

# 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 müsini 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., Borrueal, 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., Tsois, R. M., Roth, J. R., & Bäumlér, 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., MacDonald, 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.