., & Goni, I. (2009). Stimulatory role of grape pomace polyphenols on *Lactobacillus acidophilus* growth. *International Journal of Food Microbiology*, *136*, 119–122.
- Hildebrandt, M. A., Hoffmann, C., Sherrill-Mix, S. A., Keilbaugh, S. A., Hamady, M., Chen, Y. Y., Knight, R., Ahima, R. S., Bushman, F., & Wu, G. D. (2009). High-fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology*, *137*, 1716–1724.
- Hooper, L. V., & Gordon, J. I. (2001). Commensal host-bacterial relationships in the gut. *Science*, *292*, 1115–1118.
- Hoste, H., Martínez-Ortiz-De-Montellano, C., Manolaraki, F., Brunet, S., Ojeda-Robertos, N., Fourquaux, I., Torres-Acosta, J. F., & Sandoval-Castro, C. A. (2012). Direct and indirect effects of bioactive tannin-rich tropical and temperate legumes against nematode infections. *Veterinary Parasitology*, *186*, 18–27.
- Inal, J. M. (2003). Phage therapy: A reappraisal of bacteriophages as antibiotics. *Archivum Immunologiae et Therapiae Experimentalis*, *51*(4), 237–244.
- Ishihara, N., Chu, D.-C., Akachi, S., & Juneja, L. R. (2001). Improvement of intestinal microflora balance and prevention of digestive and respiratory organ diseases in calves by green tea extracts. *Livestock Production Science*, *68*, 217–229.
- Islam, M. R., Lepp, D., Yin, X., Ross, K., Delaquis, P., Erhet, D., & Diarra, M. S. (2015). Gut microbiota of organic broiler chickens fed with or without blueberry pomace. In *The 12th Annual Guelph Food Safety Symposium*, Guelph, Canada.
- Islam, M. R., Oomah, D. B., & Diarra, M. S. (2017). Potential immunomodulatory effects of non-dialyzable materials of cranberry extract in poultry production. *Poultry Science*, *96*, 341–350.
- Jami, E., & Mizrahi, I. (2012). Composition and similarity of bovine rumen microbiota across individual animals. *PLoS One*, *7*, e33306.
- Jamroz, D., Wiliczekiewicz, A., Wertelecki, T., Orda, J., & Scorupinska, J. (2005). Use of active substances of plant origin in chicken diets based on maize and domestic grains. *British Poultry Science*, *46*, 485–493.
- Jansson, J., Willing, B., Lucio, M., Fekete, A., Dicksved, J., Halfvarson, J., Tysk, C., & Schmitt-Kopplin, P. (2009). Metabolomics reveals metabolic biomarkers of Crohn's disease. *PLoS One*, *4*, e6386.
- Jung, H. J., Park, Y., Sung, W. S., Suh, B. K., Lee, J., Hahm, K. S., & Lee, D. G. (2007). Fungicidal effect of pleurocidin by membrane-active mechanism and design of enantiomeric analogue for proteolytic resistance. *Biochimica et Biophysica Acta*, *1768*(6), 1400–1405.
- Kumar, M., Babaei, P., Ji, B., & Nielsen, J. (2016). Human gut microbiota and healthy aging: Recent developments and future prospective. *Nutrition and Healthy Aging*, *4*, 3–16.
- Larrosa, M., Yanéz-Gascón, M. J., Selma, M. V., González-Sarrias, A., Toti, S., Cerón, J. J., Tomás-Barberán, F., Dolara, P., & Espín, J. C. (2009). Effect of a low dose of dietary resveratrol on colon microbiota, inflammation and tissue damage in a DSS-induced colitis rat model. *Journal of Agricultural and Food Chemistry*, *57*, 2211–2220.
- Lee, H. C., Jenner, A. M., Low, C. S., & Lee, Y. K. (2006). Effect of tea phenolics and their aromatic fecal bacterial metabolites on intestinal microbiota. *Research in Microbiology*, *157*, 876–884.
- Leleu, S., Herman, L., Heyndrickx, M., De Reu, K., Michiels, C. W., De Baerdemaeker, J., & Messens, W. (2011). Effects on *Salmonella* shell contamination and trans-shell penetration of coating hens' eggs with chitosan. *International Journal of Food Microbiology*, *145*(1), 43–48.
- Ley, R. E., Bäckhed, F., Turnbaugh, P., Lozupone, C. A., Knight, R. D., & Gordon, J. I. (2005). Obesity alters gut microbial ecology. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 11070–11075.
- Li, Y., Meng, Q., Zhou, B., & Zhou, Z. (2017). Effect of ensiled mulberry leaves and sun-dried

- mulberry fruit pomace on the fecal bacterial community composition in finishing steers. *BMC Microbiology*, 17, 97.
- Liao, S. F., & Nyachoti, M. (2017). Using probiotics to improve swine gut health and nutrient utilization. *Animal Nutrition (Zhongguo xu mu shou yi xue hui)*, 3(4), 331–343.
- Licht, T. R., Hansen, M., Bergstrom, A., Poulsen, M., Krath, B. N., Markowski, J., Dragsted, L. O., & Wilcks, A. (2010). Effects of apples and specific apple components on the cecal environment of conventional rats: Role of apple pectin. *BMC Microbiology*, 10, 13.
- Lillehoj, H., Liu, Y., Calsamiglia, S., Fernandez-Miyakawa, M. E., Chi, F., Cravens, R. L., Oh, S., & Gay, C. G. (2018). Phytochemicals as antibiotic alternatives to promote growth and enhance host health. *Veterinary Research*, 49(1), 76.
- Lo, C. M., King, A., Samuelson, L. C., Kindel, T. L., Rider, T., Jandacek, R. J., Raybould, H. E., Woods, S. C., & Tso, P. (2010). Cholecystokinin knockout mice are resistant to high-fat diet-induced obesity. *Gastroenterology*, 138(5), 1997–2005.
- Lozupone, C. A., Stombaugh, J. I., Gordon, J. I., Jansson, J. K., & Knight, R. (2012). Diversity, stability and resilience of the human gut microbiota. *Nature*, 489, 220–230.
- Lutful Kabir, S. M. (2009). The role of probiotics in the poultry industry. *International Journal of Molecular Sciences*, 10(8), 3531–3546.
- Macfarlane, G., Cummings, J., & Allison, C. (1986). Protein degradation by human intestinal bacteria. *Journal of General Microbiology*, 132, 1647–1656.
- Mancabelli, L., Ferrario, C., Milani, C., Mangifesta, M., Turrone, F., Duranti, S., Lugli, G. A., Viappiani, A., Ossiprandi, M. C., van Sinderen, D., & Ventura, M. (2016). Insights into the biodiversity of the gut microbiota of broiler chickens. *Environmental Microbiology*, 18, 4727–4738.
- Mao, S., Zhang, M., Liu, J., & Zhu, W. (2015). Characterising the bacterial microbiota across the gastrointestinal tracts of dairy cattle: Membership and potential function. *Scientific Reports*, 5, 16116. Z. Tabashsum et al.
- McDougald, L. R., Hofacre, C., Mathis, G., Fuller, L., Hargrove, J. L., Greenspan, P., & Hartle, D. K. (2008). Enhancement of resistance to coccidiosis and necrotic enteritis in broiler chickens by dietary muscadine pomace. *Avian Diseases*, 52, 646–651.
- Mitsch, P., Zitterl-Eglseer, K., Kohler, B., Gabler, C., Losa, R., & Zimpernik, I. (2004). The effect of two different blends of essential oil components on the proliferation of *Clostridium perfringens* in the intestines of broiler chickens. *Poultry Science*, 83, 669–675.
- Molan, A. L., Lila, M. A., Mawson, J., & De, S. (2009). In vitro and in vivo evaluation of the prebiotic activity of water-soluble blueberry extracts. *World Journal of Microbiology and Biotechnology*, 25, 1243–1249.
- Monsan, P., & Paul, F. (1995). In J. Wallace & A. Chesson (Eds.), *Biotechnology in animal feeds and animal feeding* (pp. 233–245). New York: VCH.
- Murphy, E. F., Cotter, P. D., Healy, S., Marques, T. M., O'Sullivan, O., Fouhy, F., Clarke, S. F., O'Toole, P. W., Quigley, E. M., Stanton, C., Ross, P. R., O'Doherty, R. M., & Shanahan, F. (2010). Composition and energy harvesting capacity of the gut microbiota: Relationship to diet, obesity and time in mouse models. *Gut*, 59, 1635–1642.
- Murugesan, G. R., Syed, B., Haldar, S., & Pender, C. (2015). Phytogetic feed additives as an alternative to antibiotic growth promoters in broiler chickens. *Frontiers in Veterinary Science*, 2, 21.
- Ochman, H., Worobey, M., Kuo, C. H., Ndjanga, J. B., Peeters, M., Hahn, B. H., & Hugenholtz, P. (2010). Evolutionary relationships of wild hominids recapitulated by gut microbial communities. *PLoS Biology*, 8, e1000546.
- Orban, J. I., Patterson, J. A., Sutton, A. L., & Richards, G. N. (1997). Effect of sucrose thermal oligosaccharide caramel, dietary vitamin-mineral level, and brooding temperature on growth and intestinal bacterial populations in broiler chickens. *Poultry Science*, 76, 482–490.
- Palazzo, F., Biscarini, F., Castellani, F., Giulia, M., Vitali, A., Grotta, L., & Martino, G. (2017). Characterization of the rumen microbiota in dairy calves receiving copper or grape-poma-

- ce feed supplementation. In *Congress of Animal Science and Production Association (ASPA)*, At Perugia.
- Patterson, J. A., Orban, J. I., Sutton, A. L., & Richards, G. N. (1997). Selective enrichment of bifidobacteria in the intestinal tract of broilers by thermally produced kestoses and effect on broiler performance. *Poultry Science*, 76, 497–500.
- Peng, M., & Biswas, D. (2017). Short chain and polyunsaturated fatty acids in host gut health and foodborne bacterial pathogen inhibition. *Critical Reviews in Food Science and Nutrition*, 57, 3987–4002.
- Peng, M., Aryal, U., Cooper, B., & Biswas, D. (2015a). Metabolites produced during the growth of probiotics in cocoa supplementation and the limited role of cocoa in host-enteric bacterial pathogen interactions. *Food Control*, 53, 124–133.
- Peng, M., Reichmann, G., & Biswas, D. (2015b). Lactobacillus casei and its byproducts alter the virulence factors of foodborne bacterial pathogens. *Journal of Functional Foods*, 15, 418–428.
- Perez-Cobas, A. E., Artacho, A., Knecht, H., Ferrús, M. L., Friedrichs, A., Ott, S. J., Moya, A., Latorre, A., & Gosalbes, M. J. (2013). Differential effects of antibiotic therapy on the structure and function of human gut microbiota. *PLoS One*, 8, e80201.
- Piva, A. (1998). Non-conventional feed additives. *Journal of Animal and Feed Sciences*, 7, 143–154.
- Pozuelo, M. J., Agis-Torres, A., Hervert-Hernández, D., López-Oliva, M. E., Muñoz-Martínez, E., Rotger, R., & Goni, I. (2012). Grape antioxidant dietary fiber stimulates Lactobacillus growth in rat cecum. *Journal of Food Science*, 77, H52–H59.
- Prakash, S., Rodes, L., Coussa-Charley, M., & Tomaro-Duchesneau, C. (2011). Gut microbiota: Next frontier in understanding human health and development of biotherapeutics. *Biologics*, 5, 71–86.
- Puupponen-Pimia, R., Nohynek, L., Meier, C., Kahkonen, M., Heinonen, M., Hopia, A., & Oksman-Caldentey, K. M. (2001). Antimicrobial properties of phenolic compounds from berries. *Journal of Applied Microbiology*, 90, 494–507.
- Queipo-Ortuño, M. I., Boto-Ordóñez, M., Murri, M., Gomez-Zumaquero, J. M., Clemente-Postigo, M., Estruch, R., Cardona Diaz, F., Andrés-Lacueva, C., & Tinahones, F. J. (2012). Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. *The American Journal of Clinical Nutrition*, 95, 1323–1334.
- Rice, W. C., Galyean, M. L., Cox, S. B., Dowd, S. E., & Cole, N. A. (2012). Influence of wet distillers grains diets on beef cattle fecal bacterial community structure. *BMC Microbiology*, 12, 25.
- Roberts, T., Wilson, J., Guthrie, A., Cookson, K., Vancraeynest, D., Schaeffer, J., Moody, R., & Clark, S. (2015). New issues and science in broiler chicken intestinal health: Intestinal microbial composition, shifts, and impacts. *World's Poultry Science Journal*, 71, 259–270.
- Rodríguez-Vaquero, M. J., Alberto, M. R., & Manca de Nadra, M. C. (2007). Antibacterial effect of phenolic compounds from different wines. *Food Control*, 18, 93–101.
- Roopchand, D. E., Carmody, R. N., Kuhn, P., Moskal, K., Rojas-Silva, P., Turnbaugh, P. J., & Raskin, I. (2015). Dietary polyphenols promote growth of the gut bacterium Akkermansia muciniphila and attenuate high-fat diet-induced metabolic syndrome. *Diabetes*, 64, 2847–2858.
- Saito, M., Hosoyama, H., Ariga, T., Kataoka, S., & Yamaji, N. (1998). Antiulcer activity of grape seed extract and procyanidins. *Journal of Agricultural and Food Chemistry*, 46, 1460–1464.
- Salaheen, S., Almario, J. A., & Biswas, D. (2014a). Inhibition of growth and alteration of host cell interactions of Pasteurella multocida with natural byproducts. *Poultry Science*, 93, 1375–1382.
- Salaheen, S., Nguyen, C., Hewes, D., & Biswas, D. (2014b). Cheap extraction of antibacterial compounds of berry pomace and their mode of action against the pathogen Campylobacter jejuni. *Food Control*, 46, 174–181.
- Salaheen, S., White, B., Bequette, B. J., & Biswas, D. (2014c). Peanut fractions boost the growth

- of *Lactobacillus casei* that alters the interactions between *Campylobacter jejuni* and host epithelial cells. *Food Research International*, 62, 1141–1146.
- Salaheen, S., Nguyen, C., Mui, C., & Biswas, D. (2015). Bioactive berry juice byproducts as alternative and natural inhibitors for *Salmonella Gallinarum* and *Salmonella Pullorum*. *Journal of Applied Poultry Research*, 24, 186–197.
- Salaheen, S., Kim, S. W., Haley, B. J., Van Kessel, J. A. S., & Biswas, D. (2017). Alternative growth promoters modulate broiler gut microbiome and enhance body weight gain. *Frontiers in Microbiology*, 8, 2088.
- Scott, K. P., Gratz, S. W., Sheridan, P. O., Flint, H. J., & Duncan, S. H. (2013). The influence of diet on the gut microbiota. *Pharmacological Research*, 69, 52–60.
- Selma, M. V., Espin, J. C., & Tomás-Barberán, F. A. (2009). Interaction between phenolics and gut microbiota: Role in human health. *Journal of Agricultural and Food Chemistry*, 57, 6485–6501.
- Sembries, S., Dongowski, G., Jacobasch, G., Mehrländer, K., Will, F., & Dietrich, H. (2003). Effects of dietary fibre-rich juice colloids from apple pomace extraction juices on intestinal fermentation products and microbiota in rats. *The British Journal of Nutrition*, 90, 607–615.
- Sembries, S., Dongowski, G., Mehrländer, K., Will, F., & Dietrich, H. (2006). Physiological effects of extraction juices from apple, grape, and red beet pomaces in rats. *Journal of Agricultural and Food Chemistry*, 54, 10269–10280.
- Shen, W., Gaskins, H. R., & McIntosh, M. K. (2013). Influence of dietary fat on intestinal microbes, inflammation, barrier function and metabolic outcomes. *The Journal of Nutritional Biochemistry*, 25, 270–280.
- Shi, L. H., Balakrishnan, K., Thiagarajah, K., Ismail, N. I. M. I., & Yin, O. S. (2016). Beneficial properties of probiotics. *Tropical Life Sciences Research*, 27, 73–90.
- Singh, B. R. (2009). *Salmonella* vaccines for animals and birds and their future perspective. *Open Vaccine Journal*, 2, 100–112.
- Singh, P., Karimi, A., Devendra, K., Waldroup, P. W., Cho, K. K., & Kwon, Y. M. (2013). Influence of penicillin on microbial diversity of the cecal microbiota in broiler chickens. *Poultry Science*, 92, 272–276.
- Spring, P., Wenk, C., Dawson, K. A., & Newman, K. E. (2000). The effect of dietary mannanoligosaccharides on cecal parameters and the concentrations of enteric bacteria in the ceca of *Salmonella*-challenged broiler chicks. *Poultry Science*, 79, 205–211.
- Terada, A., Hara, H., Nakajyo, S., Ichikawa, H., Hara, Y., Fukai, K., Kobayashi, Y., & Mitsuoka, T. (1993). Effect of supplements of tea polyphenols on the caecal flora and caecal metabolites of chicks. *Microbial Ecology in Health and Disease*, 6, 3–9.
- Torok, V. A., Allison, G. E., Percy, N. J., Ophel-Keller, K., & Hughes, R. J. (2011). Influence of antimicrobial feed additives on broiler commensal posthatch gut microbiota development and performance. *Applied and Environmental Microbiology*, 77, 3380–3390.
- Turnbaugh, P. J., Ley, R. E., Mahowald, M. A., Magrini, V., Mardis, E. R., & Gordon, J. I. (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*, 444, 1027–1031.
- Turnbaugh, P. J., Bäckhed, F., Fulton, L., & Gordon, J. I. (2008). Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host & Microbe*, 3, 213–223.
- Tzounis, X., Rodriguez-Mateos, A., Vulevic, J., Gibson, G. R., Kwik-Urbe, C., & Spencer, J. P. (2011). Prebiotic evaluation of cocoa-derived flavanols in healthy humans by using a randomized, controlled, double-blind, crossover intervention study. *The American Journal of Clinical Nutrition*, 93, 62–72.
- Tyeno, Y., Shigemori, S., & Shimosato, T. (2015). Effect of probiotics/prebiotics on cattle health and productivity. *Microbes and Environments*, 30(2), 126–132.
- Verhelst, R., Schroyen, M., Buys, N., & Niewold, T. (2014). Dietary polyphenols reduce diarrhea

- in enterotoxigenic *Escherichia coli* (ETEC) infected post-weaning piglets. *Livestock Science*, *160*, 138–140.
- Viveros, A., Chamorro, S., Pizarro, M., Arija, I., Centeno, C., & Brenes, A. (2011). Effects of dietary polyphenol-rich grape products on intestinal microflora and gut morphology in broiler chicks. *Poultry Science*, *90*, 566–578.
- Vondruskova, H., Slamova, R., Trckova, M., Zraly, Z., & Pavlik, I. (2010). Alternatives to antibiotic growth promoters in prevention of diarrhoea in weaned piglets: A review. *Veterinarni Medicina Czech*, *55*, 199–224.
- Wales, A. D., Allen, V. M., & Davies, R. H. (2010). Chemical treatment of animal feed and water for the control of *Salmonella*. *Foodborne Pathogens and Disease*, *7*, 3–15.
- Walker, A. W., Duncan, S. H., Leitch, E. C. M., Child, M. W., & Flint, H. J. (2005). pH and peptide supply can radically alter bacterial populations and short chain fatty acid ratios within microbial communities from the human colon. *Applied and Environmental Microbiology*, *71*, 3692–3700.
- Warren, C. A., & Guerrant, R. L. (2011). Pathogenic *C. difficile* is here (and everywhere) to stay. *Lancet*, *377*, 8–9.
- Williams, A. R., Krych, L., Fauzan Ahmad, H., Nejsum, P., Skovgaard, K., Nielsen, D. S., & Thamsborg, S. M. (2017). A polyphenol-enriched diet and *Ascaris suum* infection modulate mucosal immune responses and gut microbiota composition in pigs. *PLoS One*, *12*, e0186546.
- Yang, H., Hewes, D., Salaheen, S., Federman, C., & Biswas, D. (2014). Effects of blackberry juice on growth inhibition of foodborne pathogens and growth promotion of *Lactobacillus*. *Food Control*, *37*, 15–20.
- Yang, F., Hou, C., Zeng, X., & Qiao, S. (2015). The use of lactic acid bacteria as a probiotic in Swine diets. *Pathogens (Basel, Switzerland)*, *4*(1), 34–45.
- Yeoman, C. J., Chia, N., Jeraldo, P., Sipos, M., Goldenfeld, N. D., & White, B. A. (2012). The microbiome of the chicken gastrointestinal tract. *Animal Health Research Reviews*, *13*, 89–99.
- Zhang, C., Li, S., Yang, L., Huang, P., Li, W., Wang, S., Zhao, G., Zhang, M., Pang, X., Yan, Z., Liu, Y., & Zhao, L. (2013). Structural modulation of gut microbiota in life-long calorie-restricted mice. *Nature Communications*, *4*, 2163.