Güncel Tıbbi Biyoloji ve Genetik Çalışmaları V

Editör
Prof. Dr. H. Ümit LÜLEYAP (PhD)

ISBN
978-625-399-432-7

Kitap Adı
Güncel Tıbbi Biyoloji ve Genetik Çalışmaları V

Editör
H. Ümit LÜLEYAP
ORCID iD: 0000-0001-8759-1381

Yayın Koordinatörü
Yasin DİLMEN

Sayfa ve Kapak Tasarımı
Akademisyen Dizgi Ünitesi

Yayıncı Sertifika No
47518

Baskı ve Cilt
Vadi Matbaacılık

Bisac Code
MED052000

DOI
10.37609/akya.2842

Kütüphane Kimlik Kartı
Güncel Tıbbi Biyoloji ve Genetik Çalışmaları V / editör : Hüsnü Ümit Lüleyap.
Ankara : Akademisyen Yayınevi Kitabevi, 2023.
161 s. : tablo, şekil. ; 160x235 mm.
Kaynakça ve İndeks var.
ISBN 9786253994327
1. Tıbbi Biyoloj--Genetik.

UYARI

Bu üründe yer alan bilgiler sadece lisanslı tıbbi çalışanlar için kaynak olarak sunulmuştur. Herhangi bir konuda profesyonel tıbbi danışmanlık veya tıbbi tanı amacıyla kullanılmamalıdır. Akademisyen Kitabevi ve alıcı arasında herhangi bir şekilde doktor-hasta, terapist-hasta ve/veya başka bir sağlık sunum hizmeti ilişkisi oluşturmaz. Bu ürün profesyonel tıbbi kararların eşleniği veya yedeği değildir. Akademisyen Kitabevi ve bağlı şirketleri, yazarları, katılımcıları, partnerleri ve sponsorları ürün bilgilerine dayalı olarak yapılan bütün uygulamalardan doğan, insanlarda ve cihazlarda yaralanma ve/veya hasarlardan sorumlu değildir.

İlaçların veya başka kimyasalların reçete edildiği durumlarda, tavsiye edilen dozunu, ilacın uygulanacak süresi, yöntemi ve kontraendikasyonlarını belirlemek için, okuyucuya üretici tarafından her ilaca dair sunulan güncel ürün bilgisini kontrol etmesi tavsiye edilmektedir. Dozun ve hasta için en uygun tedavinin belirlenmesi, tedavi eden hekimin hastaya dair bilgi ve tecrübelerine dayanak oluşturması, hekimin kendi sorumluluğundadır.

Akademisyen Kitabevi, üçüncü bir taraf tarafından yapılan ürüne dair değişiklikler, tekrar paketlemeler ve özelleştirmelerden sorumlu değildir.

GENEL DAĞITIM

Akademisyen Kitabevi AŞ

Halk Sokak 5 / A Yenişehir / Ankara
Tel: 0312 431 16 33
siparis@akademisyen.com

www.akademisyen.com

ÖN SÖZ

Akademisyen Yayınevi yöneticileri, yaklaşık 30 yıllık yayın tecrübesini, kendi tüzel kişiliklerine aktararak uzun zamandan beri, ticarî faaliyetlerini sürdürmektedir. Anılan süre içinde, başta sağlık ve sosyal bilimler, kültürel ve sanatsal konular dahil 2700'ü aşkın kitabı yayımlamanın gururu içindedir. Uluslararası yayınevi olmanın alt yapısını tamamlayan Akademisyen, Türkçe ve yabancı dillerde yayın yapmanın yanında, küresel bir marka yaratmanın peşindedir.

Bilimsel ve düşünsel çalışmaların kalıcı belgeleri sayılan kitaplar, bilgi kayıt ortamı olarak yüzlerce yılın tanıklarıdır. Matbaanın icadıyla varoluşunu sağlam temellere oturtan kitabın geleceği, her ne kadar yeni buluşların yörüngesine taşınmış olsa da, daha uzun süre hayatımızda yer edineceği muhakkaktır.

Akademisyen Yayınevi, kendi adını taşıyan **"Bilimsel Araştırmalar Kitabı"** serisiyle Türkçe ve İngilizce olarak, uluslararası nitelik ve nicelikte, kitap yayımlama sürecini başlatmış bulunmaktadır. Her yıl mart ve eylül aylarında gerçekleşecek olan yayımlama süreci, tematik alt başlıklarla devam edecektir. Bu süreci destekleyen tüm hocalarımıza ve arka planda yer alan herkese teşekkür borçluyuz.

Akademisyen Yayınevi A.Ş.

İÇİNDEKİLER

YAZARLAR

Fethi Caner ADIGÜZEL
Kastamonu Üniversitesi Tıp Fakültesi

Dr. Öğr. Üyesi Uğur AKPULAT
Kastamonu Üniversitesi Tıp Fakültesi, Tıbbi Biyoloji AD

Dr. Öğr. Üyesi Yunus ARIKAN
Yozgat Bozok Üniversitesi Tıp Fakültesi, Tıbbi Genetik AD

Dilek DAŞ
Senior Klinik Embriyolog, ART Fertility Clinics

Doç. Dr. Huri DEDEAKAYOĞULLARI
İstinye Üniversitesi Tıp Fakültesi Tıbbi Biyokimya AD

Doç. Dr. Demet TEKDÖŞ DEMİRCİOĞLU
İstanbul Aydın Üniversitesi Tıp Fakültesi Fiziksel Tıp ve Rehabilitasyon AD

Yüksek Biyolog Ayşenur ÖZDEMİR KANAT
Kastamonu Üniversitesi, Tıp Fakültesi

Dr. Ferah KAZANCI
Necip Fazıl Şehir Hastanesi Kadın Doğum ve Çocuk Ek Hizmet Binası, Jinekolojik Onkoloji Kliniği

Prof.Dr. H. Ümit LÜLEYAP
Çukurova Üniversitesi Tıp Fakültesi,Tıbbi Biyoloji ve Genetik AD

Arş. Gör. Dr. Umut Kerem KOLAÇ
Aydın Adnan Menderes Üniversitesi, Tıp Fakültesi, Tıbbi Biyoloji AD

Dr. Öğr. Üyesi Gülper NACARKAHYA
Gaziantep Üniversitesi Tıp Fakültesi, Tıbbi Biyoloji AD

Dr. Öğr. Üyesi Seval TÜRK
Antalya Bilim Üniversitesi Diş Hekimliği Fakültesi Temel Bilimler AD

Op. Dr. Hacer KAVAK YILDIRIM
Marmara Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum AD

Bölüm 1

MİTOKONDRİYAL KATLANMAMIŞ PROTEİN YANITI VE KANSER

Umut Kerem KOLAÇ[1]

GİRİŞ

Kanser hücreleri kontrolsüz bir şekilde çoğaldıkça, aynı zamanda kendileri için de dezavantaj oluşturacak bir dizi olumsuzluğun ortaya çıkmasına neden olur. Bu nedenle kanser hücreleri, kendilerinin neden olduğu olumsuzluklara karşı kendilerini koruyacak ve/veya daha az etkileyecek savunma sistemlerine ihtiyaç duyarlar (1). Özellikle mitokondriler, kanserin farklı aşamalarında büyümeye ve hayatta kalmaya katkı sağlar (2). Ancak mitokondriler aynı zamanda genetik değişikliklere uğrar ve bozulmuş bir elektron taşıma zinciri oluşturur. Bu da aşırı miktarda mitokondriyal reaktif oksijen türleri (mtROS) üretilmesine neden olur (3, 4). Normal koşullarda ve hastalığın erken evrelerinde, mitokondriler hücresel büyüme ve hayatta kalma için faydalı olan ılımlı düzeylerde mtROS üretirler. Ancak mitokondriyal bozukluklar arttıkça, mtROS seviyeleri tolere edilebilir eşiği aşabilir ve tümör hücreleri için ölümcül hale gelebilir (5, 6). mtROS, mitokondriyal katlanmamış proteinlerin açığa çıkmasını ve bir araya gelmesini teşvik ederek, mitokondrileri giderek daha kırılgan ve işlevsiz hale getirir (3, 7). Mitokondriyal katlanmamış protein yanıtı (mtUPR), *C. elegans* ve memeli sistemlerinde gözlemlenen bir mitokondriyal stres yanıtıdır (8, 9). Kanserde mitokondriyal bütünlüğü koruyarak ve tümör büyümesini teşvik ederek önemli bir destek sistem olarak görev yapar (10). mtUPR, mtROS' un zararlı etkilerini hafifletmek için bir dizi şaperon ve proteazı harekete geçirir. Artan kanıtlar, mtUPR genlerinin *C. elegans* ve memeliler arasında korunduğunu göstermektedir (11).

Bu bölümde mtUPR' nin tümör büyümesi ve ilerlemesini desteklemede mitokondrilerin işlevsel bozukluğunu önleme yeteneği ele alınmaktadır. mtUPR' nin mitokondriyal sağlığı koruma yeteneği incelenerek, mtUPR bileşenlerinin bireysel işlevleri, klinik sonuçlarla olan ilişkileri ve tümörü teşvik edici rolleri

[1] Dr., Aydın Adnan Menderes Üniversitesi, Tıp Fakültesi, Tıbbi Biyoloji AD, ukolac@adu.edu.tr, ORCID iD: 0000-0003-0266-9069

yüksek derecede bağımlı olduğunu açıkça göstermektedir (153, 154). Bu nedenle, prostat kanseri gibi agresif ve dirençli kanserlere karşı yeni terapiler geliştirmek için önemli bir hedef olduğu söylenebilir.Formun Üstü

KAYNAKÇA

1. Luo J, Solimini NL, Elledge SJ. Principles of cancer therapy: oncogene and non-oncogene addiction. Cell. 2009;136(5):823-37.
2. Vyas S, Zaganjor E, Haigis MC. Mitochondria and cancer. Cell. 2016;166(3):555-66.
3. Murphy MP. How mitochondria produce reactive oxygen species. Biochem J. 2009;417(1):1-13.
4. Lagouge M, Larsson NG. The role of mitochondrial DNA mutations and free radicals in disease and ageing. J Intern Med. 2013;273(6):529-43.
5. Morrell CN. Reactive oxygen species: finding the right balance. Am Heart Assoc; 2008. p. 571-2.
6. Galadari S, Rahman A, Pallichankandy S, Thayyullathil F. Reactive oxygen species and cancer paradox: to promote or to suppress? Free Radical Bio Med. 2017;104:144-64.
7. Bigarella CL, Liang R, Ghaffari S. Stem cells and the impact of ROS signaling. Development. 2014;141(22):4206-18.
8. Fiorese CJ, Schulz AM, Lin Y-F, Rosin N, Pellegrino MW, Haynes CM. The transcription factor ATF5 mediates a mammalian mitochondrial UPR. Current biology. 2016;26(15):2037-43.
9. Martinus RD, Garth GP, Webster TL, Cartwright P, Naylor DJ, Høj PB, et al. Selective induction of mitochondrial chaperones in response to loss of the mitochondrial genome. European journal of biochemistry. 1996;240(1):98-103.
10. Kenny TC, Gomez ML, Germain D. Mitohormesis, UPRmt, and the complexity of mitochondrial DNA landscapes in cancer. Cancer Res. 2019;79(24):6057-66.
11. Wu Y, Williams EG, Dubuis S, Mottis A, Jovaisaite V, Houten SM, et al. Multilayered genetic and omics dissection of mitochondrial activity in a mouse reference population. Cell. 2014;158(6):1415-30.
12. Van der Bliek AM, Sedensky MM, Morgan PG. Cell biology of the mitochondrion. Genetics. 2017;207(3):843-71.
13. Taanman J-W. The mitochondrial genome: structure, transcription, translation and replication. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 1999;1410(2):103-23.
14. Kühlbrandt W. Structure and function of mitochondrial membrane protein complexes. BMC Biol. 2015;13:1-11.
15. Meyer JN, Leuthner TC, Luz AL. Mitochondrial fusion, fission, and mitochondrial toxicity. Toxicology. 2017;391:42-53.
16. Chandel NS. Metabolism of proliferating cells. Cold Spring Harb Perspect Biol. 2021;13(10):a040618.
17. Martínez-Reyes I, Chandel NS. Cancer metabolism: looking forward. Nature Reviews Cancer. 2021;21(10):669-80.
18. Hüttemann M, Lee I, Samavati L, Yu H, Doan JW. Regulation of mitochondrial oxidative phosphorylation through cell signaling. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2007;1773(12):1701-20.

19. Quinlan CL, Goncalves RL, Hey-Mogensen M, Yadava N, Bunik VI, Brand MD. The 2-oxoacid dehydrogenase complexes in mitochondria can produce superoxide/hydrogen peroxide at much higher rates than complex I. Journal of Biological Chemistry. 2014;289(12):8312-25.
20. Brand MD. Mitochondrial generation of superoxide and hydrogen peroxide as the source of mitochondrial redox signaling. Free Radical Bio Med. 2016;100:14-31.
21. Evans MD, Dizdaroglu M, Cooke MS. Oxidative DNA damage and disease: induction, repair and significance. Mutation Research/Reviews in Mutation Research. 2004;567(1):1-61.
22. Weydert CJ, Cullen JJ. Measurement of superoxide dismutase, catalase and glutathione peroxidase in cultured cells and tissue. Nat Protoc. 2010;5(1):51-66.
23. Sastre J, Pallardó FV, Viña J. The role of mitochondrial oxidative stress in aging. Free Radical Bio Med. 2003;35(1):1-8.
24. Alexeyev M, Shokolenko I, Wilson G, LeDoux S. The maintenance of mitochondrial DNA integrity—critical analysis and update. Cold Spring Harb Perspect Biol. 2013;5(5):a012641.
25. Larsen NB, Rasmussen M, Rasmussen LJ. Nuclear and mitochondrial DNA repair: similar pathways? Mitochondrion. 2005;5(2):89-108.
26. Escames G, López LC, García JA, Garcia-Corzo L, Ortiz F, Acuna-Castroviejo D. Mitochondrial DNA and inflammatory diseases. Hum Genet. 2012;131:161-73.
27. Nicolson GL. Mitochondrial dysfunction and chronic disease: treatment with natural supplements. Integrative Medicine: A Clinician's Journal. 2014;13(4):35.
28. Moro L. Mitochondrial dysfunction in aging and cancer. Journal of clinical medicine. 2019;8(11):1983.
29. Cruz-Bermúdez A, Vallejo CG, Vicente-Blanco RJ, Gallardo ME, Fernández-Moreno MÁ, Quintanilla M, et al. Enhanced tumorigenicity by mitochondrial DNA mild mutations. Oncotarget. 2015;6(15):13628.
30. Shidara Y, Yamagata K, Kanamori T, Nakano K, Kwong JQ, Manfredi G, et al. Positive contribution of pathogenic mutations in the mitochondrial genome to the promotion of cancer by prevention from apoptosis. Cancer Res. 2005;65(5):1655-63.
31. Liou G-Y, Döppler H, DelGiorno KE, Zhang L, Leitges M, Crawford HC, et al. Mutant KRas-induced mitochondrial oxidative stress in acinar cells upregulates EGFR signaling to drive formation of pancreatic precancerous lesions. Cell reports. 2016;14(10):2325-36.
32. Inigo JR, Chandra D. The mitochondrial unfolded protein response (UPRmt): shielding against toxicity to mitochondria in cancer. J Hematol Oncol. 2022;15(1):1-18.
33. Kwon J, Lee S-R, Yang K-S, Ahn Y, Kim YJ, Stadtman ER, et al. Reversible oxidation and inactivation of the tumor suppressor PTEN in cells stimulated with peptide growth factors. Proceedings of the National Academy of Sciences. 2004;101(47):16419-24.
34. Chalhoub N, Baker SJ. PTEN and the PI3-kinase pathway in cancer. Annual Review of Pathology: Mechanisms of Disease. 2009;4:127-50.
35. Chetram MA, Hinton CV. PTEN regulation of ERK1/2 signaling in cancer. J Recept Signal Transduct. 2012;32(4):190-5.
36. Lim JM, Lee KS, Woo HA, Kang D, Rhee SG. Control of the pericentrosomal H2O2 level by peroxiredoxin I is critical for mitotic progression. Journal of Cell Biology. 2015;210(1):23-33.

37. Weinberg F, Hamanaka R, Wheaton WW, Weinberg S, Joseph J, Lopez M, et al. Mitochondrial metabolism and ROS generation are essential for Kras-mediated tumorigenicity. Proceedings of the National Academy of Sciences. 2010;107(19):8788-93.
38. Qi L, Sun X, Li F-E, Zhu B-S, Braun FK, Liu Z-Q, et al. HMGB1 promotes mitochondrial dysfunction–triggered striatal neurodegeneration via autophagy and apoptosis activation. PLoS One. 2015;10(11):e0142901.
39. Tang D, Kang R, Zeh III HJ, Lotze MT. High-mobility group box 1 and cancer. Biochimica et Biophysica Acta (BBA)-Gene Regulatory Mechanisms. 2010;1799(1-2):131-40.
40. Kang R, Tang D, Schapiro N, Loux T, Livesey K, Billiar T, et al. The HMGB1/RAGE inflammatory pathway promotes pancreatic tumor growth by regulating mitochondrial bioenergetics. Oncogene. 2014;33(5):567-77.
41. Chen Q, Kirk K, Shurubor YI, Zhao D, Arreguin AJ, Shahi I, et al. Rewiring of glutamine metabolism is a bioenergetic adaptation of human cells with mitochondrial DNA mutations. Cell metabolism. 2018;27(5):1007-25. e5.
42. Khasawneh J, Schulz M, Walch A, Rozman J, De Angelis MH, Klingenspor M, et al. Inflammation and mitochondrial fatty acid β-oxidation link obesity to early tumor promotion. Proceedings of the National Academy of Sciences. 2009;106(9):3354-9.
43. Wang C, Shao L, Pan C, Ye J, Ding Z, Wu J, et al. Elevated level of mitochondrial reactive oxygen species via fatty acid β-oxidation in cancer stem cells promotes cancer metastasis by inducing epithelial–mesenchymal transition. Stem Cell Res Ther. 2019;10:1-16.
44. Neagu M, Constantin C, Popescu ID, Zipeto D, Tzanakakis G, Nikitovic D, et al. Inflammation and metabolism in cancer cell—mitochondria key player. Front Oncol. 2019;9:348.
45. Frenkel K. Carcinogen-mediated oxidant formation and oxidative DNA damage. Pharmacol Ther. 1992;53(1):127-66.
46. Wang J, Li D, Cang H, Guo B. Crosstalk between cancer and immune cells: Role of tumor-associated macrophages in the tumor microenvironment. Cancer medicine. 2019;8(10):4709-21.
47. Trush MA, Kensler TW. An overview of the relationship between oxidative stress and chemical carcinogenesis. Free Radical Bio Med. 1991;10(3-4):201-9.
48. Hahn WS, Kuzmicic J, Burrill JS, Donoghue MA, Foncea R, Jensen MD, et al. Proinflammatory cytokines differentially regulate adipocyte mitochondrial metabolism, oxidative stress, and dynamics. American Journal of Physiology-Endocrinology and Metabolism. 2014;306(9):E1033-E45.
49. El Jamal SM, Taylor EB, Abd Elmageed ZY, Alamodi AA, Selimovic D, Alkhateeb A, et al. Interferon gamma-induced apoptosis of head and neck squamous cell carcinoma is connected to indoleamine-2, 3-dioxygenase via mitochondrial and ER stress-associated pathways. Cell Div. 2016;11:1-14.
50. Cao Y, Zhang X, Shang W, Xu J, Wang X, Hu X, et al. Proinflammatory cytokines stimulate mitochondrial superoxide flashes in articular chondrocytes in vitro and in situ. PLoS One. 2013;8(6):e66444.
51. Dehne N, Mora J, Namgaladze D, Weigert A, Brüne B. Cancer cell and macrophage cross-talk in the tumor microenvironment. Current opinion in pharmacology. 2017;35:12-9.

52. Park JS, Sharma LK, Li H, Xiang R, Holstein D, Wu J, et al. A heteroplasmic, not homoplasmic, mitochondrial DNA mutation promotes tumorigenesis via alteration in reactive oxygen species generation and apoptosis. Human molecular genetics. 2009;18(9):1578-89.
53. Kwong JQ, Henning MS, Starkov AA, Manfredi G. The mitochondrial respiratory chain is a modulator of apoptosis. The Journal of cell biology. 2007;179(6):1163-77.
54. Okon IS, Coughlan KA, Zhang M, Wang Q, Zou M-H. Gefitinib-mediated reactive oxygen specie (ROS) instigates mitochondrial dysfunction and drug resistance in lung cancer cells. Journal of Biological Chemistry. 2015;290(14):9101-10.
55. Gammage PA, Frezza C. Mitochondrial DNA: the overlooked oncogenome? BMC Biol. 2019;17(1):1-10.
56. Gupta GP, Massagué J. Cancer metastasis: building a framework. Cell. 2006;127(4):679-95.
57. Kulawiec M, Owens KM, Singh KK. mtDNA G10398A variant in African-American women with breast cancer provides resistance to apoptosis and promotes metastasis in mice. J Hum Genet. 2009;54(11):647-54.
58. Imanishi H, Hattori K, Wada R, Ishikawa K, Fukuda S, Takenaga K, et al. Mitochondrial DNA mutations regulate metastasis of human breast cancer cells. PloS one. 2011;6(8):e23401.
59. Sun H-F, Yang X-l, Zhao Y, Tian Q, Chen M-T, Zhao Y-y, et al. Loss of TMEM126A promotes extracellular matrix remodeling, epithelial-to-mesenchymal transition, and breast cancer metastasis by regulating mitochondrial retrograde signaling. Cancer Lett. 2019;440:189-201.
60. Keerthiga R, Pei D-S, Fu A. Mitochondrial dysfunction, UPRmt signaling, and targeted therapy in metastasis tumor. Cell & Bioscience. 2021;11(1):1-14.
61. Liou G-Y, Storz P. Reactive oxygen species in cancer. Free Radic Res. 2010;44(5):479-96.
62. Lévy E, El Banna N, Baïlle D, Heneman-Masurel A, Truchet S, Rezaei H, et al. Causative links between protein aggregation and oxidative stress: a review. International journal of molecular sciences. 2019;20(16):3896.
63. Genova ML, Lenaz G. The interplay between respiratory supercomplexes and ROS in aging. Antioxid Redox Sign. 2015;23(3):208-38.
64. Zhao Q, Wang J, Levichkin IV, Stasinopoulos S, Ryan MT, Hoogenraad NJ. A mitochondrial specific stress response in mammalian cells. The EMBO journal. 2002;21(17):4411-9.
65. Harbauer AB, Zahedi RP, Sickmann A, Pfanner N, Meisinger C. The protein import machinery of mitochondria—a regulatory hub in metabolism, stress, and disease. Cell metabolism. 2014;19(3):357-72.
66. Liu Z, Butow RA. Mitochondrial retrograde signaling. Annu Rev Genet. 2006;40:159-85.
67. Yoneda T, Benedetti C, Urano F, Clark SG, Harding HP, Ron D. Compartment-specific perturbation of protein handling activates genes encoding mitochondrial chaperones. J Cell Sci. 2004;117(18):4055-66.
68. Haynes CM, Petrova K, Benedetti C, Yang Y, Ron D. ClpP mediates activation of a mitochondrial unfolded protein response in C. elegans. Developmental cell. 2007;13(4):467-80.

69. Nargund AM, Pellegrino MW, Fiorese CJ, Baker BM, Haynes CM. Mitochondrial import efficiency of ATFS-1 regulates mitochondrial UPR activation. Science. 2012;337(6094):587-90.
70. Nargund AM, Fiorese CJ, Pellegrino MW, Deng P, Haynes CM. Mitochondrial and nuclear accumulation of the transcription factor ATFS-1 promotes OXPHOS recovery during the UPRmt. Molecular cell. 2015;58(1):123-33.
71. Baker BM, Nargund AM, Sun T, Haynes CM. Protective coupling of mitochondrial function and protein synthesis via the eIF2α kinase GCN-2. PLoS Genet. 2012;8(6):e1002760.
72. Schulz AM, Haynes CM. UPRmt-mediated cytoprotection and organismal aging. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 2015;1847(11):1448-56.
73. Nishitoh H. CHOP is a multifunctional transcription factor in the ER stress response. The Journal of Biochemistry. 2012;151(3):217-9.
74. Papa L, Germain D. Estrogen receptor mediates a distinct mitochondrial unfolded protein response. J Cell Sci. 2011;124(9):1396-402.
75. Papa L, Germain D. SirT3 regulates the mitochondrial unfolded protein response. Molecular and cellular biology. 2014;34(4):699-710.
76. Mohrin M, Shin J, Liu Y, Brown K, Luo H, Xi Y, et al. A mitochondrial UPR-mediated metabolic checkpoint regulates hematopoietic stem cell aging. Science. 2015;347(6228):1374-7.
77. Katiyar A, Fujimoto M, Tan K, Kurashima A, Srivastava P, Okada M, et al. HSF1 is required for induction of mitochondrial chaperones during the mitochondrial unfolded protein response. FEBS Open bio. 2020;10(6):1135-48.
78. Harding HP, Zhang Y, Bertolotti A, Zeng H, Ron D. Perk is essential for translational regulation and cell survival during the unfolded protein response. Molecular cell. 2000;5(5):897-904.
79. Horibe T, Hoogenraad NJ. The chop gene contains an element for the positive regulation of the mitochondrial unfolded protein response. PloS one. 2007;2(9):e835.
80. Zhou D, Palam LR, Jiang L, Narasimhan J, Staschke KA, Wek RC. Phosphorylation of eIF2 directs ATF5 translational control in response to diverse stress conditions. Journal of Biological Chemistry. 2008;283(11):7064-73.
81. Wang YT, Lim Y, McCall MN, Huang K-T, Haynes CM, Nehrke K, et al. Cardioprotection by the mitochondrial unfolded protein response requires ATF5. American Journal of Physiology-Heart and Circulatory Physiology. 2019;317(2):H472-H8.
82. Tyynismaa H, Carroll CJ, Raimundo N, Ahola-Erkkilä S, Wenz T, Ruhanen H, et al. Mitochondrial myopathy induces a starvation-like response. Human molecular genetics. 2010;19(20):3948-58.
83. Smyrnias I, Gray SP, Okonko DO, Sawyer G, Zoccarato A, Catibog N, et al. Cardioprotective effect of the mitochondrial unfolded protein response during chronic pressure overload. J Am Coll Cardiol. 2019;73(14):1795-806.
84. Beissinger M, Buchner J. How chaperones fold proteins. Biol Chem. 1998;379(3):245-59.
85. Quirós PM, Bárcena C, López-Otín C. Lon protease: A key enzyme controlling mitochondrial bioenergetics in cancer. Molecular & cellular oncology. 2014;1(4):e968505.
86. Gottesman S, Roche E, Zhou Y, Sauer RT. The ClpXP and ClpAP proteases degrade proteins with carboxy-terminal peptide tails added by the SsrA-tagging system. Genes Dev. 1998;12(9):1338-47.

87. Young L, Leonhard K, Tatsuta T, Trowsdale J, Langer T. Role of the ABC transporter Mdl1 in peptide export from mitochondria. Science. 2001;291(5511):2135-8.
88. Bezawork-Geleta A, Brodie EJ, Dougan DA, Truscott KN. LON is the master protease that protects against protein aggregation in human mitochondria through direct degradation of misfolded proteins. Scientific reports. 2015;5(1):17397.
89. Deng P, Haynes CM, editors. Mitochondrial dysfunction in cancer: potential roles of ATF5 and the mitochondrial UPR. Semin Cancer Biol; 2017: Elsevier.
90. Vinson C, Myakishev M, Acharya A, Mir AA, Moll JR, Bonovich M. Classification of human B-ZIP proteins based on dimerization properties. Molecular and cellular biology. 2002.
91. Sun X, Jefferson P, Zhou Q, Angelastro JM, Greene LA. Dominant-negative ATF5 compromises cancer cell survival by targeting CEBPB and CEBPD. Molecular Cancer Research. 2020;18(2):216-28.
92. Feldheim J, Kessler AF, Schmitt D, Wilczek L, Linsenmann T, Dahlmann M, et al. Expression of activating transcription factor 5 (ATF5) is increased in astrocytomas of different WHO grades and correlates with survival of glioblastoma patients. Onco Targets Ther. 2018:8673-84.
93. Monaco SE, Angelastro JM, Szabolcs M, Greene LA. The transcription factor ATF5 is widely expressed in carcinomas, and interference with its function selectively kills neoplastic, but not nontransformed, breast cell lines. Int J Cancer. 2007;120(9):1883-90.
94. Hu M, Wang B, Qian D, Li L, Zhang L, Song X, et al. Interference with ATF5 function enhances the sensitivity of human pancreatic cancer cells to paclitaxel-induced apoptosis. Anticancer Res. 2012;32(10):4385-94.
95. Kong X, Meng W, Zhou Z, Li Y, Zhou B, Wang R, et al. Overexpression of activating transcription factor 5 in human rectal cancer. Exp Ther Med. 2011;2(5):827-31.
96. Chen A, Qian D, Wang B, Hu M, Lu J, Qi Y, et al. ATF5 is overexpressed in epithelial ovarian carcinomas and interference with its function increases apoptosis through the downregulation of Bcl-2 in SKOV-3 cells. Int J Gynecol Pathol. 2012;31(6):532-7.
97. Sheng Z, Li L, Zhu LJ, Smith TW, Demers A, Ross AH, et al. A genome-wide RNA interference screen reveals an essential CREB3L2-ATF5-MCL1 survival pathway in malignant glioma with therapeutic implications. Nat Med. 2010;16(6):671-7.
98. Ishihara S, Yasuda M, Ishizu A, Ishikawa M, Shirato H, Haga H. Activating transcription factor 5 enhances radioresistance and malignancy in cancer cells. Oncotarget. 2015;6(7):4602.
99. Wang H, Lin G, Zhang Z. ATF5 promotes cell survival through transcriptional activation of Hsp27 in H9c2 cells. Cell Biol Int. 2007;31(11):1309-15.
100. Liu DX, Qian D, Wang B, Yang J-M, Lu Z. p300-Dependent ATF5 acetylation is essential for Egr-1 gene activation and cell proliferation and survival. Molecular and cellular biology. 2011;31(18):3906-16.
101. Dluzen D, Li G, Tacelosky D, Moreau M, Liu DX. BCL-2 is a downstream target of ATF5 that mediates the prosurvival function of ATF5 in a cell type-dependent manner. Journal of Biological Chemistry. 2011;286(9):7705-13.
102. Karpel-Massler G, Horst BA, Shu C, Chau L, Tsujiuchi T, Bruce JN, et al. A synthetic cell-penetrating dominant-negative ATF5 peptide exerts anticancer activity against a broad spectrum of treatment-resistant cancers. Clin Cancer Res. 2016;22(18):4698-711.

103. Levy-Rimler G, Viitanen P, Weiss C, Sharkia R, Greenberg A, Niv A, et al. The effect of nucleotides and mitochondrial chaperonin 10 on the structure and chaperone activity of mitochondrial chaperonin 60. European journal of biochemistry. 2001;268(12):3465-72.
104. Sarangi U, Singh MK, Abhijnya KVV, Reddy LPA, Prasad BS, Pitke VV, et al. Hsp60 chaperonin acts as barrier to pharmacologically induced oxidative stress mediated apoptosis in tumor cells with differential stress response. Drug Target Insights. 2013;7:DTI. S12513.
105. Gammazza AM, Campanella C, Barone R, Bavisotto CC, Gorska M, Wozniak M, et al. Doxorubicin anti-tumor mechanisms include Hsp60 post-translational modifications leading to the Hsp60/p53 complex dissociation and instauration of replicative senescence. Cancer Lett. 2017;385:75-86.
106. ZUMMO G. Immunohistochemical evaluation of PCNA, p53, HSP60, HSP10 and MUC-2 presence and expression in prostate carcinogenesis. Anticancer Res. 2003;23:1325-32.
107. Rappa F, Pitruzzella A, Marino Gammazza A, Barone R, Mocciaro E, Tomasello G, et al. Quantitative patterns of Hsps in tubular adenoma compared with normal and tumor tissues reveal the value of Hsp10 and Hsp60 in early diagnosis of large bowel cancer. Cell Stress and Chaperones. 2016;21:927-33.
108. Lim SO, Park SG, Yoo J-H, Park YM, Kim H-J, Jang K-T, et al. Expression of heat shock proteins (HSP27, HSP60, HSP70, HSP90, GRP78, GRP94) in hepatitis B virus-related hepatocellular carcinomas and dysplastic nodules. World journal of gastroenterology: WJG. 2005;11(14):2072.
109. Mano R, Zilber S, Di Natale RG, Kedar D, Lifshitz DA, Yossepowitch O, et al., editors. Heat shock proteins 60 and 70 are associated with long-term outcome of T1-stage high-grade urothelial tumors of the bladder treated with intravesical Bacillus Calmette-Guérin immunotherapy. Urologic Oncology: Seminars and Original Investigations; 2018: Elsevier.
110. Vocka M, Langer D, Fryba V, Petrtyl J, Hanus T, Kalousova M, et al. Novel serum markers HSP60, CHI3L1, and IGFBP-2 in metastatic colorectal cancer. Oncol Lett. 2019;18(6):6284-92.
111. Cappello F, David S, Rappa F, Bucchieri F, Marasà L, Bartolotta TE, et al. The expression of HSP60 and HSP10 in large bowel carcinomas with lymph node metastase. BMC cancer. 2005;5(1):1-10.
112. Zhou C, Sun H, Zheng C, Gao J, Fu Q, Hu N, et al. Oncogenic HSP60 regulates mitochondrial oxidative phosphorylation to support Erk1/2 activation during pancreatic cancer cell growth. Cell death & disease. 2018;9(2):161.
113. Guo J, Li X, Zhang W, Chen Y, Zhu S, Chen L, et al. HSP60-regulated mitochondrial proteostasis and protein translation promote tumor growth of ovarian cancer. Scientific reports. 2019;9(1):12628.
114. Chalmers SA, Eidelman AS, Ewer JC, Ricca JM, Serrano A, Tucker KC, et al. A role for HMGB1, HSP60 and Myd88 in growth of murine mammary carcinoma in vitro. Cell Immunol. 2013;282(2):136-45.
115. Tang H, Li J, Liu X, Wang G, Luo M, Deng H. Down-regulation of HSP60 Suppresses the Proliferation of Glioblastoma Cells via the ROS/AMPK/mTOR Pathway. Scientific reports. 2016;6(1):28388.

116. Ghosh JC, Siegelin MD, Dohi T, Altieri DC. Heat shock protein 60 regulation of the mitochondrial permeability transition pore in tumor cells. Cancer Res. 2010;70(22):8988-93.
117. Kumar S, O'Malley J, Chaudhary AK, Inigo JR, Yadav N, Kumar R, et al. Hsp60 and IL-8 axis promotes apoptosis resistance in cancer. Br J Cancer. 2019;121(11):934-43.
118. Chandra D, Choy G, Tang DG. Cytosolic accumulation of HSP60 during apoptosis with or without apparent mitochondrial release: evidence that its pro-apoptotic or pro-survival functions involve differential interactions with caspase-3. Journal of Biological Chemistry. 2007;282(43):31289-301.
119. Ghosh JC, Dohi T, Kang BH, Altieri DC. Hsp60 regulation of tumor cell apoptosis. Journal of Biological Chemistry. 2008;283(8):5188-94.
120. Kirchhoff S, Gupta S, Knowlton A. Cytosolic heat shock protein 60, apoptosis, and myocardial injury. Circulation. 2002;105(24):2899-904.
121. Piselli P, Vendetti S, Vismara D, Cicconi R, Poccia F, Colizzi V, et al. Different expression of CD44, ICAM-1, and HSP60 on primary tumor and metastases of a human pancreatic carcinoma growing in scid mice. Anticancer Res. 2000;20(2A):825-31.
122. Barazi HO, Zhou L, Templeton NS, Krutzsch HC, Roberts DD. Identification of heat shock protein 60 as a molecular mediator of α3β1 integrin activation. Cancer Res. 2002;62(5):1541-8.
123. Zhang Y, Liu Y, Liu H, Tang WH. Exosomes: biogenesis, biologic function and clinical potential. Cell & bioscience. 2019;9(1):1-18.
124. Campanella C, Bucchieri F, Merendino AM, Fucarino A, Burgio G, Corona DF, et al. The odyssey of Hsp60 from tumor cells to other destinations includes plasma membrane-associated stages and Golgi and exosomal protein-trafficking modalities. PloS one. 2012;7(7):e42008.
125. Hayoun D, Kapp T, Edri-Brami M, Ventura T, Cohen M, Avidan A, et al. HSP60 is transported through the secretory pathway of 3-MCA-induced fibrosarcoma tumour cells and undergoes N-glycosylation. The FEBS journal. 2012;279(12):2083-95.
126. Wadhwa R, Taira K, Kaul SC. An Hsp70 family chaperone, mortalin/mthsp70/PBP74/Grp75: what, when, and where? Cell Stress Chaperones. 2002;7(3):309.
127. Amick J, Schlanger SE, Wachnowsky C, Moseng MA, Emerson CC, Dare M, et al. Crystal structure of the nucleotide-binding domain of mortalin, the mitochondrial Hsp70 chaperone. Protein Sci. 2014;23(6):833-42.
128. Kaul SC, Deocaris CC, Wadhwa R. Three faces of mortalin: a housekeeper, guardian and killer. Experimental gerontology. 2007;42(4):263-74.
129. Wu P-K, Hong S-K, Veeranki S, Karkhanis M, Starenki D, Plaza JA, et al. A mortalin/HSPA9-mediated switch in tumor-suppressive signaling of Raf/MEK/extracellular signal-regulated kinase. Molecular and Cellular Biology. 2013;33(20):4051-67.
130. Starenki D, Hong S-K, Lloyd RV, Park J-I. Mortalin (GRP75/HSPA9) upregulation promotes survival and proliferation of medullary thyroid carcinoma cells. Oncogene. 2015;34(35):4624-34.
131. Yi X, Luk JM, Lee NP, Peng J, Leng X, Guan X-Y, et al. Association of mortalin (HSPA9) with liver cancer metastasis and prediction for early tumor recurrence. Mol Cell Proteomics. 2008;7(2):315-25.
132. Wadhwa R, Takano S, Kaur K, Deocaris CC, Pereira-Smith OM, Reddel RR, et al. Upregulation of mortalin/mthsp70/Grp75 contributes to human carcinogenesis. Int J Cancer. 2006;118(12):2973-80.

133. Jin H, Ji M, Chen L, Liu Q, Che S, Xu M, et al. The clinicopathological significance of Mortalin overexpression in invasive ductal carcinoma of breast. J Exp Clin Cancer Res. 2016;35(1):1-9.
134. Liu L-X, Lu J-C, Zeng H-Y, Cai J-B, Zhang P-F, Guo X-J, et al. Mortalin stabilizes CD151-depedent tetraspanin-enriched microdomains and implicates in the progression of hepatocellular carcinoma. J Cancer. 2019;10(25):6199.
135. Park SJ, Shin JH, Jeong JI, Song JH, Jo YK, Kim ES, et al. Down-regulation of mortalin exacerbates Aβ-mediated mitochondrial fragmentation and dysfunction. Journal of Biological Chemistry. 2014;289(4):2195-204.
136. Kaul SC, Duncan EL, Englezou A, Takano S, Reddel RR, Mitsui Y, et al. Malignant transformation of NIH3T3 cells by overexpression of mot-2 protei. Oncogene. 1998;17(7):907-11.
137. Yun C-O, Bhargava P, Na Y, Lee J-S, Ryu J, Kaul SC, et al. Relevance of mortalin to cancer cell stemness and cancer therapy. Scientific reports. 2017;7(1):42016.
138. Na Y, Kaul SC, Ryu J, Lee J-S, Ahn HM, Kaul Z, et al. Stress chaperone mortalin contributes to epithelial-to-mesenchymal transition and cancer metastasis. Cancer Res. 2016;76(9):2754-65.
139. Lu W, Lee N, Kaul S, Lan F, Poon R, Wadhwa R, et al. Mortalin–p53 interaction in cancer cells is stress dependent and constitutes a selective target for cancer therapy. Cell Death Differ. 2011;18(6):1046-56.
140. Wadhwa R, Takano S, Robert M, Yoshida A, Nomura H, Reddel RR, et al. Inactivation of tumor suppressor p53 by mot-2, a hsp70 family member. Journal of Biological Chemistry. 1998;273(45):29586-91.
141. Wadhwa R, Takano S, Kaur K, Aida S, Yaguchi T, Kaul Z, et al. Identification and characterization of molecular interactions between mortalin/mtHsp70 and HSP60. Biochem J. 2005;391(2):185-90.
142. Ben-Zvi A, Miller EA, Morimoto RI. Collapse of proteostasis represents an early molecular event in Caenorhabditis elegans aging. Proceedings of the National Academy of Sciences. 2009;106(35):14914-9.
143. Cha SS, An YJ, Lee CR, Lee HS, Kim YG, Kim SJ, et al. Crystal structure of Lon protease: molecular architecture of gated entry to a sequestered degradation chamber. The EMBO journal. 2010;29(20):3520-30.
144. Quirós PM, Español Y, Acín-Pérez R, Rodríguez F, Bárcena C, Watanabe K, et al. ATP-dependent Lon protease controls tumor bioenergetics by reprogramming mitochondrial activity. Cell reports. 2014;8(2):542-56.
145. Ghosh JC, Seo JH, Agarwal E, Wang Y, Kossenkov AV, Tang H-Y, et al. Akt phosphorylation of mitochondrial Lonp1 protease enables oxidative metabolism and advanced tumor traits. Oncogene. 2019;38(43):6926-39.
146. Gibellini L, Losi L, De Biasi S, Nasi M, Lo Tartaro D, Pecorini S, et al. LonP1 differently modulates mitochondrial function and bioenergetics of primary versus metastatic colon cancer cells. Front Oncol. 2018;8:254.
147. Liu C, Wang H, Li H, Chen X, Wu X, Lu B, et al. Inhibition of LONP1 Suppresses Pancreatic Cancer Progression Via c-Jun N-Terminal Kinase Pathway–Meditated Epithelial-Mesenchymal Transition. Pancreas. 2019;48(5):629-35.
148. Kao T, Chiu Y, Fang W, Cheng C, Kuo C, Juan H, et al. Mitochondrial Lon regulates apoptosis through the association with Hsp60–mtHsp70 complex. Cell death & disease. 2015;6(2):e1642-e.

149. Wang J, Hartling JA, Flanagan JM. The structure of ClpP at 2.3 Å resolution suggests a model for ATP-dependent proteolysis. Cell. 1997;91(4):447-56.
150. Seo JH, Rivadeneira DB, Caino MC, Chae YC, Speicher DW, Tang H-Y, et al. The mitochondrial unfoldase-peptidase complex ClpXP controls bioenergetics stress and metastasis. PLoS Biol. 2016;14(7):e1002507.
151. Zhang Y, Maurizi MR. Mitochondrial ClpP activity is required for cisplatin resistance in human cells. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2016;1862(2):252-64.
152. Luo J, Zeng B, Tao C, Lu M, Ren G. ClpP regulates breast cancer cell proliferation, invasion and apoptosis by modulating the Src/PI3K/Akt signaling pathway. PeerJ. 2020;8:e8754.
153. Kumar R, Chaudhary AK, Woytash J, Inigo JR, Gokhale AA, Bshara W, et al. A mitochondrial unfolded protein response inhibitor suppresses prostate cancer growth in mice via HSP60. J Clin Invest. 2022;132(13).
154. Shkedi A, Taylor IR, Echtenkamp F, Ramkumar P, Alshalalfa M, Rivera-Márquez GM, et al. Selective vulnerabilities in the proteostasis network of castration-resistant prostate cancer. Cell Chemical Biology. 2022;29(3):490-501. e4.

Bölüm 2

KRONİK HASTALIKLARDA POTANSİYEL BİYOBELİRTEÇ OLARAK CircRNA'LAR

Ayşenur ÖZDEMİR KANAT[1]
Uğur AKPULAT[2]

GİRİŞ

Kodlayıcı olmayan RNA'lar (ncRNA'lar) ökaryotlarda gen ifadesinin düzenlenmesi ve protein sentezinde önemli rol oynar (1). Uzun kodlayıcı olmayan RNA'lar (lncRNA'lar) sınıfında yer alan dairesel RNA'lar (circRNA'lar), poli-A kuyruğu ve 5' başlığı bulunmayan, iki ucu kovalent olarak kapalı, dokuya özgü ifadesi olan endojen RNA'lardır (2-4). CircRNA'lar, ilk keşfedildiklerinde mRNA'ların uçbirleştirme (splicing) ile işlenmesi esnasında ortaya çıkan yan ürünler olarak düşünülmüştür (5). Yüksek ölçekli RNA dizileme ve biyoinformatik araçların gelişmesi ve yaygınlaşması ile circRNA'ların biyogenezi, işlevleri ve özgünlüğü hakkında çok sayıda güncel verinin üretilmesi sağlanmıştır (6, 7). Şimdiye kadar, prokaryotlar, tek hücreli ökaryotlar, balıklar ve memeliler olmak üzere farklı canlı türlerinin tümünde circRNA'ların varlığı gösterilmiştir (8-11).

CircRNA'lar, bilindik uçbirleştirme ile işlenen mRNA'lardan farklı olarak, tersine uçbirleştirme (back-splicing) mekanizması ile 5' ve 3' uçların kovalent olarak birleştirildiği kimyasal bir süreç ile üretilmektedir. Köken aldıkları genlerin transkripsiyonu esnasında RNA polimeraz II (Pol II) tarafından sentezlenirler (12, 13). Öncü-mRNA'dan köken aldıkları dizi içeriğine göre circRNA'lar genel olarak üç kategoride sınıflandırılmaktadır (Şekil 1'de); eksonik circRNA'lar (ecircRNA'lar), intronik circRNA'lar (ciRNA) ve ekson-intron circRNA'lar (ElciRNA'lar) (14). Lokalizasyonları görev aldıkları yere göre değişiklik göstermektedir. Bazıları çekirdekteki süreçlere katılırken bir kısmı sitoplazmada hedef molekülleri ile etkileşime geçmektedir; bununla birlikte eksozomlar aracılığı ile vücut sıvılarına ve diğer hücrelere aktarılan circRNA'lar da bulunmaktadır (15, 16) Henüz

[1] Yüksek Biyolog, Kastamonu Üniversitesi, Tıp Fakültesi, aokanat@ogr.kastamonu.edu.tr, ORCID iD: 0000-0002-7273-2011

[2] Dr. Öğr. Üyesi, Kastamonu Üniversitesi Tıp Fakültesi, Tıbbi Biyoloji AD., uakpulat@kastamonu.edu.tr, ORCID iD: 0000-0001-8126-8209

arasından circ_0005008 ve circ_0005198'in ifadelerinin istatistiksel olarak en anlamlı ifade farklılığı sergilediği belirlenmiştir. Sonrasında sistemik lupus eritematozus (SLE) ve sağlıklı bireylere göre RA hastaların plazmasında circ_0005008 ve circ_0005198'in ifadesinin daha yüksek olduğu tespit edilmiştir (112). RA hastalarında yapılan benzer çalışmada, 24 RA hastası ve 24 sağlıklı bireylerin PBMC hücrelerinde RT-qPCR analizi ile 6 circRNA (hsa_circ_0082689, hsa_circ_0087798, hsa_circ_0000175, hsa_circ_0008410, hsa_circ_0049356 ve hsa_circ_0032959) tespit edilmiştir. Sağlıklı bireylere göre RA hastalarının PMBC hücrelerinde hsa_circ_0000175 ve hsa_circ_0008410'un istatistiksel olarak en anlamlı ifade farklılığına sahip oldukları tespit edilmiştir. Devamında yapılan geniş kapsamlı kohort çalışmaları sonucunda sağlıklı bireyler ve diğer romatizmal rahatsızlık bulunan hastalara göre RA hastalarında hsa_circ_0000175 ve hsa_circ_0008410'un ifadelerinin yüksek olduğu belirlenmiştir (113).

SONUÇ

Kardiyovasküler hastalıklar, kanser, diyabet ve nörodejeneratif bozukluklar gibi çeşitli kronik hastalıkların moleküler patogenezine katılan genlerin ifadesini düzenleyen ve ilgili hücresel yolaklardaki çeşitli moleküllerle doğrudan etkileşime giren birçok circRNA tanımlanmıştır. Hastalıkla ilişkili olarak ifade değişimi sergileyen bu circRNA'ların, aynı zamanda kararlı ve uzun ömürlü olmalarından dolayı sıvı biyopsilerde tespit edilebilir olduklarının gösterilmesi, circRNA'ları bu tür hastalıkların tanı ve tedavi süreçlerinin takibinde önemli bir biyobelirteç adayı yapmıştır. Şimdiye kadar birçok kronik hastalık için çok sayıda circRNA'nın bir biyobelirteç olarak kullanılabileceğinin gösterilmiş olması yakın zamanda bu moleküllerin hastalıkların takibinde kullanılabileceğine işaret etmektedir.

KAYNAKÇA

1. Brandenburger T, Salgado Somoza A, Devaux Y, Lorenzen JM. Noncoding RNAs in acute kidney injury. Kidney Int. 2018;94(5):870-81.
2. Zhang Z, Yang T, Xiao J. Circular RNAs: Promising Biomarkers for Human Diseases. EBioMedicine. 2018;34:267-74.
3. Wang Y, Liu J, Ma J, Sun T, Zhou Q, Wang W, et al. Exosomal circRNAs: biogenesis, effect and application in human diseases. Mol Cancer. 2019;18(1):116.
4. Chen LL, Yang L. Regulation of circRNA biogenesis. RNA Biol. 2015;12(4):381-8.
5. Cocquerelle C, Mascrez B, Hetuin D, Bailleul B. Mis-splicing yields circular RNA molecules. FASEB J. 1993;7(1):155-60.
6. Liu CX, Chen LL. Circular RNAs: Characterization, cellular roles, and applications. Cell. 2022;185(12):2016-34.

7. Chen LL. The expanding regulatory mechanisms and cellular functions of circular RNAs. Nat Rev Mol Cell Biol. 2020;21(8):475-90.
8. Ford E, Ares M, Jr. Synthesis of circular RNA in bacteria and yeast using RNA cyclase ribozymes derived from a group I intron of phage T4. Proc Natl Acad Sci U S A. 1994;91(8):3117-21.
9. Grabowski PJ, Zaug AJ, Cech TR. The intervening sequence of the ribosomal RNA precursor is converted to a circular RNA in isolated nuclei of Tetrahymena. Cell. 1981;23(2):467-76.
10. Rbbani G, Nedoluzhko A, Galindo-Villegas J, Fernandes JMO. Function of Circular RNAs in Fish and Their Potential Application as Biomarkers. Int J Mol Sci. 2021;22(13).
11. Le Bras A. Repertoires of circRNAs in mammals. Lab Animal. 2019;48(5):138-.
12. Ashwal-Fluss R, Meyer M, Pamudurti NR, Ivanov A, Bartok O, Hanan M, et al. circRNA biogenesis competes with pre-mRNA splicing. Mol Cell. 2014;56(1):55-66.
13. Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature. 2013;495(7441):333-8.
14. Meng X, Li X, Zhang P, Wang J, Zhou Y, Chen M. Circular RNA: an emerging key player in RNA world. Brief Bioinform. 2017;18(4):547-57.
15. Kristensen LS, Andersen MS, Stagsted LVW, Ebbesen KK, Hansen TB, Kjems J. The biogenesis, biology and characterization of circular RNAs. Nat Rev Genet. 2019;20(11):675-91.
16. Ju M, Kim D, Son G, Han J. Circular RNAs in and out of Cells: Therapeutic Usages of Circular RNAs. Mol Cells. 2023;46(1):33-40.
17. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, et al. Natural RNA circles function as efficient microRNA sponges. Nature. 2013;495(7441):384-8.
18. Human circRNA Database. circBank (Accessed:15 July 2023) [Available from: http://www.circbank.cn/.
19. circBase: a database for circular RNAs. circBase (Accessed:15 July 2023) [Available from: http://www.circbase.org/.
20. circ2Traits. The first comprehensive knowledgebase for potential association of circular RNAs with diseases in human (Accessed:15 July 2023) [Available from: http://gyanxet-beta.com/circdb/
21. Su M, Xiao Y, Ma J, Tang Y, Tian B, Zhang Y, et al. Circular RNAs in Cancer: emerging functions in hallmarks, stemness, resistance and roles as potential biomarkers. Molecular cancer. 2019;18(1):1-17.
22. Lei M, Zheng G, Ning Q, Zheng J, Dong D. Translation and functional roles of circular RNAs in human cancer. Mol Cancer. 2020;19(1):30.
23. Yang Y, Yujiao W, Fang W, Linhui Y, Ziqi G, Zhichen W, et al. The roles of miRNA, lncRNA and circRNA in the development of osteoporosis. Biol Res. 2020;53(1):40.
24. Zhang M, Bai X, Zeng X, Liu J, Liu F, Zhang Z. circRNA-miRNA-mRNA in breast cancer. Clin Chim Acta. 2021;523:120-30.
25. Tong KL, Tan KE, Lim YY, Tien XY, Wong PF. CircRNA-miRNA interactions in atherogenesis. Mol Cell Biochem. 2022;477(12):2703-33.
26. Zhong Q, Huang J, Wei J, Wu R. Circular RNA CDR1as sponges miR-7-5p to enhance E2F3 stability and promote the growth of nasopharyngeal carcinoma. Cancer Cell Int. 2019;19:252.

27. Okholm TLH, Sathe S, Park SS, Kamstrup AB, Rasmussen AM, Shankar A, et al. Transcriptome-wide profiles of circular RNA and RNA-binding protein interactions reveal effects on circular RNA biogenesis and cancer pathway expression. Genome Med. 2020;12(1):112.
28. Li XX, Xiao L, Chung HK, Ma XX, Liu X, Song JL, et al. Interaction between HuR and circPABPN1 Modulates Autophagy in the Intestinal Epithelium by Altering ATG16L1 Translation. Mol Cell Biol. 2020;40(6).
29. Li Z, Huang C, Bao C, Chen L, Lin M, Wang X, et al. Exon-intron circular RNAs regulate transcription in the nucleus. Nat Struct Mol Biol. 2015;22(3):256-64.
30. Chen N, Zhao G, Yan X, Lv Z, Yin H, Zhang S, et al. A novel FLI1 exonic circular RNA promotes metastasis in breast cancer by coordinately regulating TET1 and DNMT1. Genome Biol. 2018;19(1):218.
31. Wen SY, Qadir J, Yang BB. Circular RNA translation: novel protein isoforms and clinical significance. Trends Mol Med. 2022;28(5):405-20.
32. Pamudurti NR, Bartok O, Jens M, Ashwal-Fluss R, Stottmeister C, Ruhe L, et al. Translation of CircRNAs. Mol Cell. 2017;66(1):9-21 e7.
33. Legnini I, Di Timoteo G, Rossi F, Morlando M, Briganti F, Sthandier O, et al. Circ-ZNF609 Is a Circular RNA that Can Be Translated and Functions in Myogenesis. Mol Cell. 2017;66(1):22-37 e9.
34. Strimbu K, Tavel JA. What are biomarkers? Curr Opin HIV AIDS. 2010;5(6):463-6.
35. Fuentes-Arderiu X. What is a biomarker? It's time for a renewed definition. Clin Chem Lab Med. 2013;51(9):1689-90.
36. Karczewski KJ, Snyder MP. Integrative omics for health and disease. Nat Rev Genet. 2018;19(5):299-310.
37. Ahadi S, Zhou W, Schussler-Fiorenza Rose SM, Sailani MR, Contrepois K, Avina M, et al. Personal aging markers and ageotypes revealed by deep longitudinal profiling. Nat Med. 2020;26(1):83-90.
38. Li Y, Zheng Q, Bao C, Li S, Guo W, Zhao J, et al. Circular RNA is enriched and stable in exosomes: a promising biomarker for cancer diagnosis. Cell Res. 2015;25(8):981-4.
39. Enuka Y, Lauriola M, Feldman ME, Sas-Chen A, Ulitsky I, Yarden Y. Circular RNAs are long-lived and display only minimal early alterations in response to a growth factor. Nucleic Acids Res. 2016;44(3):1370-83.
40. Szabo L, Morey R, Palpant NJ, Wang PL, Afari N, Jiang C, et al. Statistically based splicing detection reveals neural enrichment and tissue-specific induction of circular RNA during human fetal development. Genome Biol. 2015;16(1):126.
41. Liang D, Tatomer DC, Luo Z, Wu H, Yang L, Chen LL, et al. The Output of Protein-Coding Genes Shifts to Circular RNAs When the Pre-mRNA Processing Machinery Is Limiting. Mol Cell. 2017;68(5):940-54 e3.
42. Misir S, Wu N, Yang BB. Specific expression and functions of circular RNAs. Cell Death Differ. 2022;29(3):481-91.
43. Maass PG, Glazar P, Memczak S, Dittmar G, Hollfinger I, Schreyer L, et al. A map of human circular RNAs in clinically relevant tissues. J Mol Med (Berl). 2017;95(11):1179-89.
44. Zheng Q, Bao C, Guo W, Li S, Chen J, Chen B, et al. Circular RNA profiling reveals an abundant circHIPK3 that regulates cell growth by sponging multiple miRNAs. Nat Commun. 2016;7:11215.

45. Rybak-Wolf A, Stottmeister C, Glazar P, Jens M, Pino N, Giusti S, et al. Circular RNAs in the Mammalian Brain Are Highly Abundant, Conserved, and Dynamically Expressed. Mol Cell. 2015;58(5):870-85.
46. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2019. Eur Heart J. 2020;41(1):12-85.
47. Jakobi T, Czaja-Hasse LF, Reinhardt R, Dieterich C. Profiling and Validation of the Circular RNA Repertoire in Adult Murine Hearts. Genomics Proteomics Bioinformatics. 2016;14(4):216-23.
48. Werfel S, Nothjunge S, Schwarzmayr T, Strom TM, Meitinger T, Engelhardt S. Characterization of circular RNAs in human, mouse and rat hearts. J Mol Cell Cardiol. 2016;98:103-7.
49. Khan MA, Reckman YJ, Aufiero S, van den Hoogenhof MM, van der Made I, Beqqali A, et al. RBM20 Regulates Circular RNA Production From the Titin Gene. Circ Res. 2016;119(9):996-1003.
50. Tan WL, Lim BT, Anene-Nzelu CG, Ackers-Johnson M, Dashi A, See K, et al. A landscape of circular RNA expression in the human heart. Cardiovasc Res. 2017;113(3):298-309.
51. Aufiero S, van den Hoogenhof MMG, Reckman YJ, Beqqali A, van der Made I, Kluin J, et al. Cardiac circRNAs arise mainly from constitutive exons rather than alternatively spliced exons. RNA. 2018;24(6):815-27.
52. Geng HH, Li R, Su YM, Xiao J, Pan M, Cai XX, et al. The Circular RNA Cdr1as Promotes Myocardial Infarction by Mediating the Regulation of miR-7a on Its Target Genes Expression. PLoS One. 2016;11(3):e0151753.
53. Vausort M, Salgado-Somoza A, Zhang L, Leszek P, Scholz M, Teren A, et al. Myocardial Infarction-Associated Circular RNA Predicting Left Ventricular Dysfunction. J Am Coll Cardiol. 2016;68(11):1247-8.
54. Salgado-Somoza A, Zhang L, Vausort M, Devaux Y. The circular RNA MICRA for risk stratification after myocardial infarction. Int J Cardiol Heart Vasc. 2017;17:33-6.
55. Li Q, Wang Y, An Y, Wang J, Gao Y. The Particular Expression Profiles of Circular RNA in Peripheral Blood of Myocardial Infarction Patients by RNA Sequencing. Front Cardiovasc Med. 2022;9:810257.
56. Zhao Z, Li X, Gao C, Jian D, Hao P, Rao L, et al. Peripheral blood circular RNA hsa_circ_0124644 can be used as a diagnostic biomarker of coronary artery disease. Sci Rep. 2017;7:39918.
57. Wang L, Shen C, Wang Y, Zou T, Zhu H, Lu X, et al. Identification of circular RNA Hsa_circ_0001879 and Hsa_circ_0004104 as novel biomarkers for coronary artery disease. Atherosclerosis. 2019;286:88-96.
58. Bao X, Zheng S, Mao S, Gu T, Liu S, Sun J, et al. A potential risk factor of essential hypertension in case-control study: Circular RNA hsa_circ_0037911. Biochem Biophys Res Commun. 2018;498(4):789-94.
59. Zheng S, Gu T, Bao X, Sun J, Zhao J, Zhang T, et al. Circular RNA hsa_circ_0014243 may serve as a diagnostic biomarker for essential hypertension. Exp Ther Med. 2019;17(3):1728-36.
60. Tian M, Xue J, Dai C, Jiang E, Zhu B, Pang H. CircSLC8A1 and circNFIX can be used as auxiliary diagnostic markers for sudden cardiac death caused by acute ischemic heart disease. Sci Rep. 2021;11(1):4695.

61. Matilla-Duenas A, Corral-Juan M, Rodriguez-Palmero Seuma A, Vilas D, Ispierto L, Morais S, et al. Rare Neurodegenerative Diseases: Clinical and Genetic Update. Adv Exp Med Biol. 2017;1031:443-96.
62. Wu DP, Zhao YD, Yan QQ, Liu LL, Wei YS, Huang JL. Circular RNAs: emerging players in brain aging and neurodegenerative diseases. J Pathol. 2023;259(1):1-9.
63. Kuo MC, Liu SC, Hsu YF, Wu RM. The role of noncoding RNAs in Parkinson's disease: biomarkers and associations with pathogenic pathways. J Biomed Sci. 2021;28(1):78.
64. Li J, Sun C, Cui H, Sun J, Zhou P. Role of circRNAs in neurodevelopment and neurodegenerative diseases. J Mol Neurosci. 2021;71(9):1743-51.
65. Moreno-Garcia L, Lopez-Royo T, Calvo AC, Toivonen JM, de la Torre M, Moreno-Martinez L, et al. Competing Endogenous RNA Networks as Biomarkers in Neurodegenerative Diseases. Int J Mol Sci. 2020;21(24).
66. Li Y, Fan H, Sun J, Ni M, Zhang L, Chen C, et al. Circular RNA expression profile of Alzheimer's disease and its clinical significance as biomarkers for the disease risk and progression. Int J Biochem Cell Biol. 2020;123:105747.
67. Liu L, Chen X, Chen YH, Zhang K. Identification of Circular RNA hsa_Circ_0003391 in Peripheral Blood Is Potentially Associated With Alzheimer's Disease. Front Aging Neurosci. 2020;12:601965.
68. Li Y, Lv Z, Zhang J, Ma Q, Li Q, Song L, et al. Profiling of differentially expressed circular RNAs in peripheral blood mononuclear cells from Alzheimer's disease patients. Metab Brain Dis. 2020;35(1):201-13.
69. Zheng D, Tahir RA, Yan Y, Zhao J, Quan Z, Kang G, et al. Screening of Human Circular RNAs as Biomarkers for Early Onset Detection of Alzheimer's Disease. Front Neurosci. 2022;16:878287.
70. Piscopo P, Manzini V, Rivabene R, Crestini A, Le Pera L, Pizzi E, et al. A Plasma Circular RNA Profile Differentiates Subjects with Alzheimer's Disease and Mild Cognitive Impairment from Healthy Controls. Int J Mol Sci. 2022;23(21).
71. Lu Y, Tan L, Wang X. Circular HDAC9/microRNA-138/Sirtuin-1 Pathway Mediates Synaptic and Amyloid Precursor Protein Processing Deficits in Alzheimer's Disease. Neurosci Bull. 2019;35(5):877-88.
72. Xiao Y, Chen H, Liao J, Zhang Q, He H, Lei J, et al. The Potential Circular RNAs Biomarker Panel and Regulatory Networks of Parkinson's Disease. Front Neurosci. 2022;16:893713.
73. Duan Y, Wang Y, Liu Y, Jin Z, Liu C, Yu X, et al. Circular RNAs in Parkinson's Disease: Reliable Biological Markers and Targets for Rehabilitation. Mol Neurobiol. 2023;60(6):3261-76.
74. Zhong L, Ju K, Chen A, Cao H. Circulating CircRNAs Panel Acts as a Biomarker for the Early Diagnosis and Severity of Parkinson's Disease. Front Aging Neurosci. 2021;13:684289.
75. Ravanidis S, Bougea A, Karampatsi D, Papagiannakis N, Maniati M, Stefanis L, et al. Differentially Expressed Circular RNAs in Peripheral Blood Mononuclear Cells of Patients with Parkinson's Disease. Mov Disord. 2021;36(5):1170-9.
76. Cardamone G, Paraboschi EM, Solda G, Liberatore G, Rimoldi V, Cibella J, et al. The circular RNA landscape in multiple sclerosis: Disease-specific associated variants and exon methylation shape circular RNA expression profile. Mult Scler Relat Disord. 2023;69:104426.

77. Iparraguirre L, Munoz-Culla M, Prada-Luengo I, Castillo-Trivino T, Olascoaga J, Otaegui D. Circular RNA profiling reveals that circular RNAs from ANXA2 can be used as new biomarkers for multiple sclerosis. Hum Mol Genet. 2017;26(18):3564-72.
78. Erratum: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2020;70(4):313.
79. Bachmayr-Heyda A, Reiner AT, Auer K, Sukhbaatar N, Aust S, Bachleitner-Hofmann T, et al. Correlation of circular RNA abundance with proliferation--exemplified with colorectal and ovarian cancer, idiopathic lung fibrosis, and normal human tissues. Sci Rep. 2015;5:8057.
80. Mohanty A, Mohanty SK, Rout S, Pani C. Liquid Biopsy, the hype vs. hope in molecular and clinical oncology. Semin Oncol. 2021;48(3):259-67.
81. Wu X, Shi M, Lian Y, Zhang H. Exosomal circRNAs as promising liquid biopsy biomarkers for glioma. Front Immunol. 2023;14:1039084.
82. Yin WB, Yan MG, Fang X, Guo JJ, Xiong W, Zhang RP. Circulating circular RNA hsa_circ_0001785 acts as a diagnostic biomarker for breast cancer detection. Clin Chim Acta. 2018;487:363-8.
83. Li X, Lin YL, Shao JK, Wu XJ, Li X, Yao H, et al. Plasma exosomal hsa_circ_0079439 as a novel biomarker for early detection of gastric cancer. World J Gastroenterol. 2023;29(22):3482-96.
84. Zhang W, Zheng M, Kong S, Li X, Meng S, Wang X, et al. Circular RNA hsa_circ_0007507 May Serve as a Biomarker for the Diagnosis and Prognosis of Gastric Cancer. Front Oncol. 2021;11:699625.
85. Yang F, Ma C, Qiu J, Feng X, Yang K. Identification of circRNA_001846 as putative non-small cell lung cancer biomarker. Bioengineered. 2021;12(1):8690-7.
86. Peng Z, Hu Q, Fang S, Zhang X, Hong X, Tao L, et al. Circulating circTOLLIP serves as a diagnostic biomarker for liquid biopsy in non-small cell lung cancer. Clin Chim Acta. 2021;523:415-22.
87. Yang F, Liu DY, Guo JT, Ge N, Zhu P, Liu X, et al. Circular RNA circ-LDLRAD3 as a biomarker in diagnosis of pancreatic cancer. World J Gastroenterol. 2017;23(47):8345-54.
88. Zhao SY, Wang J, Ouyang SB, Huang ZK, Liao L. Salivary Circular RNAs Hsa_Circ_0001874 and Hsa_Circ_0001971 as Novel Biomarkers for the Diagnosis of Oral Squamous Cell Carcinoma. Cell Physiol Biochem. 2018;47(6):2511-21.
89. Hong L, Xu L, Jin L, Xu K, Tang W, Zhu Y, et al. Exosomal circular RNA hsa_circ_0006220, and hsa_circ_0001666 as biomarkers in the diagnosis of pancreatic cancer. J Clin Lab Anal. 2022;36(6):e24447.
90. Li T, Zhou T, Wu J, Lv H, Zhou H, Du M, et al. Plasma exosome-derived circGAPVD1 as a potential diagnostic marker for colorectal cancer. Transl Oncol. 2023;31:101652.
91. Zheng P, Gao H, Xie X, Lu P. Plasma Exosomal hsa_circ_0015286 as a Potential Diagnostic and Prognostic Biomarker for Gastric Cancer. Pathol Oncol Res. 2022;28:1610446.
92. Li T, Shao Y, Fu L, Xie Y, Zhu L, Sun W, et al. Plasma circular RNA profiling of patients with gastric cancer and their droplet digital RT-PCR detection. J Mol Med (Berl). 2018;96(1):85-96.
93. Zhao Q, Chen S, Li T, Xiao B, Zhang X. Clinical values of circular RNA 0000181 in the screening of gastric cancer. J Clin Lab Anal. 2018;32(4):e22333.

94. Chen S, Li T, Zhao Q, Xiao B, Guo J. Using circular RNA hsa_circ_0000190 as a new biomarker in the diagnosis of gastric cancer. Clin Chim Acta. 2017;466:167-71.
95. Wang Q, Zhang Q, Sun H, Tang W, Yang L, Xu Z, et al. Circ-TTC17 Promotes Proliferation and Migration of Esophageal Squamous Cell Carcinoma. Dig Dis Sci. 2019;64(3):751-8.
96. Zhang X, Zhou H, Jing W, Luo P, Qiu S, Liu X, et al. The Circular RNA hsa_circ_0001445 Regulates the Proliferation and Migration of Hepatocellular Carcinoma and May Serve as a Diagnostic Biomarker. Dis Markers. 2018;2018:3073467.
97. Zhu K, Zhan H, Peng Y, Yang L, Gao Q, Jia H, et al. Plasma hsa_circ_0027089 is a diagnostic biomarker for hepatitis B virus-related hepatocellular carcinoma. Carcinogenesis. 2020;41(3):296-302.
98. Zhu X, Wang X, Wei S, Chen Y, Chen Y, Fan X, et al. hsa_circ_0013958: a circular RNA and potential novel biomarker for lung adenocarcinoma. FEBS J. 2017;284(14):2170-82.
99. Tan S, Sun D, Pu W, Gou Q, Guo C, Gong Y, et al. Circular RNA F-circEA-2a derived from EML4-ALK fusion gene promotes cell migration and invasion in non-small cell lung cancer. Mol Cancer. 2018;17(1):138.
100. Chi BJ, Zhao DM, Liu L, Yin XZ, Wang FF, Bi S, et al. Downregulation of hsa_circ_0000285 serves as a prognostic biomarker for bladder cancer and is involved in cisplatin resistance. Neoplasma. 2019;66(2):197-202.
101. Xie Y, Li J, Li P, Li N, Zhang Y, Binang H, et al. RNA-Seq Profiling of Serum Exosomal Circular RNAs Reveals Circ-PNN as a Potential Biomarker for Human Colorectal Cancer. Front Oncol. 2020;10:982.
102. Zhang L, Xu T, Li Y, Pang Q, Ding X. Serum hsa_circ_0000615 is a prognostic biomarker of sorafenib resistance in hepatocellular carcinoma. J Clin Lab Anal. 2022;36(11):e24741.
103. Peng X, Zhao L, Yao L, Dong J, Wu W, Luo T. Exosomal ERBB2IP contributes to tumor growth via elevating PSAT1 expression in non-small cell lung carcinoma. Thorac Cancer. 2023;14(19):1812-23.
104. Kang Y, You J, Gan Y, Chen Q, Huang C, Chen F, et al. Serum and Serum Exosomal CircRNAs hsa_circ_0001492, hsa_circ_0001439, and hsa_circ_0000896 as Diagnostic Biomarkers for Lung Adenocarcinoma. Front Oncol. 2022;12:912246.
105. Wang Y, Pei L, Yue Z, Jia M, Wang H, Cao LL. The Potential of Serum Exosomal hsa_circ_0028861 as the Novel Diagnostic Biomarker of HBV-Derived Hepatocellular Cancer. Front Genet. 2021;12:703205.
106. Shuai M, Hong J, Huang D, Zhang X, Tian Y. Upregulation of circRNA_0000285 serves as a prognostic biomarker for nasopharyngeal carcinoma and is involved in radiosensitivity. Oncol Lett. 2018;16(5):6495-501.
107. Chen X, Chen RX, Wei WS, Li YH, Feng ZH, Tan L, et al. PRMT5 Circular RNA Promotes Metastasis of Urothelial Carcinoma of the Bladder through Sponging miR-30c to Induce Epithelial-Mesenchymal Transition. Clin Cancer Res. 2018;24(24):6319-30.
108. Zhao Z, Li X, Jian D, Hao P, Rao L, Li M. Hsa_circ_0054633 in peripheral blood can be used as a diagnostic biomarker of pre-diabetes and type 2 diabetes mellitus. Acta Diabetol. 2017;54(3):237-45.
109. Lu YK, Chu X, Wang S, Sun Y, Zhang J, Dong J, et al. Identification of Circulating hsa_circ_0063425 and hsa_circ_0056891 as Novel Biomarkers for Detection of Type 2 Diabetes. J Clin Endocrinol Metab. 2021;106(7):e2688-e99.

110. Yin W, Luo S, Qiu J, Xiao Z, Zhang Z, Xie Z, et al. Identification of hsa_circRNA_100632 as a novel molecular biomarker for fulminant type 1 diabetes. Front Immunol. 2023;14:1075970.
111. Jiang B, Zhang J, Sun X, Yang C, Cheng G, Xu M, et al. Circulating exosomal hsa_circRNA_0039480 is highly expressed in gestational diabetes mellitus and may be served as a biomarker for early diagnosis of GDM. J Transl Med. 2022;20(1):5.
112. Ouyang Q, Liu C, Lu X, Liang R, Zhao J, Yang M. Identification of Circular RNAs Circ_0005008 and Circ_0005198 in Plasma as Novel Biomarkers for New-Onset Rheumatoid Arthritis. Front Pharmacol. 2021;12:722017.
113. Luo Q, Zeng L, Zeng L, Rao J, Zhang L, Guo Y, et al. Expression and clinical significance of circular RNAs hsa_circ_0000175 and hsa_circ_0008410 in peripheral blood mononuclear cells from patients with rheumatoid arthritis. Int J Mol Med. 2020;45(4):1203-12.

Bölüm 3

CircRNA'LARIN KANSER PATOGENEZİNDEKİ İŞLEVİ VE ÖNEMİ

Fethi Caner ADIGÜZEL[1]
Uğur AKPULAT[2]

GİRİŞ

Dairesel RNA'lar (circRNA'lar), büyük çoğunluğu kodlayıcı işleve sahip olmayan, mRNA'ların aksine, 5' başlığı ve 3' kuyruğu bulunmayan, uçları kovalent bağ ile birleşmiş halka yapılarıyla karakterize endojen RNA moleküllerdir [1, 2]. Şimdiye kadar çok sayıda circRNA tanımlanmıştır. Büyük bir çoğunluğuna biyoinformatik araçlarla işlev atfedilmesine rağmen sadece az bir kısmının biyolojik sistemlerdeki işlevi açıklanabilmiştir. Genel olarak miRNA süngeri olarak işlev göstermektedirler. Bu sayede, miRNA'ların hedef transkriptleri ile etkileşimini engelleyebilecekleri gibi miRNA'ların hücre içerisinde görev alacakları yerlere taşınmasına da aracılık edebilmektedirler. Bazı circRNA'lar protein süngeri olarak RBP'lerle (RNA bağlayıcı protein) etkileşime geçmektedir. Bir kısmı da protein iskelesi gibi davranarak, enzimlerle substratları arasındaki etkileşime aracılık edebilmektedir ya da belirli proteinleri hücrede işlev görecekleri yerlere taşıyabilmektedir. Ayrıca, büyük çoğunluğunun kodlamayan RNA olmasına rağmen bir kısmının belirli durumlarda translasyona uğradıkları gösterilmiştir [3-5].

CircRNA'ların yaygın görülen ve yaşam kalitesini büyük ölçüde düşüren birçok kanser ile ilişkili olduğu gösterilmiştir [6, 7]. Kanser, dünyanın her yerinde önde gelen ölüm nedenlerinden biridir ve artan insan ömrünün önündeki önemli bir bariyerdir. GLOBOCAN 2020 verilerine göre dünya genelinde en yaygın teşhis konulan kanserler; meme (2,26 milyon vaka), akciğer (2,20 milyon vaka), kolon ve rektum (1.87 milyon vaka), prostat (1,41 milyon vaka), deri (1,20 milyon vaka) ve mide (1,09 milyon vaka) kanserleridir. Dünya genelinde 2020 yılında yaklaşık 10 milyon kansere bağlı ölüm meydana gelmiştir. En yaygın ölüme neden olan kanser türleri; akciğer (1.80 milyon), kolon ve rektum (916 bin), karaciğer (830

[1] Kastamonu Üniversitesi Tıp Fakültesi, fcaner.adiguzel@gmail.com, ORCID iD: 0009-0009-4626-9797
[2] Dr. Öğr. Üyesi, Kastamonu Üniversitesi Tıp Fakültesi, Tıbbi Biyoloji AD, uakpulat@kastamonu.edu.tr, ORCID iD:0000-0001-8126-8209

KAYNAKÇA

1. Yang, L., J.E. Wilusz, and L.L. Chen, *Biogenesis and Regulatory Roles of Circular RNAs.* Annu Rev Cell Dev Biol, 2022. **38**: p. 263-289.
2. Meng, S., et al., *CircRNA: functions and properties of a novel potential biomarker for cancer.* Mol Cancer, 2017. **16**(1): p. 94.
3. Kristensen, L.S., et al., *The biogenesis, biology and characterization of circular RNAs.* Nat Rev Genet, 2019. **20**(11): p. 675-691.
4. Liang, Y., et al., *A Brief Review of circRNA Biogenesis, Detection, and Function.* Curr Genomics, 2021. **22**(7): p. 485-495.
5. Obi, P. and Y.G. Chen, *The design and synthesis of circular RNAs.* Methods, 2021. **196**: p. 85-103.
6. Su, M., et al., *Circular RNAs in Cancer: emerging functions in hallmarks, stemness, resistance and roles as potential biomarkers.* Mol Cancer, 2019. **18**(1): p. 90.
7. Chen, L. and G. Shan, *CircRNA in cancer: Fundamental mechanism and clinical potential.* Cancer Lett, 2021. **505**: p. 49-57.
8. Sung, H., et al., *Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.* CA Cancer J Clin, 2021. **71**(3): p. 209-249.
9. Li, Y., et al., *circ-EIF6 encodes EIF6-224aa to promote TNBC progression via stabilizing MYH9 and activating the Wnt/beta-catenin pathway.* Mol Ther, 2022. **30**(1): p. 415-430.
10. Wu, H., et al., *CircARL8B Contributes to the Development of Breast Cancer Via Regulating miR-653-5p/HMGA2 Axis.* Biochem Genet, 2021. **59**(6): p. 1648-1665.
11. Jiang, J. and X. Cheng, *Circular RNA circABCC4 acts as a ceRNA of miR-154-5p to improve cell viability, migration and invasion of breast cancer cells in vitro.* Cell Cycle, 2020. **19**(20): p. 2653-2661.
12. Qi, L., et al., *circHIPK3 (hsa_circ_0000284) Promotes Proliferation, Migration and Invasion of Breast Cancer Cells via miR-326.* Onco Targets Ther, 2021. **14**: p. 3671-3685.
13. Gao, N. and B. Ye, *Circ-SOX4 drives the tumorigenesis and development of lung adenocarcinoma via sponging miR-1270 and modulating PLAGL2 to activate WNT signaling pathway.* Cancer Cell Int, 2020. **20**: p. 2.
14. Yao, Y., et al., *CircRNA has_circ_0001946 promotes cell growth in lung adenocarcinoma by regulating miR-135a-5p/SIRT1 axis and activating Wnt/beta-catenin signaling pathway.* Biomed Pharmacother, 2019. **111**: p. 1367-1375.
15. Zhang, Y., H. Zhao, and L. Zhang, *Identification of the tumor-suppressive function of circular RNA FOXO3 in non-small cell lung cancer through sponging miR-155.* Mol Med Rep, 2018. **17**(6): p. 7692-7700.
16. Tan, S., et al., *Circular RNA F-circEA-2a derived from EML4-ALK fusion gene promotes cell migration and invasion in non-small cell lung cancer.* Mol Cancer, 2018. **17**(1): p. 138.
17. Liu, T., Z. Song, and Y. Gai, *Circular RNA circ_0001649 acts as a prognostic biomarker and inhibits NSCLC progression via sponging miR-331-3p and miR-338-5p.* Biochem Biophys Res Commun, 2018. **503**(3): p. 1503-1509.
18. Zhang, P.F., et al., *Correction to: Circular RNA circFGFR1 promotes progression and anti-PD-1 resistance by sponging miR-381-3p in non-small cell lung cancer cells.* Mol Cancer, 2020. **19**(1): p. 21.

19. Wei, S., et al., *The circRNA circPTPRA suppresses epithelial-mesenchymal transitioning and metastasis of NSCLC cells by sponging miR-96-5p.* EBioMedicine, 2019. **44**: p. 182-193.
20. Hang, D., et al., *A novel plasma circular RNA circFARSA is a potential biomarker for non-small cell lung cancer.* Cancer Med, 2018. **7**(6): p. 2783-2791.
21. Zong, L., et al., *Increased expression of circRNA_102231 in lung cancer and its clinical significance.* Biomed Pharmacother, 2018. **102**: p. 639-644.
22. Chen, L., et al., *Circular RNA 100146 functions as an oncogene through direct binding to miR-361-3p and miR-615-5p in non-small cell lung cancer.* Mol Cancer, 2019. **18**(1): p. 13.
23. Yao, Y., Q. Hua, and Y. Zhou, *CircRNA has_circ_0006427 suppresses the progression of lung adenocarcinoma by regulating miR-6783-3p/DKK1 axis and inactivating Wnt/beta-catenin signaling pathway.* Biochem Biophys Res Commun, 2019. **508**(1): p. 37-45.
24. Gao, S., et al., *Circular RNA hsa_circ_0007059 restrains proliferation and epithelial-mesenchymal transition in lung cancer cells via inhibiting microRNA-378.* Life Sci, 2019. **233**: p. 116692.
25. Wan, L., et al., *Circular RNA-ITCH Suppresses Lung Cancer Proliferation via Inhibiting the Wnt/beta-Catenin Pathway.* Biomed Res Int, 2016. **2016**: p. 1579490.
26. Gao, F., et al., *Circ-ZNF124 downregulation inhibits non-small cell lung cancer progression partly by inactivating the Wnt/beta-catenin signaling pathway via mediating the miR-498/YES1 axis.* Anticancer Drugs, 2021. **32**(3): p. 257-268.
27. Zhao, M., W. Ma, and C. Ma, *Circ_0067934 promotes non-small cell lung cancer development by regulating miR-1182/KLF8 axis and activating Wnt/beta-catenin pathway.* Biomed Pharmacother, 2020. **129**: p. 110461.
28. Li, X.Y., et al., *Enhanced expression of circular RNA hsa_circ_000984 promotes cells proliferation and metastasis in non-small cell lung cancer by modulating Wnt/beta-catenin pathway.* Eur Rev Med Pharmacol Sci, 2019. **23**(8): p. 3366-3374.
29. Ding, L., et al., *Upregulation of circ_001569 predicts poor prognosis and promotes cell proliferation in non-small cell lung cancer by regulating the Wnt/beta-catenin pathway.* Oncol Lett, 2018. **16**(1): p. 453-458.
30. Xie, H., et al., *Emerging roles of circRNA_001569 targeting miR-145 in the proliferation and invasion of colorectal cancer.* Oncotarget, 2016. **7**(18): p. 26680-91.
31. Hao, S., et al., *Emerging roles of circular RNAs in colorectal cancer.* Onco Targets Ther, 2019. **12**: p. 4765-4777.
32. Chen, H., et al., *Circ-PRKDC Contributes to 5-Fluorouracil Resistance of Colorectal Cancer Cells by Regulating miR-375/FOXM1 Axis and Wnt/beta-Catenin Pathway.* Onco Targets Ther, 2020. **13**: p. 5939-5953.
33. Ma, Z., et al., *circ5615 functions as a ceRNA to promote colorectal cancer progression by upregulating TNKS.* Cell Death Dis, 2020. **11**(5): p. 356.
34. Li, W., et al., *circCCT3 Modulates Vascular Endothelial Growth Factor A and Wnt Signaling to Enhance Colorectal Cancer Metastasis Through Sponging miR-613.* DNA Cell Biol, 2020. **39**(1): p. 118-125.
35. Geng, Y., et al., *Hsa_circ_0009361 acts as the sponge of miR-582 to suppress colorectal cancer progression by regulating APC2 expression.* Clin Sci (Lond), 2019. **133**(10): p. 1197-1213.

36. Jin, Y.D., et al., *Hsa_circ_0005075 predicts a poor prognosis and acts as an oncogene in colorectal cancer via activating Wnt/beta-catenin pathway.* Eur Rev Med Pharmacol Sci, 2019. **23**(8): p. 3311-3319.
37. Ge, Z., et al., *CircMTO1 inhibits cell proliferation and invasion by regulating Wnt/beta-catenin signaling pathway in colorectal cancer.* Eur Rev Med Pharmacol Sci, 2018. **22**(23): p. 8203-8209.
38. Jin, Y., et al., *Circular RNA hsa_circ_0000523 regulates the proliferation and apoptosis of colorectal cancer cells as miRNA sponge.* Braz J Med Biol Res, 2018. **51**(12): p. e7811.
39. Huang, G., et al., *cir-ITCH plays an inhibitory role in colorectal cancer by regulating the Wnt/beta-catenin pathway.* PLoS One, 2015. **10**(6): p. e0131225.
40. Gu, H., et al., *circ_0038718 promotes colon cancer cell malignant progression via the miR-195-5p/Axin2 signaling axis and also effect Wnt/beta-catenin signal pathway.* BMC Genomics, 2021. **22**(1): p. 768.
41. Zhang, X., et al., *Hsa_circ_0026628 promotes the development of colorectal cancer by targeting SP1 to activate the Wnt/beta-catenin pathway.* Cell Death Dis, 2021. **12**(9): p. 802.
42. Yang, L., et al., *CircRASSF2 facilitates the proliferation and metastasis of colorectal cancer by mediating the activity of Wnt/beta-catenin signaling pathway by regulating the miR-195-5p/FZD4 axis.* Anticancer Drugs, 2021. **32**(9): p. 919-929.
43. Yang, S., et al., *Circular RNA SMARCA5 functions as an anti-tumor candidate in colon cancer by sponging microRNA-552.* Cell Cycle, 2021. **20**(7): p. 689-701.
44. Tang, W., et al., *Silencing CDR1as inhibits colorectal cancer progression through regulating microRNA-7.* Onco Targets Ther, 2017. **10**: p. 2045-2056.
45. Zeng, K., et al., *CircHIPK3 promotes colorectal cancer growth and metastasis by sponging miR-7.* Cell Death Dis, 2018. **9**(4): p. 417.
46. He, J.H., et al., *The CircRNA-ACAP2/Hsa-miR-21-5p/ Tiam1 Regulatory Feedback Circuit Affects the Proliferation, Migration, and Invasion of Colon Cancer SW480 Cells.* Cell Physiol Biochem, 2018. **49**(4): p. 1539-1550.
47. Xu, X.W., et al., *Circular RNA hsa_circ_000984 promotes colon cancer growth and metastasis by sponging miR-106b.* Oncotarget, 2017. **8**(53): p. 91674-91683.
48. Zhang, J., et al., *Has_circ_0055625 from circRNA profile increases colon cancer cell growth by sponging miR-106b-5p.* J Cell Biochem, 2019. **120**(3): p. 3027-3037.
49. Zhu, M., et al., *Circular BANP, an upregulated circular RNA that modulates cell proliferation in colorectal cancer.* Biomed Pharmacother, 2017. **88**: p. 138-144.
50. Zheng, X., et al., *A novel protein encoded by a circular RNA circPPP1R12A promotes tumor pathogenesis and metastasis of colon cancer via Hippo-YAP signaling.* Mol Cancer, 2019. **18**(1): p. 47.
51. Ren, C., et al., *Circular RNA hsa_circ_0001178 facilitates the invasion and metastasis of colorectal cancer through upregulating ZEB1 via sponging multiple miRNAs.* Biol Chem, 2020. **401**(4): p. 487-496.
52. Chen, L.Y., et al., *NSD2 circular RNA promotes metastasis of colorectal cancer by targeting miR-199b-5p-mediated DDR1 and JAG1 signalling.* J Pathol, 2019. **248**(1): p. 103-115.
53. Chen, R.X., et al., *N(6)-methyladenosine modification of circNSUN2 facilitates cytoplasmic export and stabilizes HMGA2 to promote colorectal liver metastasis.* Nat Commun, 2019. **10**(1): p. 4695.

54. Li, X., et al., *Circular RNA circITGA7 inhibits colorectal cancer growth and metastasis by modulating the Ras pathway and upregulating transcription of its host gene ITGA7.* J Pathol, 2018. **246**(2): p. 166-179.
55. Lu, H., et al., *FBXW7 circular RNA regulates proliferation, migration and invasion of colorectal carcinoma through NEK2, mTOR, and PTEN signaling pathways in vitro and in vivo.* BMC Cancer, 2019. **19**(1): p. 918.
56. Liu, R., et al., *Circ_0082182 promotes oncogenesis and metastasis of colorectal cancer in vitro and in vivo by sponging miR-411 and miR-1205 to activate the Wnt/beta-catenin pathway.* World J Surg Oncol, 2021. **19**(1): p. 51.
57. Zhang, L., et al., *CircAGFG1 drives metastasis and stemness in colorectal cancer by modulating YY1/CTNNB1.* Cell Death Dis, 2020. **11**(7): p. 542.
58. Zhu, P., et al., *Circular RNA Hsa_circ_0004018 Inhibits Wnt/beta-Catenin Signaling Pathway by Targeting microRNA-626/DKK3 in Hepatocellular Carcinoma.* Onco Targets Ther, 2020. **13**: p. 9351-9364.
59. Guo, W., et al., *Polymorphisms and expression pattern of circular RNA circ-ITCH contributes to the carcinogenesis of hepatocellular carcinoma.* Oncotarget, 2017. **8**(29): p. 48169-48177.
60. Liang, W.C., et al., *Translation of the circular RNA circbeta-catenin promotes liver cancer cell growth through activation of the Wnt pathway.* Genome Biol, 2019. **20**(1): p. 84.
61. Tan, A., Q. Li, and L. Chen, *CircZFR promotes hepatocellular carcinoma progression through regulating miR-3619-5p/CTNNB1 axis and activating Wnt/beta-catenin pathway.* Arch Biochem Biophys, 2019. **661**: p. 196-202.
62. Zhu, Q., et al., *CircRNA circ_0067934 promotes tumor growth and metastasis in hepatocellular carcinoma through regulation of miR-1324/FZD5/Wnt/beta-catenin axis.* Biochem Biophys Res Commun, 2018. **497**(2): p. 626-632.
63. Peng, Y. and H.H. Wang, *Cir-ITCH inhibits gastric cancer migration, invasion and proliferation by regulating the Wnt/beta-catenin pathway.* Sci Rep, 2020. **10**(1): p. 17443.
64. Sun, H., et al., *Hsa_circ_0001649 restrains gastric carcinoma growth and metastasis by downregulation of miR-20a.* J Clin Lab Anal, 2020. **34**(6): p. e23235.
65. Liu, W.G. and Q. Xu, *Upregulation of circHIPK3 promotes the progression of gastric cancer via Wnt/beta-catenin pathway and indicates a poor prognosis.* Eur Rev Med Pharmacol Sci, 2019. **23**(18): p. 7905-7912.
66. Yang, C. and S. Han, *The circular RNA circ0005654 interacts with specificity protein 1 via microRNA-363 sequestration to promote gastric cancer progression.* Bioengineered, 2021. **12**(1): p. 6305-6317.
67. Shi, Q., et al., *CircCNIH4 inhibits gastric cancer progression via regulating DKK2 and FRZB expression and Wnt/beta-catenin pathway.* J Biol Res (Thessalon), 2021. **28**(1): p. 19.
68. Wang, L., et al., *Circ_SMAD4 promotes gastric carcinogenesis by activating wnt/beta-catenin pathway.* Cell Prolif, 2021. **54**(3): p. e12981.
69. Zhang, M., et al., *circRNA-miRNA-mRNA in breast cancer.* Clin Chim Acta, 2021. **523**: p. 120-130.
70. Wang, C., et al., *CircRNAs in lung cancer - Biogenesis, function and clinical implication.* Cancer Lett, 2020. **492**: p. 106-115.
71. Zhang, P.F., et al., *Circular RNA circFGFR1 promotes progression and anti-PD-1 resistance by sponging miR-381-3p in non-small cell lung cancer cells.* Mol Cancer, 2019. **18**(1): p. 179.

72. Li, A., et al., *Circular RNA in colorectal cancer.* J Cell Mol Med, 2021. **25**(8): p. 3667-3679.
73. Fang, G., et al., *CircRNA_100290 promotes colorectal cancer progression through miR-516b-induced downregulation of FZD4 expression and Wnt/beta-catenin signaling.* Biochem Biophys Res Commun, 2018. **504**(1): p. 184-189.
74. Li, R., et al., *CircRNA: a rising star in gastric cancer.* Cell Mol Life Sci, 2020. **77**(9): p. 1661-1680.
75. Wei, L., et al., *Noncoding RNAs in gastric cancer: implications for drug resistance.* Mol Cancer, 2020. **19**(1): p. 62.

Bölüm 4

PIWI-ETKİLEŞİMLİ RNA'LAR (PİRNA): TANIMI VE HASTALIKLARDAKİ ROLÜ

Hacer KAVAK YILDIRIM[1]
Seval TÜRK[2]
Dilek DAŞ[3]
Demet TEKDÖŞ DEMİRCİOĞLU[4]
Huri DEDEAKAYOĞULLARI[5]

GİRİŞ

İnsan genomunun yaklaşık %2'sinin protein kodladığı, geriye kalan büyük çoğunluğunun fonksiyonel olmadığı anlaşılmış; her ne kadar ncRNA'lar daha önce "evrimsel çöp" olarak görülse de, yeni araştırmalar bunların birçok bağlantı yolunu önemli ölçüde değiştirdiğini gösteriyor. Yeni nesil derin dizileme gibi son teknolojik gelişmeler, genomun büyük bir kısmının RNA'lara çevrildiğini göstermiştir. ncRNA'nın, gen susturmaya katkıda bulunmak için DNA'ya bağlanarak çekirdekte veya protein ekspresyonunu etkilemek için mRNA'yı düzenleyerek sitoplazmada işlev gördüğü ve temel hücresel süreçleri düzenleyen, büyüyen bir molekül ailesini içerdiği keşfedilmiştir (1). ncRNA'lar, düzenleyici ncRNA'lar ve hizmetçi ncRNA'lar olmak üzere farklı işlevlere sahip iki grup altında incelenmiş ve düzenleyici ncRNA'lar da transkript boyutuna göre uzun kodlamayan RNA (lncRNA)'lar ve kısa kodlamayan RNA (sncRNA)'lar olarak sınıflandırılmıştır. Kısa ncRNA da miRNA (mikroRNA), siRNA (küçük karışan RNA) ve piRNA (PIWI etkileşimli RNA) sınıflarından oluşmaktadır (2). 24-32 nükleotit (nt) büyüklüğünde bir sncRNA molekülü sınıfı olan piRNA'lar, argonaute proteinlerin (AGO) bir alt ailesi olan PIWI (P elementi ile indüklenen

[1] Op. Dr. Marmara Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum AD, hacerkavak@gmail.com, ORCID iD: 0000-0001-9791-5706

[2] Dr. Öğr. Üyesi. Antalya Bilim Üniversitesi Diş Hekimliği Fakültesi Temel Bilimler AD, seval.turk@antalya.edu.tr, ORCID iD: 0000-0002-0850-4671

[3] Senior Klinik Embriyolog, ART Fertility Clinics, ORCID iD:

[4] Doç.Dr. İstanbul Aydın Üniversitesi Tıp Fakültesi Fiziksel Tıp ve Rehabilitasyon AD, dtekdosdemircioglu@aydın.edu.tr, ORCID iD: 0000-0001-5946-3542

[5] Doç.Dr. İstinye Üniversitesi Tıp Fakültesi Tıbbi Biyokimya AD, huridedeakay@gmail.com ORCID iD: 0000-00032706-9625

KAYNAKÇA

1. Loganathan T., Doss C GP. Non-coding RNAs in human health and disease: potential function as biomarkers and therapeutic targets. *Functional & Integrative Genomics*. 2023; 23,33, 2-56. Doi:10.1007/s10142-022-00947-4
2. Yu Y., Xiao J., Hann S. S. The emerging roles of PIWI-interacting RNA in human cancers, *Cancer Management and Research.* 2019; 11, 5895-5909, DOI: 10.2147/CMAR.S209300
3. Loganathan, T., Doss C, G.P. Non-coding RNAs in human health and disease: potential function as biomarkers and therapeutic targets. *Functional & Integrative Genomics.* 2023; 23, 33 DOI: 10.1007/s10142-022-00947-4
4. Girard, A., Sachidanandam, R., Hannon, G. *et al.* A germline-specific class of small RNAs binds mammalian Piwi proteins. *Nature.* 2006; 442, 199–202. https://doi.org/10.1038/
5. Pandya, G. M., Ramani, U. V., Janmeda, M.,et al. piRNA: Basics and their Association with PIWI proteins. *Current Trends in Biotechnology and Pharmacy*. 2014; 8(3), 303-308.
6. Anzelon, T.A., Chowdhury, S., Hughes, S.M. *et al.* Structural basis for piRNA targeting. *Nature.* 2021; 597, 285–289 DOI:10.1038/s41586-021-03856-x
7. Cox, D. N., Chao, A., Baker, J et al. A novel class of evolutionarily conserved genes defined by piwi are essential for stem cell self-renewal. *Genes & development*. 1998; 12(23), 3715-3727. DOI: 10.1101/gad.12.23.3715
8. Aravin, A., Gaidatzis, D., Pfeffer, S. *et al.* A novel class of small RNAs bind to MILI protein in mouse testes. *Nature.* 442, 203–207 (2006). DOI: 10.1038/nature04916
9. Ross, R., Weiner, M. & Lin, H. PIWI proteins and PIWI-interacting RNAs in the soma. *Nature.* 2014; 505, 353–359 DOI:10.1038/nature12987
10. Yan, Z., Hu, H. Y., Jiang, X et al Widespread expression of piRNA-like molecules in somatic tissues. *Nucleic acids research*. 2011;*39*(15), 6596-6607. DOI:10.1093/nar/gkr298
11. Wang, X., Ramat, A., Simonelig, M. *et al.* Emerging roles and functional mechanisms of PIWI-interacting RNAs. *Nature Reviews Molecular Cell Biology*. 2023; 24, 123–141 DOI:10.1038/s41580-022-00528-0
12. Peters L, Meister G. Argonaute proteins: mediators of RNA silencing. *Molecular cell.* 2007;26:611-623. DOI 10.1016/j.molcel.2007.05.001
13. Cox, D. N., Chao, A., & Lin, H. Piwi encodes a nucleoplasmic factor whose activity modulates the number and division rate of germline stem cells. *Development*. 2000;*127*(3), 503-514. DOI:10.1242/dev.127.3.503
14. Brennecke, J., Aravin, A. A et al. Discrete small RNA-generating loci as master regulators of transposon activity in Drosophila. *Cell*. 2007; 128(6), 1089-1103. DOI:10.1016/j.cell.2007.01.043
15. Chen, S., Ben, S., Xin, J., Li, S., Zheng, R., Wang, H., ... & Wang, M. (2021). The biogenesis and biological function of PIWI-interacting RNA in cancer. *Journal of Hematology & Oncology*. 14(1), 1-18.
16. Fu, Q., & Wang, P. J. Mammalian piRNAs: Biogenesis, function, and mysteries. *Spermatogenesis*. 2014:*4*(1), e27889. DOI:10.4161/spmg.27889

17. Bamezai, S., Rawat, V. P., & Buske, C. Concise review: The Piwi-piRNA axis: pivotal beyond transposon silencing. *Stem Cells*. 2012;*30*(12), 2603-2611. DOI:10.1002/stem.1237
18. Shen, E. Z., Chen, H., Ozturk, A. R., Tu, S., Shirayama, M., Tang, W., ... & Mello, C. C. (2018). Identification of piRNA binding sites reveals the argonaute regulatory landscape of the C. elegans germline. *Cell*. 172(5), 937-951.
19. Izumi, N., Shoji, K., Suzuki, Y. et al. Zucchini consensus motifs determine the mechanism of pre-piRNA production. *Nature*. 2020;578, 311–316. DOI:10.1038/s41586-020-1966-9
20. Kawaoka, S., Izumi, N., Katsuma, S et al. 3′ end formation of PIWI-interacting RNAs in vitro. *Molecular cell*. 2011;*43*(6), 1015-1022. DOI 10.1016/j.molcel.2011.07.029
21. Timofeeva AV, Chagovets VV, Drapkina YS, et al. Cell-Free, Embryo-Specific sncRNA as a Molecular Biological Bridge between Patient Fertility and IVF Efficiency. *International Journal of Molecular Sciences*. 2019; Jun 14;20(12):2912. DOI:10.3390/ijms20122912.
22. Toporcerová S, Špaková I, Šoltys K, et al. Small Non-Coding RNAs as New Biomarkers to Evaluate the Quality of the Embryo in the IVF Process. *Biomolecules*. 2022; 12(11):1687. DOI:10.3390/biom12111687
23. Gardner DK, Balaban B. Assessment of human embryo development using morphological criteria in an era of time-lapse, algorithms and 'OMICS': is looking good still important? *Molecular Human Reproduction*. 2016;22(10):704-718. doi: 10.1093/molehr/gaw057
24. Gardner D.K., Schoolcraft W.B. Towards Reproductive Certainty: Infertility and Genetics Beyond 1999: The Plenary Proceedings of the 11th World Congress on *In Vitro Fertilization and Human Reproductive Genetics*. Parthenon Press; New York, NY, USA: 1999. In-vitro culture of human blastocysts; pp. 378–388.
25. Gardner DK, Lane M, Stevens J, Schoolcraft WB. Noninvasive assessment of human embryo nutrient consumption as a measure of developmental potential. *Fertil Steril*. 2001 ;76(6):1175-80. doi: 10.1016/s0015-0282(01)02888-6.
26. Poli M, Ori A, Child T, et al. Characterization and quantification of proteins secreted by single human embryos prior to implantation. *EMBO molecular medicine*. 2015;7(11):1465-79. DOI:10.15252/emmm.201505344.
27. Hale BJ, Yang CX, Ross JW. Small RNA regulation of reproductive function. *Molecular reproduction and development*. 2014;81(2):148-59. DOI:10.1002/mrd.22272.
28. Capalbo A, Ubaldi FM, Cimadomo D, et al. MicroRNAs in spent blastocyst culture medium are derived from trophectoderm cells and can be explored for human embryo reproductive competence assessment. *Fertil Steril*. 2016;105(1):225-35.e1-3. DOI:10.1016/j.fertnstert.2015.09.014.
29. Timofeeva A, Drapkina Y, Fedorov I, Chagovets V, Makarova N, Shamina M, Kalinina E, Sukhikh G. Small Noncoding RNA Signatures for Determining the Developmental Potential of an Embryo at the Morula Stage. *International Journal of Molecular Science*. 2020;10;21(24):9399. DOI:10.3390/ijms21249399.
30. Cimadomo D, Rienzi L, Giancani A, et al. Definition and validation of a custom protocol to detect miRNAs in the spent media after blastocyst culture: searching for biomarkers of implantation. *Human Reproduction*. 2019;29;34(9):1746-1761. DOI: 10.1093/humrep/dez119.

31. Roovers EF, Rosenkranz D, Mahdipour M, et al. Piwi proteins and piRNAs in mammalian oocytes and early embryos. *Cell reports.* 2015;31;10(12):2069-82. DOI:10.1016/j.celrep.2015.02.062.
32. Yuan S, Schuster A, Tang C, et al. Sperm-borne miRNAs and endo-siRNAs are important for fertilization and preimplantation embryonic development. *Development.* 2016;15;143(4):635-47. DOI 10.1242/dev.131755.
33. Svoboda P, Flemr M. The role of miRNAs and endogenous siRNAs in maternal-to-zygotic reprogramming and the establishment of pluripotency. *EMBO Reports.* 2010;11(8):590-7. DOI:10.1038/embor.2010.102.
34. Siomi MC, Sato K, Pezic D, et al. PIWI-interacting small RNAs: the vanguard of genome defence. *Nature reviews Molecular cell biology*. 2011;12(4):246-58. DOI: 10.1038/nrm3089.
35. Capalbo A, Ubaldi FM, Cimadomo D, et al. MicroRNAs in spent blastocyst culture medium are derived from trophectoderm cells and can be explored for human embryo reproductive competence assessment. *Fertil Steril.* 2016;105(1):225-35.e1-3. DOI:10.1016/j.fertnstert.2015.09.014.
36. Noli L, Capalbo A, Dajani Y, et al. Human Embryos Created by Embryo Splitting Secrete Significantly Lower Levels of miRNA-30c. *Stem Cells Development.* 2016;15;25(24):1851862. DOI:10.1089/scd.2016.0212.
37. Shokrzadeh, N, Alivand, MR, Abedelahi, A, et al. Upregulation of HB-EGF, Msx.1, and miRNA Let-7a by administration of calcitonin through mTOR and ERK1/2 pathways during a window of implantation in mice. *Molecular Reproduction and Development.* 2018;85: 790– 801. DOI:10.1002/mrd.23061
38. Ji Q, Xie Z, Gan W, et al. Identification and Characterization of PIWI-Interacting RNAs in Spinyhead Croakers (Collichthys lucidus) by Small RNA Sequencing. *Fishes.* 2022; 7(5):297. DOI:10.3390/fishes7050297
39. Lee YJ, Moon SU, Park MG, et al. Multiplex bioimaging of piRNA molecular pathway-regulated theragnostic effects in a single breast cancer cell using a piRNA molecular beacon. *Biomaterials.* 2016;101:143-55. DOI:10.1016/j.biomaterials.2016.05.052.
40. Weng W, Liu N, Toiyama Y, et al. Novel evidence for a PIWI-interacting RNA (piRNA) as an oncogenic mediator of disease progression, and a potential prognostic biomarker in colorectal cancer. *Molecular Cancer.* 2018;30;17(1):16. DOI:10.1186/s12943-018-0767-3.
41. Costanzo V, Bardelli A, Siena S, et al. Exploring the links between cancer and placenta development. *Open Biology.* 2018;8(6):180081. DOI:10.1098/rsob.180081.
42. C. Ferretti, L. Bruni, V. Dangles-Marie, et al. Molecular circuits shared by placental and cancer cells, and their implications in the proliferative, invasive and migratory capacities of trophoblasts, *Human Reproduction Update.* 2007;13: 2, 121–141, DOI:10.1093/humupd/dml048
43. Guo X, Yi H, Li TC, et al. Role of Vascular Endothelial Growth Factor (VEGF) in Human Embryo Implantation: Clinical Implications. *Biomolecules.* 2021;11(2):253. DOI:10.3390/biom11020253
44. Varas-Godoy, M., Acuña-Gallardo, S., Venegas-Duarte, S., et al. Angiogenic Properties of Menstrual Stem Cells Are Impaired in Women with a History of Preeclampsia. *Stem Cells International.* 2019; Article ID 1916542, 12 pages, DOI:10.1155/2019/1916542

45. Rosenbluth EM, Shelton DN, Wells LM, et al. Human embryos secrete microRNAs into culture media--a potential biomarker for implantation. *Fertil Steril.* 2014;101(5):1493-500. DOI:10.1016/j.fertnstert.2014.01.058.
46. Ochoa-Bernal MA, Fazleabas AT. Physiologic Events of Embryo Implantation and Decidualization in Human and Non-Human Primates. International Journal of *Molecular Science.* 2020;13;21(6):1973. DOI:10.3390/ijms21061973.
47. Fernandez EI, Ferreira AS, Cecílio MHM, et al. Artificial intelligence in the IVF laboratory: overview through the application of different types of algorithms for the classification of reproductive data. *Journal of Assisted Reproduction and Genetics.* 2020;37(10):2359-2376. DOI: 10.1007/s10815-020-01881-9.
48. Mann, JM, Wei, C, Chen, C. How genetic defects in piRNA trimming contribute to male infertility. *Andrology.* 2023; 11: 911–917. DOI:10.1111/andr.13324
49. Meritxell Jodar, Sellappan Selvaraju, Edward Sendler et al. The presence, role and clinical use of spermatozoal RNAs, *Human Reproduction Update.* 2013, 19(6), 604–624, DOI:10.1093/humupd/dmt031
50. Greenberg, M. V., Bourc'his. The diverse roles of DNA methylation in mammalian development and disease. *Nature reviews Molecular cell biology*, 2019;20(10), 590-607. DOI:10.1038/s41580-019-0159-6
51. De Carvalho, D. D., You, J. S., Jones, P. A. DNA methylation and cellular reprogramming. *Trends in cell biology.* 2010;20(10),609-617. DOI:10.1016/j.tcb.2010.08.003
52. Berdasco, M., & Esteller, M. Aberrant epigenetic landscape in cancer: how cellular identity goes awry. *Developmental cell.* 2010;19(5), 698-711. DOI:10.1016/j.devcel.2010.10.005
53. Bourc'his, D., Bestor, T. H. Meiotic catastrophe and retrotransposon reactivation in male germ cells lacking Dnmt3L. *Nature.* 2004;431(7004), 96-99. DOI:10.1038/nature02886
54. Vander Borght, M., Wyns, C. Fertility and infertility: Definition and epidemiology. *Clinical Biochemistry.* 2018;62, 2-10. DOI:10.1016/j.clinbiochem.2018.03.012
55. He, L., Wu, X., Wu, R et al. Seminal plasma piRNA array analysis and identification of possible biomarker piRNAs for the diagnosis of asthenozoospermia. *Experimental and Therapeutic Medicine.* 2022; 23(5), 1-12. DOI:10.3892/etm.2022.11275
56. Heyn, H., Ferreira, H. J., Bassas, L. et al. Epigenetic disruption of the PIWI pathway in human spermatogenic disorders. *PloS one.* 2012;7(10), e47892. DOI: 10.1371/journal.pone.0047892
57. Meerschaut, F. V., Nikiforaki, D., Heindryckx, B et al. Assisted oocyte activation following ICSI fertilization failure. *Reproductive biomedicine online.* 2014;28(5), 560-571. DOI:10.1016/j.rbmo.2014.01.008
58. Swain, J. E., & Pool, T. B. ART failure: oocyte contributions to unsuccessful fertilization. *Human reproduction update.* 2008;14(5), 431-446. DOI:10.1093/humupd/dmn025
59. Sadeghi, M. R., Lakpour, N., Heidari-Vala et al. Relationship between sperm chromatin status and ICSI outcome in men with obstructive azoospermia and unexplained infertile normozoospermia. *Romanian Journal of Morphology and Embryology.* 2011;52(2), 645-51.

60. Cui, L., Fang, L., Shi, B et al. Spermatozoa expression of piR-31704, piR-39888, and piR-40349 and their correlation to sperm concentration and fertilization rate after ICSI. *Reproductive Sciences.* 2018;25(5), 733-739. DOI:10.1177/1933719117725822
61. Cao, C., Wen, Y., Wang, X., et al.. Testicular piRNA profile comparison between successful and unsuccessful micro-TESE retrieval in NOA patients. *Journal of assisted reproduction and genetics.* 2018; 35,801-808. DOI:10.1007/s10815-018-1134-4
62. Kamaliyan, Z., Pouriamanesh, S., Amin-Beidokhti et al. HIWI2 rs508485 polymorphism is associated with non-obstructive azoospermia in iranian patients. *Reports of biochemistry & molecular biology.* 2017;5(2), 108.
63. Gilbert, I., Macaulay, A., & Robert, C. Oocyte developmental competence and embryo quality: distinction and new perspectives. *Animal Reproduction.* 2018;12(3), 397-407.
64. Jukam, D., Shariati, S. A. M., Skotheim, J. M. Zygotic genome activation in vertebrates. *Developmental cell.* 2017;42(4), 316-332. DOI:10.1016/j.devcel.2017.07.026
65. Graf, A., Krebs, S., Heininen-Brown, M et al. Genome activation in bovine embryos: review of the literature and new insights from RNA sequencing experiments. *Animal reproduction science.* 2014;149(1-2), 46-58. DOI:10.1016/j.anireprosci.2014.05.016
66. Cuthbert, J. M., Russell, S. J., White, K. L. et al. The maternal-to-zygotic transition in bovine in vitro-fertilized embryos is associated with marked changes in small non-coding RNAs. *Biology of Reproduction.* 2019;100(2), 331-350 DOI:10.1093/biolre/ioy190
67. Li, Y., Liang, Z., Liang, Z. et al. Abnormal PIWI-interacting RNA profile and its association with the deformed extracellular matrix of oocytes from recurrent oocyte maturation arrest patients. *Fertility and Sterility.* 2021;115(5), 1318-1326. DOI:10.1016/j.fertnstert.2020.11.037
68. Chen D, Zhang Z, Chen B, Ji D, Hao Y, Zhou P, Wei Z, Cao Y. Altered microRNA and Piwi-interacting RNA profiles in cumulus cells from patients with diminished ovarian reserve. *Biology of Reproduction.* 2017;97(1):91-103. doi: 10.1093/biolre/iox062. DOI:10.1093/biolre/iox062
69. Zhao PP, Yao MJ, Chang SY et al. Novel function of PIWIL1 in neuronal polarization and migration via regulation of microtubule-associated proteins. *Molecular Brain.* 2015;8(1):39. DOI: 10.1186/s13041-015-0131-0.
70. Perrat PN, DasGupta S, Wang J et al. Transposition-driven genomic heterogeneity in the Drosophila brain. *Science.* 2013;340(6128):91–5 DOI: 10.1126/science.1231965
71. Phay M, Kim HH, Yoo S. Analysis of piRNA-like small non-coding RNAs present in axons of adult sensory neurons. *Molecular Neurobiology.* 2018;55(1):483– 94 DOI: 10.1007/s12035-016-0340-2
72. Sohn EJ, Jo YR, Park HT. Downregulation MIWI-piRNA regulates the migration of Schwann cells in peripheral nerve injury. *Biochemical and Biophysical Research Communications.* 2019;519(3):605–12DOI: 10.1016/j.bbrc.2019.09.008
73. Rajasethupathy P, Antonov I, Sheridan R et al. A role for neuronal piRNAs in the epigenetic control of memory-related synaptic plasticity. *Cell.* 2012;149(3):693–707. DOI: 10.1016/j.cell.2012.02.057
74. Leighton LJ, Wei W, Marshall PR et al. Disrupting the hippocampal Piwi pathway enhances contextual fear memory in mice. *Neurobiology of Learning and Memory*. 2019;161:202–9. DOI: 10.1016/j.nlm.2019.04.002

75. Qiu W, Guo X, Lin X et al. Transcriptome-wide piRNA profiling in humabrains of Alzheimer's disease. *Neurobiology of Aging.* 2017;57:170–7. DOI: 10.1016/j.neurobiolaging.2017.05.020
76. Schulze M, Sommer A, Plötz S et al. Sporadic Parkinson's disease derived neuronal cells show disease-specific mRNA and small RNA signatures with abundant deregulation of piRNAs. *Acta neuropathologica communications.* 2018;6(1):58. DOI: 10.1186/s40478-018-0561-x
77. Feigin VL, Nichols E, Alam T et al. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. The *Lancet Neurology.* 2019;18(5):459-80. DOI: 10.1016/S1474-4422(18)30499-X
78. Dharap A, Nakka VP, Vemuganti R. Altered expression of PIWI RNA in the rat brain after transient focal ischemia. *Stroke*. 2011;42(4):1105–9. DOI: 10.1161/STROKEAHA.110.598391
79. Siegel, RL., Miller, KD., Jemal, A. Cancer statistics, 2017. *CA: A Cancer Journal for Clinicians.* 2017; 67(1):7–30. DOI:10.3322/caac.21395
80. Hashim, ARF., Marchese, G., et al. RNA sequencing identifies specific PIWI-interacting small non-coding RNA expression patterns in breast cancer. *Oncotarget.* 2014;5(20):9901–10. DOI: 10.18632/oncotarget.2476
81. Chalbatani, G. M., Dana, H., Memari, F., et al.(2019). Biological function and molecular mechanism of piRNA in cancer. *Practical laboratory medicin*e. 2019; 13, e00113. DOI: 10.1016/j.plabm.2018.e00113
82. Peng, L., Song, L., Liu, C, et al. piR-55490 inhibits the growth of lung carcinoma by suppressing mTOR signaling. *Tumor Biology.* 2016;37(2):2749–56. DOI:10.1007/s13277-015-4056-0
83. Torre, LA., Bray, F., Siegel, RL, et al.. Global cancer statistics, 2012. *CA: A Cancer Journal for Clinicians.* 2015;65(2):87–108. DOI: 10.3322/caac.21262
84. Siddiqi, S., Matushansky, I. Piwis and piwi-interacting RNAs in the epigenetics of cancer. *Journal of Cell Biochemistry.* 2012;113(2):373–80. DOI: 10.1002/jcb.23363
85. Cheng, J., Deng, H., Xiao, B, et al. piR-823, a novel non-coding small RNA, demonstrates in vitro and in vivo tumor suppressive activity in human gastric cancer cells. *Cancer Letters*. 2012;315(1):12–7. DOI: 10.1016/j.canlet.2011.10.004
86. Cheng, J., Guo, JM., Xiao, BX, et al. piRNA, the new non-coding RNA, is aberrantly expressed in human cancer cells. *Clinica Chimica Acta.* 2011;412(17–18):1621–5. DOI: 10.1016/j.cca.2011.05.015
87. Martinez, VD., Enfield, KSS., Rowbotham, DA, et al. An atlas of gastric PIWI-interacting RNA transcriptomes and their utility for identifying signatures of gastric cancer recurrence. *Gastric Cancer.* 2016;19 (2):660–5. DOI: 10.1007/s10120-015-0487-y
88. Weng, W., Liu, N., Toiyama, Y, et al. Novel evidence for a PIWI-interacting RNA (piRNA) as an oncogenic mediator of disease progression, and a potential prognostic biomarker in colorectal cancer. *Molecular Cancer.* 2018;17(1):16. DOI:10.1186/s12943-018-0767-3
89. Mai, D., Ding, P., Tan, L, et al. PIWI-interacting RNA-54265 is oncogenic and a potential therapeutic target in colorectal adenocarcinoma. *Theranostics.* 2018;8(19):5213–30. DOI: 10.7150/thno.28001

90. Yin, J., Jiang, XY., Qi, W, et al. piR-823 contributes to colorectal tumorigenesis by enhancing the transcriptional activity of HSF1. *Cancer Science.* 2017;108(9):1746–56. DOI: 10.1111/cas.13300
91. Law, PT., Qin, H., Ching, AK, et al. Deep sequencing of small RNA transcriptome reveals novel non-coding RNAs in hepatocellular carcinoma. *Journal of Hepatology.* 2013;58(6):1165–73. DOI: 10.1016/j.jhep.2013.01.032
92. Rizzo, FRA., Marchese, G, et al. Specific patterns of PIWI-interacting small noncoding RNA expression in dysplastic liver nodules and hepatocellular carcinoma. *Oncotarget.* 2016;7(34):54650–61. DOI: 10.18632/oncotarget.10567
93. Li, Y., Wu, X., Gao, H, et al. Piwi-interacting RNAs (piRNAs) are dysregulated in renal cell carcinoma and associated with tumor metastasis and Cancer-specific survival. *Molecular Medicine.* 2015;21:381–8. DOI: 10.2119/molmed.2014.00203
94. Busch, J., Ralla, B., Jung, M, et al. Piwi-interacting RNAs as novel prognostic markers in clear cell renal cell carcinomas. *Journal of experimental & clinical cancer research.* 2015;34:61. DOI: 10.1186/s13046-015-0180-3
95. Cordeiro, A., Navarro, A., Gaya, A, et al. PiwiRNA-651 as marker of treatment response and survival in classical Hodgkin lymphoma. *Oncotarget.* 2016;7(29):46002–13. DOI: 10.18632/oncotarget.10015
96. Liu, X., Zheng, J., Xue, Y, et al. PIWIL3/OIP5-AS1/miR-367-3p/CEBPA feedback loop regulates the biological behavior of glioma cells. *Theranostics.* 2018;8(4):1084–105. DOI: 10.7150/thno.21740
97. Jacobs, DI., Qin, Q., Fu, A, et al.piRNA-8041 is downregulated in human glioblastoma and suppresses tumor growth in vitro and in vivo. *Oncotarget.* 2018;9(102):37616–26. DOI: 10.18632/oncotarget.26331
98. Shen, S., Yu, H., Liu, X,et al. PIWIL1/piRNA-DQ593109 regulates the permeability of the blood-tumor barrier via the MEG3/miR-330-5p/ RUNX3 Axis. *Molecular Therapy-Nucleic Acids.* 2018;10:412–25. DOI: 10.1016/j.omtn.2017.12.020.
99. Leng, X., Ma, J., Liu, Y, et al. Mechanism of piRDQ590027/MIR17HG regulating the permeability of glioma conditioned normal BBB. *Journal of experimental & clinical cancer research.* 2018;37(1):246. DOI: 10.1186/s13046-018-0886-0
100. Das, B., Roy, J., Jain, N, et al. Tumor suppressive activity of PIWI-interacting RNA in human fibrosarcoma mediated through repression of RRM2. *Molecular carcinogenesis.* 2019;58(3):344–57. DOI: 10.1002/mc.22932
101. Singh, G., Roy, J., Rout, P, et al. Genome-wide profiling of the PIWI interacting RNA-mRNA regulatory networks in epithelial ovarian cancers. *PLoS One.* 2018;13(1):e0190485. DOI: 10.1371/journal.pone.0190485

Bölüm 5

EKZOSOMAL miRNA'ların PEDİATRİK KANSERLERDEKİ POTANSİYEL ROLÜ

Gülper NACARKAHYA[1]

GİRİŞ

Hücre dışı veziküller (EV), hücre dışı boşluğa salgılanan tüm zar veziküllerini içerir (1). Ektozomlar, dökülen veziküller, mikro veziküller ve mikropartiküller terimleri plazma zarının doğrudan dışa doğru tomurcuklanmasından kaynaklanan genellikle çapları 150-1000 nm arasında değişen büyük veziküllerdir. Çapları 30 ila 100 nm arasında değişen daha küçük veziküller ekzosom olarak adlandırılır. Bu vesiküler cisimcikler multivesiküler cisimler (MVB'ler) olarak adlandırılmakta olup, hücre içinde oluşarak plazma zarı ile füzyon yoluyla hücre dışı boşluğa salgılanırlar (2). Veziküllerin ekstrasellüler matriksteki farklı hücre tipleriyle olan etkileşimi immün sistem, kanser ve birçok kronik hastalıkla ilişkilidir. Bunlar sadece sitozol ve artık zar proteinlerini taşımazlar (3,4). Ekzosomlar, hücresel olmayan iletişim araçlarıdır, hücresel proteinler, nükleik asitler dahil olmak üzere sinyal moleküllerini de taşırlar (5). Ekzosomlar, birçok vücut sıvılarından ve hücre kültürü ortamından izole edilebilirler (6,7). Ekzosomların in vivo olarak güvenilir bir çözünürlükte görüntülenememesi, izlenememesi ve izolasyonundaki mevcut deneysel sıkıntılar ekzosomlarla yapılan çalışmalarda sorun teşkil etmektedir. Ekzosomlar köken aldıkları hücrelerden salındıktan sonra; hücrelerde büyüme ve farklılaşma gibi olayları düzenlemek için çeşitli kargo proteinleri ve genetik bilgi taşırlar ve hücrelerin biyolojik tepkilerini etkin bir şekilde değiştirirler. Hastalığı teşvik edici veya kısıtlayıcı olabilirler. Hastalık teşhisi ve prognozu için biyobelirteçler olarak kullanılabilirler. Örneğin, ekzosomlardaki çift sarmallı DNA'lar, birincil ve/veya metastatik kanser hücrelerindeki mutasyonları yansıttıkları için kanser tanısı için klinik biyobelirteçler olarak kullanılabilirler (8). Dolaşan ekzosomal DNA, pankreas kanserinin potansiyel biyobelirteçleri olan KRASG12D ve TP53R273H mutasyonlarının tespitini mümkün kılmıştır

[1] Dr. Öğr. Üyesi , Gaziantep Üniversitesi Tıp Fakültesi, Tıbbi Biyoloji AD, gulperkoyuncu@gmail.com, ORCID iD: 0000-0002-8512-8833

miRNA-373 meme kanserlerinde, miR-1290 and miR-375 prostat kanserlerinde ve daha birçok ekzosomal miRNA lar kanser biyobelirteçleri olarak kullanılmaktadır (90-92) . Ekzosomal miR-28, miR-31a ve miR-130 diyabetik periferik nöropatinin gelişimininde biyobelirteç olarak kullanılır (93). Ekzosomal miRNA'lar kanser tedavisinde ileri tedavi seçenekleri sunmaktadır. Kanser odaklı ekzosomal miRNAları doğru hedeflere yönlendirerek pro-tümorijenik ve pro-metastatik sinyallere ve ilaç direncine de katkıda bulunabilmektedirler. Bu özellikleri biyobelirteç olarak kanserin erken teşhisinde hizmet edebilecekleri düşüncesine yol açmıştır. Ekzosomların tümöre kolay ulaşım ve antitümör etkilerinden dolayı, ekzosom bazlı antikanser tedavileri için ilaç dağıtım araçları veya hücresiz aşılar olarak tasarlanıp hücre bazlı tedavilerin yerini alabilirler. Ancak ekzosomların tümör ve antitümör etkilerinden dolayı daha detaylı çalışmalara şüphesiz ihtiyaç vardır. Buna göre, ekzosomların verimini ve saflığını iyileştirmeye yönelik yöntemlerin optimize edilmesi, hem etki mekanizmasının araştırılması hem de terapötik amaçlar açısından en önemli öncelik olacaktır.

KAYNAKÇA

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, *Cancer Journal for Clinicians*, 2018;68(1):7–30.
2. Gould SJ, Raposo G. As we wait: Coping with an imperfect nomenclature for extracellu- lar vesicle, *Journal Of Extracellular Vesicles*, 2013;2. doi:10.3402/jev.v2i0.20389.
3. Colombo M, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles*, Annual Review of Cell And Developmental Biology,* 2014;30:255–89
4. Raposo G, Nijman HW, Stoorvogel W, et al. B lymphocytes secrete antigen-presenting vesicles, *Journal Of Experimental Medicine*,1996;183(3):1161–72.
5. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. *Journal Of Cell Biology*. 2013;200(4):373–83.
6. Tetta C, Ghigo E, Silengo L, et al. Extracellular vesicles as an emerging mechanism of cell-to-cell communication. *Endocrine*. 2013;44(1):11–9.
7. Witwer KW, Buzas EI, Bemis LT, et al. Standardization of sample collection, isolation and analysis methods in extracellular vesicle research, *Journal Of Extracellular Vesicles.* 2013;2. doi:10.3402/jev.v2i0.20360
8. Thakur BK, Zhang H, Becker A, et al. Double-stranded DNA in exosomes: a novel biomarker in cancer detection, *Cell Research* 24 (2014) 766–769, DOI: 10.1038/cr.2014.44. [PubMed: 24710597]
9. Yang S, Che SP, Kurywchak P, et al., Detection of mutant KRAS and TP53 DNA in circulating exosomes from healthy individuals and patients with pancreatic cancer, *Cancer Biology And Therapy*., 18 (2017) 158–165, DOI: 10.1080/15384047.2017.1281499. [PubMed: 28121262]

10. Kamerkar S, LeBleu VS, Sugimoto H, et al. Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer, *Nature,* 546 (2017) 498503, DOI: 10.1038/ nature22341. [PubMed: 28607485]
11. Alvarez-Erviti L, Seow Y, Yin H, et al. Wood MJ, Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes, *Nature Biotechnology* 29 (2011) 341–345, DOI: 10.1038/nbt.1807. [PubMed: 21423189]
12. Atay, S, Godwin, A.K. Tumor-derived exosomes: A message delivery system for tumor progression. *Communicative And İntegrative Biolog*. 2014, 7, e28231. [CrossRef] [Pu- bMed]
13. Lakkaraju, A, Rodriguez-Boulan, E. Itinerant exosomes: Emerging roles in cell and tissue polarity. *Trends in Cell Biology*. 2008, 18, 199–209. [CrossRef] [PubMed]
14. Taylor, D.D. Lyons, K. Gerçel-Taylor, C. Shed membrane fragment-associated markers for endometrial and ovarian cancers. *Gynecologic Oncology.*2002, 84, 443–448. [Cros- sRef] [PubMed]
15. Taylor, D.D.; Zacharias, W.; Gercel-Taylor, C. Exosome isolation for proteomic analyses and RNA profiling. Methods *Molecular Biology* 2011, 728, 235–246.
16. Colletti, M. Petretto, A, Galardi, A, et al. Proteomic Analysis of Neuroblastoma-Derived Exosomes: New Insights into a Metastatic Signature. *Proteomics* 2017, 17, 23–24. [CrossRef]
17. Taylor D.D, Gercel-Taylor, C. MicroRNA signatures of tumor-derived exosomes as di- agnostic biomarkers of ovarian cancer. *Gynecologic Oncology*.. 2008, 110, 13–21
18. M. Miyanishi, K, Tada, M, Koike, Y, et al., "Identification of Tim4 as a phosphatidylserine receptor," *Nature,* 2007.450, (7168), 435–439
19. Ostenfeld MS, Jeppesen DK, Laurberg JR, et al. Cellular disposal of miR23b by RAB27-dependent exosome release is linked to acquisition of metastatic properties, *Cancer Research* 2014 (74) ,5758–5771, DOI: 10.1158/0008-5472.CAN-13-3512. [PubMed: 25261234]
20. Chen WX, Liu XM, Lv MM, et al. Exosomes from drug-resistant breast cancer cells transmit chemoresistance by a horizontal transfer of microRNAs, *PLoS One*, 9 (2014) e95240, DOI: 10.1371/journal.pone.0095240. [PubMed: 24740415]
21. [78]. Qin X, Yu S, Zhou L, et al. Cisplatin-resistant lung cancer cell-derived exosomes increase cisplatin resistance of recipient cells in exosomal miR-100–5p-dependent manner, *International journal of nanotechnology and nanomedicine* 2017 (12) 3721–3733, DOI: 10.2147/ IJN.S131516. [PubMed: 28553110]
22. Kerscher AE ve Slack FJ. Oncomirs-microRNAs with a role in cancer, *Nature Reviews. Clinical Oncology*.2006 Apr;6(4):259-69. doi: 10.1038/nrc1840. PMID: 16557279.
23. Cooks, T., Pateras, I. S., Jenkins, L. M., et al. Mutant P53 Cancers Reprogram Macrophages to Tumor Supporting Macrophages via Exosomal miR-1246, *Nature communications*. 2018, 9 (1), 771. doi:10.1038/ s41467-018-03224-w
24. Zhou, C, Wei, W, Ma, J, et al. Cancersecreted Exosomal miR-1468-5p Promotes Tumor Immune Escape via the Immunosuppressive Reprogramming of Lymphatic Vessels, *Molecular Therapy* 2021, 29 (4), 1512–1528. doi:10.1016/j.ymthe.2020.12.034
25. Ilié, M, and Hofman, P. Pros: Can Tissue Biopsy Be Replaced by Liquid Biopsy? *Translational Lung Cancer Research* 2016. 5 (4), 420–423. doi:10.21037/tlcr.2016.08.06
26. Topuz E. Aydıner A. (Ed.) "Pediatrik Onkolojinin Temel Klinik Onkoloji Temel ilkeler ve Hemsirelik Bakımı. *İstanbul Üniversitesi Onkoloji Enstitüsü Yayınlan* 1997(4), 82- 88. 123-129.

27. Mott SR, James SR, Sperhac AM Nursing Care Of Children And Familes.. *Addison-Wesley*, 1990, Second Edition, California, 1781-1843.
28. *National Canser Instıtue* (1999). "National Canccr lnstitute Research Causes of Cancers in Children". http://cancernet.nci.nih.gov.
29. Knudson AG Jr, Strong LC. Mutation and cancer: neuroblastoma and pheochromocytoma. *American Journal Of Human Genetics*, 1972 (24), 514-532.
30. Yano H, Chao MV. Neurotrophin receptor structure and interactions *Pharmaceutica Acta Helvetiae,* 2000 (74), 253-60.
31. Patapoutian A, Reichardt LF. Trk receptors: mediators of neurotrophin action. *Current Opinion ın Neurobiology* 2001(11), 272-280.
32. Nakagawara A, Arima-Nakagawara M, Scavarda NJ, et al. Association between high levels of expression of the TRK gene and favorable outcome in human neuroblastoma. *New England journal of medicin*e, 1993(328), 847-854.
33. Nakagawara A, Azar CG, Scavarda NJ, et al., Expression and function of TRK-B and BDNF in human neuroblastomas. *Molecular Cell Biology* 1994(14),759-67.
34. Challagundla KB, Wise PM, Neviani P, et al.,Exosome-mediated transfer of microRNAs within the tumor microenvironment and neuroblastoma resistance to chemotherapy. *Journal of the National Cancer Institute* 2015 May 13,107(7):djv135. doi: 10.1093/jnci/djv135. PMID: 25972604; PMCID: PMC4651042.
35. Ma J, Xu M, Yin M, et al. Exosomal hsa-miR199a3p promotes proliferation and migration in neuroblastoma, *Frontiers in Oncology* 2019(9), 459. doi: 10.3389/fonc.2019.00459
36. Chen W, Hao X, Yang B, et al. MYCN amplified neuroblastoma cell derived exosomal miR175p promotes proliferation and migration of non MYCN amplified cells. *Molecular Medicine Reports* ,2021, 23(4):245. doi: 10.3892/mmr.2021.11884
37. Wang J, Liu S, Shi J, et al. The role of miRNA in the diagnosis, prognosis, and treatment of osteosarcoma. *Cancer Biother Radiopharm*. 2019,34(10), 605–613.
38. Kansara M, Teng MW, Smyth MJ, et al. Translational biology of osteosarcoma, *Nature Reviews. Cancer,* 2014,14(11),722–735.
39. Czarnecka A. M. Synoradzki K, Firlej W, et al. Molecular Biology of Osteosarco- ma. *Cancers* 2020, 2 (8), 10.3390/cancers12082130
40. Raimondi L, De Luca A, Gallo A, et al. Osteosarcoma Cell-Derived Exosomes Affect Tumor Microenvironment by Specific Packaging of microRNAs, Carcinogenesis, 2020, 41 (5), 666–677.
41. Fujiwara T, Uotani K, Yoshida A, et al. Clinical Significance of Circulating miR-25-3p as a Novel Diagnostic and Prognostic Biomarker in Osteosarcoma. *Oncotar- get* 2017,8 (20), 33375–33392. 10.18632/oncotarget.16498
42. Liu W, Long Q, Zhang W, et al. miRNA-221-3p Derived from M2-Polarized Tumor-Associated Macrophage Exosomes Aggravates the Growth and Metastasis of Osteosarcoma through SOCS3/JAK2/STAT3 axis. *Aging* (Albany NY) 2021, 13 (15), 19760–19775.
43. Zhang H, Wang J, Ren T, et al. Bone Marrow Mesenchymal Stem Cell-Derived Exosomal miR-206 Inhibits Osteosarcoma Progression by Targeting TRA2B. *Cancer Letter*, 2020, 490, 54–65.
44. Gong, L, Bao, Q, Hu, C, et al. Exosomal miR675 from Metastatic Osteosarcoma Promotes Cell Migration and Invasion by Targeting CALN1. *Biochemical And Biophysical Research Communications*. 2018, 500 (2), 170–176. doi:10. 1016/j.bbrc.2018.04.016

45. Sun, T. et al. miR-375-3p negatively regulates osteogenesis by targeting and decreasing the expression levels of LRP5 and β-catenin. *PLoS One*, 2017 (12)
46. Zhao, H. et al. Transforming growth factor β1/Smad4 signaling affects osteoclast diffe- rentiation via regulation of miR-155 expression, *Molecular Cells*, 2017(40), 211–221.
47. Yang C, Yang H, Liu J, et al. Focus on exosomes: novel pathogenic components of leukemia, *American Journal Of Cancer Research,* 2019 (9),1815–1829.
48. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes, *Science,* 2020 Feb 7;367(6478):eaau6977. doi: 10.1126/science.aau6977. PMID: 32029601
49. Kumar B, Garcia M, Weng L, et al. Acute myeloid leukemia transforms the bone marrow niche into a leukemia-permissive microenvironment through exosome secretion. *Leukemia.* 2018,Mar 32(3),575-587. doi: 10.1038/leu.2017.259
50. Whiteside TL. Exosomes and tumor-mediated immune suppression, *Journal Of Clinical İnvestigation,* 2016(126),1216–1223.
51. Wang J, Hendrix A, Hernot S, et al.,Bone marrow stromal cell-derived exosomes as communicators in drug resistance in multiple myeloma cells. *Blood.* 2014(124), 555–566.
52. Melo SA, Sugimoto H, O'Connell JT, et al. Cancer exosomes perform cell-independent microRNA biogenesis and promote tumorigenesis. *Cancer Cell,* 2014 (26),707–721
53. Kim, J.A. Shim, J.S, Lee, G.Y, et al.,Microenvironmental remodeling as a parameter and prognostic factor of heterogeneous leukemogenesis in acute myelogenous leukemia, *Cancer Research*, 2015 (75), 2222–2231.
54. Brzozowa-Zasada, M, Piecuch, A, Dittfeld, A, et al. Notch signalling pathway as an on- cogenic factor involved in cancer development*, Contemporary Oncology*, 2016, 20(4), 267-272.
55. Beverly, L. J, Felsher, D. W, Capobianco, A. J. Suppression of p53 by Notch in lymphomagenesis: implications for initiation and regression. *Cancer Research*, 2005, 65(16), 7159-7168.
56. Mihailovich M, Bremang M, Spadotto V, et al. miR-17-92 fine-tunes MYC expression and function to ensure optimal B cell lymphoma growth, *Nature Communications*. 2015 Nov 10(6) 8725. doi: 10.1038/ncomms9725.
57. Koolivand, M, Ansari M, Piroozian, F, et al., Alleviating the progression of acute myeloid leukemia (AML) by sulforaphane through controlling miR-155 levels, *Molecular Biology Reports* 2018, 45, 2491–2499
58. Umezu, T, Ohyashiki, K, Kuroda, M, et al., Leukemia cell to endothelial cell communication via exosomal miRNAs, *Oncogene* 2019, 32, 2747–2755
59. Akinduro, O, Weber, T.S, Ang, H, et al., Proliferation dynamics of acute myeloid leukaemia and haematopoietic progenitors competing for bone marrow space, *Nature Communications,* 2018 (9), 519. [CrossRef]
60. Boyd, A.L, Campbell C.J, Hopkins C.I, et al. Niche displacement of human leukemic stem cells uniquely allows their competitive replacement with healthy HSPCs. *Journal Of Experimental Medicine.*. 2014 (211), 1925–1935. [CrossRef]
61. Abdelhamed, S, Butler J.T, Doron B, et al., Extracellular vesicles impose quiescence on residual hematopoietic stem cells in the leukemic niche, *European Molecular Biology Organization Reports2019*(20), 47546.

62. Gulino, R, Forte S, Parenti, R et al. MicroRNA and pediatric tumors: Future perspectives. *Acta Histochem*, 2015 (117), 339–354. [CrossRef]
63. Allen, C.E, Kelly K.M, Bollard C.M, Pediatric lymphomas and histiocytic disorders of childhood, *Pediatric clinics of North America* 2015Feb;62(1),139-165. doi: 10.1016/j.pcl.2014.09.010.
64 .Zhao L, Liu W, Xiao J, et al., The role of exosomes and "exosomal shuttle microRNA" in tumorigenesis and drug resistance , *Cancer Letter.* 2015(356) (2 Pt B), 339 – 346
65. Bach DH, Hong JY, Park HJ, et al., The role of exosomes and miRNAs in drug-resistance of cancer cells, *International journal of cancer,* 2017, Jul 15;141(2):220-230. doi: 10.1002/ijc.30669.
66. Feng, Y, Zhong, M, Zeng, S, et al., Exosome-derived miRNAs as predictive biomarkers for diffuse large B-cell lymphoma chemotherapy resistance. *Epigenomics* 2019(11), 35–51
67. Zhou B, Wang S, Mayr C, et al., MiR-150, amicroRNA expressed in mature B and T cells, blocks early Bcell development when expressed prematurely. *Proceedings of the National Academy of Sciences of the United States of America* 2007 (104), 7080–7085
68. Metzler M, Wilda M, Busch K, et al., High expression of precursor microRNA-155/BIC RNA inchildren with Burkitt lymphoma, *Genes Chromosomes Cancer,* 2004, Feb;39(2),167-169. doi: 10.1002/gcc.10316.
69. Kluiver J, van den Berg A, de Jong D, et al., Regulation of pri-microRNA BIC transcription and processing in Burkitt lymphoma. *Oncogene*, 2007(26), 3769–3776
70. Millar AJW, Cox S, Davidson A., Management of bilateral Wilms tumours. *Pediatric Surgery İnternational*. 2017,33 (7), 737–745
71. Bianco P, Cao X, Frenette PS, et al. The meaning, the sense and the significance: translating the science of mesenchymal stem cells into medicine, *Natural Medicine* 2013,19(1),35–42
72. Vakhshiteh F, Atyabi F, Ostad SN. Mesenchymal stem cell exosomes: a two-edged sword in cancer therapy. *International Journal of Nanomedicine.* 2019(14),2847–2859.
73. Abbaszadeh H, Ghorbani F, Derakhshani M, et al. Human umbilical cord mesenchymal stem cell-derived extracellular vesicles: a novel therapeutic paradigm. *International Journal Of Physiology.* 2020,235(2), 706–717
74. Huang H, Zhong P, Zhang J, et al., Human umbilical cord-mesenchymal stem cells-de- rived exosomes carrying microRNA-15a-5p possess therapeutic effects on Wilms tu- mor via regulating septin 2. *Bioengineered.* 2022 Mar 13(3), 6136-6149.
75. Garcia Z, Silio V, Marqués M, et al. A PI3K activity-independent function of p85 regulatory subu-nit in control of mammalian cytokinesis, *European Molecular Biology Organization..* 2006,25(20), 4740–4751
76. Taheri M, Hussen BM, Abdullah SR, et al., Dysregulation of non-coding RNAs in Wilms tumor. *Pathology, Research And Practice,* 2023 Jun(246),154523. doi: 10.1016/j.prp.2023.154523. Epub 2023 May 8. PMID: 37201386.
77. Udaka YT, Packer RJ. Pediatric brain tumors, *Neurology Clinica*, 2018, 36(3), 533–556.
78. P. Zhao, J. Cheng, B. Li, D. et al., Up-regulation of the expressions of MiR-149-5p and MiR-99a-3p in exosome inhibits the progress of pituitary adenomas, *Cell Biology And Toxicology,* 2021, 37 (4), 633–651.

79. Cieśla M, Dulak J, Józkowicz A., MicroRNAs and epigenetic mechanisms of rhabdomyosarcoma development, *International Journal Of Biochemistry And Cell Biology,* 2014(53),482–92.
80. Sun M, Huang F, Yu D, et al., Autoregulatory loop between TGF-β1/miR-411-5p/SPRY4 and MAPK pathway in rhabdomyosarcoma modulates proliferation and dif- ferentiation. *Cell Death And Disease,* 2015 Aug 20,6(8), e1859. doi: 10.1038/cddis.2015.225.
81. Li Y, Foster W, Deasy BM, et al., Transforming growth factor-beta1 induces the differentiation of myogenic cells into fibrotic cells in injured skeletal muscle: a key event in muscle fibrogenesis, *American Journal Of Pathology* 2004 (164), 1007–1019.
82. Sun Q, Zhang Y, Yang G, et al. Transforming growth factor-beta-regulated miR-24 promotes skeletal muscle differentiation. *Nucleic Acids Research* 2008(36), 2690–2699.
83. Wang S, Guo L, Dong L, et al., TGF-beta1 signal pathway may contribute to rhabdomyosarcoma development by inhibiting differentiation, *Cancer Science*, 2010 (101),1108–1116.
84. Wang SL, Yao HH, Guo LL, et al. Selection of optimal sites for TGFB1 gene silencing by chitosan-TPP nanoparticle-mediated delivery of shRNA. *Cancer Genetics And Cytogenetics.* 2009(190), 8–14.
85. Sun MM, Li JF, Guo LL, et al. TGF-beta1 suppression of microRNA-450b-5p expression: a novel mechanism for blocking myogenic differentiation of rhabdomyosarcoma*, Oncogene* 2014 (33), 2075–2086
86. Ghayad S.E, Rammal, G, Ghamloush, F, et al., Exosomes derived from embryonal and alveolar rhabdomyosarcoma carry differential miRNA cargo and promote invasion of recipient fibroblasts, *Scientific Reports*, 2016(6), 37088
87. Xie Y, Dang W, Zhang S, et al. The role of exosomal noncoding RNAs in cancer. *Molecular Cancer,* 2019,18(1),37.
88. Corcoran C, Rani S, O'Driscoll L. miR-34a is an intracellular and Exosomal predictive biomarker for response to docetaxel with clinical relevance to prostate cancer progression. *Prostate.* 2014 Sep;74(13),1320-1334. doi: 10.1002/pros.22848.
89. Wei YF, Lai XF, Yu ST, et al., Exosomal miR-221/222 enhances tamoxifen resistance in recipient ER-positive breast cancer cells, *Breast Cancer Research And Treatment,* 2014(147),423–431.
90. Rotelli MT, Di Lena M, Cavallini A, et al., Fecal microRNA profile in patients with colorectal carcinoma before and after curative surgery, *International Journal Of Colorectal Disease,* 2015 Jul;30(7),891-898, doi: 10.1007/s00384-015-2248-0
91. Eichelser C, Stückrath I, Müller V, et al., Increased serum levels of circulating exosomal microRNA-373 in receptor-negative breast cancer patients, *Oncotarget*. 2014(5),9650–9663.
92. Huang XY, Yuan TZ, Liang MH et al., Exosomal miR-1290 and miR-375 as prognostic markers in castration-resistant prostate cancer. *European Urology* 2015(67),33–41.
93. J ia L, Chopp M, Wang L, et al.,. Exosomes derived from high-glucose-stimulated Schwann cells promote development of diabetic peripheral neuropathy. *Federation of American Societies for Experimental Biology,* 2018 Jun 22, 32(12):fj201800597R. doi: 10.1096/fj.201800597R.

Bölüm 6

MULTİGEN TESTLERİ ; MEME VE OVER KANSERİ HASTALARINDA KULLANIMI

Ferah KAZANCI[1]

GİRİŞ:

Kanser, dünyada en sık izlenen ve çok önemli sonuçlara sebeb olan genetik bir hastalıkdır. Tüm kanserler normal işlevleri hücre büyümesi ve DNA'nın bütünlüğünü korumak olan genlerde oluşan mutasyonların birikmesi sonucu gelişirler(1). Tümör baskılayıcı genler, DNA onarım genleri ve proto-onkogenlerin mutasyonları karsinogenezde kilit rol oynayan genetik değişikliklerdir. Mutasyonlar olguların çoğunda çevresel maruziyete bağlı olarak gerçekleşirken bazı ailelerde bireylerde spesifik maliginitelere yatkınlık çevresel maruziyetten bağımsız olarak izlenir(2). Ailesel veya kalıtsal kanserler olarak tanımladığımız bu grup hastalık tüm kanserlerin %5-10'unu oluştururlar. Risk altnda olan bireylerde; tümör gelişimi beklenenden daha erken yaşta izlenir, kardeşleri ve çocuklarında mutasyonun kalıtılma olasılığı çoğu olguda otozomal dominant kalıtım ile ilişkili olduğu için %50'dir. Risk altındaki bireylerin saptanması hem tarama hem de klinik yönetim açısından önem taşımaktadır. Bunlardan dolayı genetik testlerin kanserlerdeki önemi, kullanımı son zamanlarda çok artmakta ve fakat beraberinde bu testlerin birçok kompleks sonuçları hem klinisyenleri hemde hasta ve risk altındaki bireyleri etkilemektedir. Bu bölümde özellikle meme ve over kanseri hastalarındaki genetik testleri ve klinikte kullanımı anlatılacaktır.

MEME VE OVER KANSERİNDEKİ GENETİK BULGULAR

Meme kanseri sık görülen kanser türü olması ile ve over kanseri de en yüksek mortalite oranlı jinekolojik kanser olması ile kadın populasyonu etkileyen iki önemli maliginitedir. Meme ve over kanserlerin %5-10'unu herediter olup, *BRCA1* (113705 OMIM) ve *BRCA2*'nin (600185 OMIM) germline mutasyonları ile kanseri gelişimi arasında güçlü bir ilişki vardır(3). *BRCA1* mutasyon

[1] Dr., Necip Fazıl Şehir Hastanesi Kadın Doğum ve Çocuk Ek Hizmet Binası, Jinekolojik Onkoloji Kliniği, ferahkazanci@hotmail.com, ORCID iD: 0000-0002-3910-0821

BRCA1/2 testlerinin yanında uygun multigen panel testleri uygulanarak, klinik yönetim yapılmaktadır.

KAYNAKLAR

1. Hanahan D. Hallmarks of Cancer: New Dimensions Cancer Discov 2022;12:31–46 doi: 10.1158/2159-8290.CD-21-1059
2. Verma, P. S., & Agrawal, V. K. (2006). Cell Biology, Genetics, Molecular Biology, Evolution & Ecology (1 ed.). S .Chand and company Ltd.
3. Valencia OM, Samuel SE, Viscusi RK, et al. The Role of Genetic Testing in Patients With Breast Cancer: A Review. JAMA Surg. 2017;152(6):589-594. doi: 10.1001/jamasurg.2017.0552
4. Malone KE, Begg CB, Haile RW, et al. Population-based study of the risk of second primary contralateral breast cancer associated with carrying a mutation in BRCA1 or BRCA2. J Clin Oncol. 2010;28(14):2404-10. doi: 10.1200/JCO.2009.24.2495.
5. Xia B, Sheng Q, Nakanishi K, et al. Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Mol Cell. 2006;22(6):719-729. doi: 10.1016/j.molcel.2006.05.022.
6. Hatano Y, Tamada M, Matsuo M, et al. Molecular Trajectory of *BRCA1 and BRCA2* Mutations. Front Oncol. 2020;10:361. doi: 10.3389/fonc.2020.00361
7. Kurian AW, Hare EE, Mills MA, et al. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. J Clin Oncol. 2014;32(19):2001-9. doi: 10.1200/JCO.2013.53.6607.
8. Kurian AW, Ward KC, Hamilton AS, et al. Uptake, Results, and Outcomes of Germline Multiple-Gene Sequencing After Diagnosis of Breast Cancer. JAMA Oncol. 2018;4(8):1066-1072. doi: 10.1001/jamaoncol.2018.0644.
9. Hall MJ, Forman AD, Pilarski R, et al. Gene panel testing for inherited cancer risk. J Natl Compr Canc Netw. 2014;12(9):1339-46. doi: 10.6004/jnccn.2014.0128
10. Walsh T, Lee MK, Casadei S,et al. Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. Proc Natl Acad Sci U S A. 2010 13;107(28):12629-33. doi: 10.1073/pnas.1007983107.
11. Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol. 2016;13(9):581-8. doi: 10.1038/nrclinonc.2016.90.
12. van Marcke C, De Leener A, Berlière M,et al. Routine use of gene panel testing in hereditary breast cancer should be performed with caution. Crit Rev Oncol Hematol. 2016 ;108:33-39. doi: 10.1016/j.critrevonc.2016.10.008.
13. Samadder NJ, Riegert-Johnson D, Boardman L, et al. Comparison of Universal Genetic Testing vs Guideline-Directed Targeted Testing for Patients With Hereditary Cancer Syndrome. JAMA Oncol. 2021;7(2):230-237. doi: 10.1001/jamaoncol.2020.6252.
14. Eggington JM, Bowles KR, Moyes K, et al. A comprehensive laboratory-based program for classification of variants of uncertain significance in hereditary cancer genes. Clinical Genetics 2014, 86(3):229-237. doi: 10.1111/cge.12315.
15. Kapoor NS, Curcio LD, Blakemore CA,et al.Multigene Panel Testing Detects Equal Rates of Pathogenic BRCA1/2 Mutations and has a Higher Diagnostic Yield Compared to Limited BRCA1/2 Analysis Alone in Patients at Risk for Hereditary Breast Cancer. Ann Surg Oncol. 2015;22(10):3282-8. doi: 10.1245/s10434-015-4754-2.

16. Kurian AW, Ward KC, Abrahamse P, et al.Time Trends in Receipt of Germline Genetic Testing and Results for Women Diagnosed With Breast Cancer or Ovarian Cancer, 2012-2019. J Clin Oncol. 2021;39(15):1631-1640. doi: 10.1200/JCO.20.02785.
17. Kurian AW, Li Y, Hamilton AS, et al. Gaps in Incorporating Germline Genetic Testing Into Treatment Decision-Making for Early-Stage Breast Cancer. J Clin Oncol. 2017;35(20):2232-2239. doi: 10.1200/JCO.2016.71.6480.
18. Makhnoon S, Bednar EM, Krause KJ, et al. Clinical management among individuals with variant of uncertain significance in hereditary cancer: A systematic review and meta-analysis. Clin Genet. 2021;100(2):119-131. doi: 10.1111/cge.13966
19. Renaux-Petel M, Charbonnier F, Théry JC, et al. Contribution of de novo and mosaic *TP53* mutations to Li-Fraumeni syndrome. J Med Genet. 2018 Mar;55(3):173-180. doi: 10.1136/jmedgenet-2017-104976.
20. NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High- Risk Assesment: Breast, Ovarian,and Pancreatic Version2.2024. NCCCN.org.
21. Domchek SM, Robson ME. Update on Genetic Testing in Gynecologic Cancer. J Clin Oncol. 2019;37(27):2501-2509. doi: 10.1200/JCO.19.00363.

Bölüm 7

POLİKİSTİK OVER SENDROMU VE GENETİK ÇALIŞMALAR

Yunus ARIKAN[1]

GİRİŞ

Polikistik over sendromu (PCOS) genetik altyapısı tam olarak çözülememiş, poligenik, multifaktoriyel ve üreme çağındaki kadınlarda en fazla görülen bir endokrinopatidir. İçerisinde klinik/biyokimyasal hiperandrojenizm, dislipidemi, oligo/anavulasyon ve polikistik over morfolojisi gibi kriterlerin incelendiği 3 farklı tanı kriteri ile PCOS tanısı konulmaktadır. Tanı kriteri olarak yer almasa da insülin direnci hastaların büyük bir kısmında bulunmaktadır.

Otozomal dominant kalıtım gösterme potansiyeli diğer mendelyan kalıtım tiplerden daha sık olan PCOS'da hem genetik düzey hem de biyokimyasal markır bulma düzeyinde çalışmalar devam etmektedir. Genetik çalışmalarda kullanılan yöntemler geliştikçe daha fazla sayıda aday gen daha fazla sayıda PCOS'lu hastanın aynı anda çalışılmasını sağlamıştır. Dolayısıyla her geçen gün daha fazla sayıda aday gen PCOS'lu hastalarda ortaya çıkarılmaktadır.

Çalışmamızda başlangıcından son güncel gelişmelere kadar PCOS'dan sorumlu aday genler, aday varyasyon veya mutasyonların hem spesifik popülasyonlarda hem de meta-analiz çalışmalarında PCOS'u ve çeşitli fenotiplerini açıklama potansiyelleri verilmiştir.

Polikistik over morfolojisini gösterebilmek için hala altın standart olarak kullanılan transvajinal ultrason görüntülemenin yerini alabilecek daha az iş/insan/maliyet yükü gerektiren markır bulma çalışmalarında umut vaadedici gelişmeler ortaya çıkarılmaya devam etmektedir.

ETİYOLOJİSİ VE TANI KRİTERLERİ

Polikistik over sendromu (PCOS) ilk kez 1935 yılında Stein ve Leventhal'ın obezite, kıllanma, infertilite ve amenore semptomları ile birlikte, genişleyen

[1] Dr. Öğr. Üyesi, Yozgat Bozok Üniversitesi Tıp Fakültesi, Tıbbi Genetik AD, asilkan2@hotmail.com, ORCID iD: 0000-0001-5585-6795

Son olarak NGS teknolojisini PCOS'lu kadınların mitokondriyal DNA'larında kullanan bir araştırma, hem mitokondriyal DNA kopya sayısını PCOS'lu hastalarda kontrol grubuna daha düşük bulmuş hem de *MT-ATP6* geninde (pThr67Ala) ve *MT-ATP8* geninde (p.Asn46Ser) mutasyonlarını içine alacak şekilde oksidatif fosforilasyon genlerinde 183 farklı varyant ortaya çıkarmıştır (141).

SONUÇ

PCOS, multifaktoriyel, poligenik ve farklı tanı kriterlerine göre tanı konan ve kadınlarda üreme sistemi ile birlikte diğer bazı sistemlerin de etkilendiği metabolik sendrom bulgularının gözlendiği bir endokrinopatidir.

Aday gen bulma çalışmaları hala devam etmektedir. Meta analiz çalışmaları ile birlikte daha homojen hasta gruplarının dahil edildiği NGS çalışmaları hastalık için gerekli olan biyomarkır bulma çabalarını sonuçlandıracak gibi görünse de hala transvajinal ultrason görüntülemenin önüne geçebilmiş değildir.

KAYNAKÇA

1. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol. 1935;
2. Cooper HE, Spellacy WN, Prem KA, Cohen WD. Hereditary factors in the Stein-Leventhal syndrome. Am J Obstet Gynecol. 1968;
3. Givens JR, Wiser WL, Coleman SA, Wilroy RS, Andersen RN, Fish SA. Familial ovarian hyperthecosis: A study of two families. Am J Obstet Gynecol. 1971;
4. Mandel FP, Chang RJ, Dupont B, Pollack MS, Levine LS, New MI, et al. HLA Genotyping in Family Members and Patients with Familial Polycystic Ovarian Disease. J Clin Endocrinol Metab. 1983;
5. HAGUE WM, ADAMS J, REEDERS ST, PETO TEA, JACOBS HS. FAMILIAL POLYCYSTIC OVARIES: A GENETIC DISEASE? Clin Endocrinol (Oxf). 1988;
6. Lunde O, Magnus P, Sandvik L, Høglo S. Familial clustering in the polycystic ovarian syndrome. Gynecol Obstet Invest. 1989;
7. Mattsson L-Å, Cullberg G, Hamberger L, Samsioe G, Silfverstolpe G. Lipid metabolism in women with polycystic ovary syndrome: possible implications for an increased risk of coronary heart disease. Fertil Steril. 1984 Oct;42(4):579–84.
8. WILD RA, PAINTER PC, COULSON PB, CARRUTH KB, RANNEY GB. Lipoprotein Lipid Concentrations and Cardiovascular Risk in Women with Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 1985 Nov;61(5):946–51.
9. Graf MJ, Richards CJ, Brown V, Meissner L, Dunaif A. The independent effects of hyperandrogenaemia, hyperinsulinaemia, and obesity on lipid and lipoprotein profiles in women. Clin Endocrinol (Oxf). 1990 Jul;33(1):119–31.
10. Rojanasakul A, Chailurkit L, Sirimongkolkasem R, Chaturachinda K. Serum lipids and lipoproteins in women with polycystic ovarian disease with different body mass index. Int J Gynaecol Obstet. 1988 Dec;27(3):401–6.

11. Conway GS, Agrawal R, Betteridge DJ, Jacobs HS. Risk factors for coronary artery disease in lean and obese women with the polycystic ovary syndrome. Clin Endocrinol (Oxf). 1992 Aug;37(2):119–25.
12. Omar HA, Logsdon S, Richards J. Clinical profiles, occurrence, and management of adolescent patients with HAIR-AN syndrome. ScientificWorldJournal. 2004 Jul 8;4:507–11.
13. O'Brien B, Dahiya R, Kimble R. Hyperandrogenism, insulin resistance and acanthosis nigricans (HAIR-AN syndrome): an extreme subphenotype of polycystic ovary syndrome. BMJ Case Rep. 2020 Apr 9;13(4).
14. Franks S, Gharani N, Waterworth D, Batty S, White D, Williamson R, et al. The genetic basis of polycystic ovary syndrome. Hum Reprod. 1997;
15. Carmina E, Lobo RA. Polycystic Ovary Syndrome (PCOS): Arguably the Most Common Endocrinopathy Is Associated with Significant Morbidity in Women. J Clin Endocrinol Metab. 1999 Jun;84(6):1897–9.
16. Khan MJ, Ullah A, Basit S. Genetic basis of polycystic ovary syndrome (PCOS): Current perspectives. Application of Clinical Genetics. 2019.
17. Ates S, Sevket O, Sudolmus S, Dane B, Ozkal F, Uysal O, et al. Different phenotypes of polycystic ovary syndrome in Turkish women: Clinical and endocrine characteristics. Gynecol Endocrinol. 2013;
18. Duz S. Polycystic Ovary Syndrome [Polikistik Over Sendromu]. Med Sci | Int Med J. 2016;5(2):583.
19. Kuttenn F, Couillin P, Girard F, Billaud L, Vincens M, Boucekkine C, et al. Late-Onset Adrenal Hyperplasia in Hirsutism. N Engl J Med. 1985 Jul 25;313(4):224–31.
20. DEWAILLY D, VANTYGHEM-HAUDIQUET M-C, SAINSARD C, BUVAT J, CAPPOEN JP, ARDAENS K, et al. Clinical and Biological Phenotypes in Late-Onset 21 Hydroxylase Deficiency. J Clin Endocrinol Metab. 1986 Aug;63(2):418–23.
21. Carmina E, Rosato F, Jannì A, Rizzo M, Longo RA. Relative Prevalence of Different Androgen Excess Disorders in 950 Women Referred because of Clinical Hyperandrogenism. J Clin Endocrinol Metab. 2006 Jan;91(1):2–6.
22. Moran C, Azziz R. 21-Hydroxylase-Deficient Nonclassic Adrenal Hyperplasia: The Great Pretender. Semin Reprod Med. 2003;21(3):295–300.
23. Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, Stephens KC, et al. Androgen Excess in Women: Experience with Over 1000 Consecutive Patients. J Clin Endocrinol Metab. 2004 Feb;89(2):453–62.
24. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2013 Dec;98(12):4565–92.
25. Hannah-Shmouni F, Morissette R, Sinaii N, Elman M, Prezant TR, Chen W, et al. Revisiting the prevalence of nonclassic congenital adrenal hyperplasia in US Ashkenazi Jews and Caucasians. Genet Med. 2017 Nov;19(11):1276–9.
26. Deswal R, Narwal V, Dang A, Pundir C. The Prevalence of Polycystic Ovary Syndrome: A Brief Systematic Review. J Hum Reprod Sci. 2020;13(4):261.
27. Mohammed A. Association Between Polycystic Ovary Syndrome and Polymorphisms of CYP11A Gene Among Sample of Iraqi Women Introduction: Molecular Analysis: Gene selection Polymerase chain reaction (PCR). J Univ Shanghai Sci Technol. 2020;22:712–25.

28. Reddy KR, Deepika MLN, Supriya K, Latha KP, Rao SSL, Rani VU, et al. CYP11A1 microsatellite (tttta)n polymorphism in PCOS women from South India. J Assist Reprod Genet. 2014 Jul 4;31(7):857–63.
29. Abdel-Mageed W, Dabous E, Gerguis A. ASSOCIATION BETWEEN POLYMORPHISMS OF THE CYP11A1 GENE AND POLYCYSTIC OVARY SYNDROME IN EGYPTIAN FEMALE. Res J Appl Biotechnol. 2016 Nov 1;2(1):19–28.
30. Zhang C, Zhang X, Xia Y, Cao Y, Wang W, Xu P, et al. Association between polymorphisms of the CYP11A1 gene and polycystic ovary syndrome in Chinese women. Mol Biol Rep. 2012 Aug 15;39(8):8379–85.
31. Pusalkar M, Meherji P, Gokral J, Chinnaraj S, Maitra A. CYP11A1 and CYP17 promoter polymorphisms associate with hyperandrogenemia in polycystic ovary syndrome. Fertil Steril. 2009 Aug;92(2):653–9.
32. Diamanti-Kandarakis E, Bartzis MI, Bergiele AT, Tsianateli TC, Kouli CR. Microsatellite polymorphism (tttta)n at −528 base pairs of gene CYP11α influences hyperandrogenemia in patients with polycystic ovary syndrome. Fertil Steril. 2000 Apr;73(4):735–41.
33. Ashraf S, Rasool SUA, Nabi M, Ganie MA, Jabeen F, Rashid F, et al. CYP17 gene polymorphic sequence variation is associated with hyperandrogenism in Kashmiri women with polycystic ovarian syndrome. Gynecol Endocrinol. 2021 Mar 4;37(3):230–4.
34. Munawar Lone N, Babar S, Sultan S, Malik S, Nazeer K, Riaz S. Association of the *CYP17* and *CYP19* gene polymorphisms in women with polycystic ovary syndrome from Punjab, Pakistan. Gynecol Endocrinol. 2021 May 4;37(5):456–61.
35. Rahimi Z, Mohammadi E. The CYP17 MSP AI (T-34C) and CYP19A1 (Trp39Arg) variants in polycystic ovary syndrome: A case-control study. Int J Reprod Biomed. 2019 May 29;
36. Diamanti-Kandarakis E, Bartzis MI, Zapanti ED, Spina GG, Filandra FA, Tsianateli TC, et al. Polymorphism T→C (−34 bp) of gene CYP17 promoter in Greek patients with polycystic ovary syndrome. Fertil Steril. 1999 Mar;71(3):431–5.
37. Kaur R, Kaur T, Kaur A. Genetic association study from North India to analyze association of CYP19A1 and CYP17A1 with polycystic ovary syndrome. J Assist Reprod Genet. 2018 Jun 22;35(6):1123–9.
38. Echiburú B, Pérez-Bravo F, Maliqueo M, Sánchez F, Crisosto N, Sir-Petermann T. Polymorphism T → C (−34 base pairs) of gene CYP17 promoter in women with polycystic ovary syndrome is associated with increased body weight and insulin resistance: a preliminary study. Metabolism. 2008 Dec;57(12):1765–71.
39. Ayyob AN, Al-Badran AI, Abood RA. Association of TTTA polymorphism in CYP19 gene with endometrial and ovarian cancers risk in Basrah. Gene Reports. 2019 Sep;16:100453.
40. Xita N, Lazaros L, Georgiou I, Tsatsoulis A. CYP19 gene: a genetic modifier of polycystic ovary syndrome phenotype. Fertil Steril. 2010 Jun;94(1):250–4.
41. Mehdizadeh A, Kalantar SM, Sheikhha MH, Aali BS, Ghanei A. Association of SNP rs.2414096 CYP19 gene with polycystic ovarian syndrome in Iranian women. Int J Reprod Biomed. 2017 Sep 1;15(8):491–6.
42. Dou Q, Tan L, Ma L, Sun Y. The relationship between the *CYP19* alleles rs727479A/C, rs700518A/G, and rs700519C/T and pregnancy outcome after assisted reproductive technology in patients with polycystic ovary syndrome in a Chinese population: A population-based study. Kaohsiung J Med Sci. 2017 Nov 14;33(11):558–66.

43. Xu P, Zhang XL, Xie GB, Zhang CW, Shen SM, Zhang XX, et al. The (TTTA) n polymorphism in intron 4 of CYP19 and the polycystic ovary syndrome risk in a Chinese population. Mol Biol Rep. 2013 Aug 10;40(8):5041–7.
44. Lazaros L, Xita N, Hatzi E, Takenaka A, Kaponis A, Makrydimas G, et al. *CYP19* gene variants affect the assisted reproduction outcome of women with polycystic ovary syndrome. Gynecol Endocrinol. 2013 May 6;29(5):478–82.
45. Wang Y. SNP rs2470152 in CYP19 is correlated to aromatase activity in Chinese polycystic ovary syndrome patients. Mol Med Rep. 2011 Oct 3;
46. Witchel SF, Aston CE. The role of heterozygosity for CYP21 in the polycystic ovary syndrome. J Pediatr Endocrinol Metab. 2000;13 Suppl 5:1315–7.
47. Escobar-Morreale HF, San Millán JL, Smith RR, Sancho J, Witchel SF. The presence of the 21-hydroxylase deficiency carrier status in hirsute women: phenotype-genotype correlations. Fertil Steril. 1999 Oct;72(4):629–38.
48. Witchel SF, Lee PA, Suda-Hartman M, Hoffman EP. Hyperandrogenism and manifesting heterozygotes for 21-hydroxylase deficiency. Biochem Mol Med. 1997 Dec;62(2):151–8.
49. Glintborg D, Hermann AP, Brusgaard K, Hangaard J, Hagen C, Andersen M. Significantly higher adrenocorticotropin-stimulated cortisol and 17-hydroxyprogesterone levels in 337 consecutive, premenopausal, caucasian, hirsute patients compared with healthy controls. J Clin Endocrinol Metab. 2005 Mar;90(3):1347–53.
50. Ramadhan RS. ARN. JAL. Investigating pathogenic SNPs in androgen receptor with direct influence on polycystic ovary syndrome (PCOS) in women. Egypt J Med Hum Genet. 2022;23(1):1–10.
51. Nam H, Kim C-H, Cha M-Y, Kim J-M, Kang B-M, Yoo H-W. Polycystic ovary syndrome woman with heterozygous androgen receptor gene mutation who gave birth to a child with androgen insensitivity syndrome. Obstet Gynecol Sci. 2015 Mar;58(2):179–82.
52. CARSON-JURICA MA, SCHRADER WT, O'MALLEY BW. Steroid Receptor Family: Structure and Functions. Endocr Rev. 1990 May;11(2):201–20.
53. Cirik DA, Dilbaz B. What do we know about metabolic syndrome in adolescents with PCOS? J Turkish Ger Gynecol Assoc. 2014 Mar 25;15(1):49–55.
54. Chamberlain NL, Driver ED, Miesfeld RL. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. Nucleic Acids Res. 1994;22(15):3181–6.
55. Irvine RA, Yu MC, Ross RK, Coetzee GA. The CAG and GGC microsatellites of the androgen receptor gene are in linkage disequilibrium in men with prostate cancer. Cancer Res. 1995 May 1;55(9):1937–40.
56. L.J. Moran HJTMNPMCRJNGAW. Sex hormone binding globulin, but not testosterone, is associated with the metabolic syndrome in overweight and obese women with polycystic ovary syndrome. J Endocrinol Invest. 2013;36:1004–10.
57. Lim SS, Kakoly NS, Tan JWJ, Fitzgerald G, Bahri Khomami M, Joham AE, et al. Metabolic syndrome in polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression. Obes Rev. 2019 Feb 19;20(2):339–52.
58. Martinez-Garcia MA, Gambineri A, Alpanes M, Sanchon R, Pasquali R, Escobar-Morreale HF. Common variants in the sex hormone-binding globulin gene (SHBG) and polycystic ovary syndrome (PCOS) in Mediterranean women. Hum Reprod. 2012 Dec 1;27(12):3569–76.

59. Cousin P, Calemard-Michel L, Lejeune H, Raverot G, Yessaad N, Emptoz-Bonneton A, et al. Influence of SHBG gene pentanucleotide TAAAA repeat and D327N polymorphism on serum sex hormone-binding globulin concentration in hirsute women. J Clin Endocrinol Metab. 2004 Feb;89(2):917–24.
60. Xita N, Tsatsoulis A, Chatzikyriakidou A, Georgiou I. Association of the (TAAAA)n repeat polymorphism in the sex hormone-binding globulin (SHBG) gene with polycystic ovary syndrome and relation to SHBG serum levels. J Clin Endocrinol Metab. 2003 Dec;88(12):5976–80.
61. Nahar A, Cho S-H. Current perspectives in Leber congenital amaurosis type 8 mouse modeling. Dev Dyn. 2022;
62. Ferk P, Teran N, Gersak K. The (TAAAA)n microsatellite polymorphism in the SHBG gene influences serum SHBG levels in women with polycystic ovary syndrome. Hum Reprod. 2007 Apr 1;22(4):1031–6.
63. Coutinho EA, Kauffman AS. The Role of the Brain in the Pathogenesis and Physiology of Polycystic Ovary Syndrome (PCOS). Med Sci (Basel, Switzerland). 2019 Aug 2;7(8).
64. Suganuma N, Furui K, Furuhashi M, Asada Y, Kikkawa F, Tomoda Y. Screening of the mutations in luteinizing hormone beta-subunit in patients with menstrual disorders. Fertil Steril. 1995 May;63(5):989–95.
65. Tapanainen JS, Koivunen R, Fauser BC, Taylor AE, Clayton RN, Rajkowa M, et al. A new contributing factor to polycystic ovary syndrome: the genetic variant of luteinizing hormone. J Clin Endocrinol Metab. 1999 May;84(5):1711–5.
66. Ramanujam LN, Liao WX, Roy AC, Loganath A, Goh HH, Ng SC. Association of molecular variants of luteinizing hormone with menstrual disorders. Clin Endocrinol (Oxf). 1999 Aug;51(2):243–6.
67. Batista MCP, Duarte E de F, Borba MD dos R, Zingler E, Mangussi-Gomes J, dos Santos BTA, et al. Trp28Arg/Ile35Thr LHB gene variants are associated with elevated testosterone levels in women with polycystic ovary syndrome. Gene. 2014 Oct 15;550(1):68–73.
68. Ignacak M, Starzyk J, Dziatkowiak H, Trzeciak WH. Study of the family of a patient with male-limited precocious puberty (MPP) due to T1193C transition in exon 11 of LH receptor gene. J Endocrinol Invest. 2002 Mar;25(3):259–63.
69. Latronico AC, Shinozaki H, Guerra G, Pereira MA, Lemos Marini SH, Baptista MT, et al. Gonadotropin-independent precocious puberty due to luteinizing hormone receptor mutations in Brazilian boys: a novel constitutively activating mutation in the first transmembrane helix. J Clin Endocrinol Metab. 2000 Dec;85(12):4799–805.
70. Themmen APN. An update of the pathophysiology of human gonadotrophin subunit and receptor gene mutations and polymorphisms. Reproduction. 2005 Sep;130(3):263–74.
71. Gu B-H, Park J-M, Baek K-H. Genetic variations of follicle stimulating hormone receptor are associated with polycystic ovary syndrome. Int J Mol Med. 2010 Jul;26(1):107–12.
72. Aittomäki K, Dieguez Lucena J, Pakarinen P, Sistonen P, Tapanainen J, Gromoll J, et al. Mutation in the follicle-stimulating hormone receptor gene causes hereditary hypergonadotropic ovarian failure. Cell. 1995 Sep;82(6):959–68.

73. Valkenburg O, Uitterlinden AG, Piersma D, Hofman A, Themmen APN, de Jong FH, et al. Genetic polymorphisms of GnRH and gonadotrophic hormone receptors affect the phenotype of polycystic ovary syndrome. Hum Reprod. 2009 Aug;24(8):2014–22.
74. Kim JJ, Choi YM, Hong MA, Chae SJ, Hwang K, Yoon SH, et al. FSH receptor gene p. Thr307Ala and p. Asn680Ser polymorphisms are associated with the risk of polycystic ovary syndrome. J Assist Reprod Genet. 2017 Aug;34(8):1087–93.
75. Qiu L, Liu J, Hei Q. Association between two polymorphisms of follicle stimulating hormone receptor gene and susceptibility to polycystic ovary syndrome: a meta-analysis. Chinese Med Sci J = Chung-kuo i hsueh k'o hsueh tsa chih. 2015 Mar;30(1):44–50.
76. Chen D-J, Ding R, Cao J-Y, Zhai J-X, Zhang J-X, Ye D-Q. Two follicle-stimulating hormone receptor polymorphisms and polycystic ovary syndrome risk: a meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2014 Nov;182:27–32.
77. Kaur M, Singh S, Kaur A. Polymorphisms in FSHR modulating susceptibility to polycystic ovary syndrome: an updated meta-analysis. J Ovarian Res. 2023 Sep 1;16(1):183.
78. Tian Y, Zhao H, Chen H, Peng Y, Cui L, Du Y, et al. Variants in FSHB Are Associated With Polycystic Ovary Syndrome and Luteinizing Hormone Level in Han Chinese Women. J Clin Endocrinol Metab. 2016 May;101(5):2178–84.
79. Tong Y, Liao WX, Roy AC, Ng SC. Association of AccI polymorphism in the follicle-stimulating hormone beta gene with polycystic ovary syndrome. Fertil Steril. 2000 Dec;74(6):1233–6.
80. Nectaria X, Leandros L, Ioannis G, Agathocles T. The importance of ERα and ERβ gene polymorphisms in PCOS. Gynecol Endocrinol. 2012 Jul;28(7):505–8.
81. Mir R, Tayeb FJ, Barnawi J, Jalal MM, Saeedi NH, Hamadi A, et al. Biochemical Characterization and Molecular Determination of Estrogen Receptor-α (ESR1 PvuII-rs2234693 T>C) and MiRNA-146a (rs2910164 C>G) Polymorphic Gene Variations and Their Association with the Risk of Polycystic Ovary Syndrome. Int J Environ Res Public Health. 2022 Mar 6;19(5).
82. van Rooij IAJ, Broekmans FJM, Scheffer GJ, Looman CWN, Habbema JDF, de Jong FH, et al. Serum antimullerian hormone levels best reflect the reproductive decline with age in normal women with proven fertility: a longitudinal study. Fertil Steril. 2005 Apr;83(4):979–87.
83. Laven JSE, Mulders AGMGJ, Visser JA, Themmen AP, De Jong FH, Fauser BCJM. Anti-Müllerian hormone serum concentrations in normoovulatory and anovulatory women of reproductive age. J Clin Endocrinol Metab. 2004 Jan;89(1):318–23.
84. Cook CL, Siow Y, Brenner AG, Fallat ME. Relationship between serum müllerian-inhibiting substance and other reproductive hormones in untreated women with polycystic ovary syndrome and normal women. Fertil Steril. 2002 Jan;77(1):141–6.
85. Fallat ME, Siow Y, Marra M, Cook C, Carrillo A. Müllerian-inhibiting substance in follicular fluid and serum: a comparison of patients with tubal factor infertility, polycystic ovary syndrome, and endometriosis. Fertil Steril. 1997 May;67(5):962–5.
86. Teede H, Misso M, Tassone EC, Dewailly D, Ng EH, Azziz R, et al. Anti-Müllerian Hormone in PCOS: A Review Informing International Guidelines. Trends Endocrinol Metab. 2019 Jul;30(7):467–78.
87. Gorsic LK, Dapas M, Legro RS, Hayes MG, Urbanek M. Functional Genetic Variation in the Anti-Müllerian Hormone Pathway in Women With Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2019 Jul 1;104(7):2855–74.

88. Gorsic LK, Kosova G, Werstein B, Sisk R, Legro RS, Hayes MG, et al. Pathogenic Anti-Müllerian Hormone Variants in Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2017 Aug 1;102(8):2862–72.
89. Qin L, Zhao S, Yang P, Cao Y, Zhang J, Chen Z-J, et al. Variation analysis of anti-Müllerian hormone gene in Chinese women with polycystic ovary syndrome. Endocrine. 2021 Apr;72(1):287–93.
90. Verdiesen RMG, van der Schouw YT, van Gils CH, Verschuren WMM, Broekmans FJM, Borges MC, et al. Genome-wide association study meta-analysis identifies three novel loci for circulating anti-Müllerian hormone levels in women. Hum Reprod. 2022 May 3;37(5):1069–82.
91. Hoyos LR, Visser JA, McLuskey A, Chazenbalk GD, Grogan TR, Dumesic DA. Loss of anti-Müllerian hormone (AMH) immunoactivity due to a homozygous AMH gene variant rs10417628 in a woman with classical polycystic ovary syndrome (PCOS). Hum Reprod. 2020 Oct 1;35(10):2294–302.
92. Evliyaoglu O, Imöhl M, Weiskirchen R, van Helden J. Age-specific reference values improve the diagnostic performance of AMH in polycystic ovary syndrome. Clin Chem Lab Med. 2020 Jul 28;58(8):1291–301.
93. Chen X, Yang D, Li L, Feng S, Wang L. Abnormal glucose tolerance in Chinese women with polycystic ovary syndrome. Hum Reprod. 2006 Aug;21(8):2027–32.
94. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2010;16(4):347–63.
95. Lee H, Oh J-Y, Sung Y-A, Chung H, Cho WY. The prevalence and risk factors for glucose intolerance in young Korean women with polycystic ovary syndrome. Endocrine. 2009 Oct;36(2):326–32.
96. Jones H, Sprung VS, Pugh CJA, Daousi C, Irwin A, Aziz N, et al. Polycystic ovary syndrome with hyperandrogenism is characterized by an increased risk of hepatic steatosis compared to nonhyperandrogenic PCOS phenotypes and healthy controls, independent of obesity and insulin resistance. J Clin Endocrinol Metab. 2012 Oct;97(10):3709–16.
97. Zhang B, Wang J, Shen S, Liu J, Sun J, Gu T, et al. Association of Androgen Excess with Glucose Intolerance in Women with Polycystic Ovary Syndrome. Biomed Res Int. 2018;2018:6869705.
98. Richards JS, Hedin L. Molecular aspects of hormone action in ovarian follicular development, ovulation, and luteinization. Annu Rev Physiol. 1988;50:441–63.
99. Cara JF, Rosenfield RL. Insulin-like growth factor I and insulin potentiate luteinizing hormone-induced androgen synthesis by rat ovarian thecal-interstitial cells. Endocrinology. 1988 Aug;123(2):733–9.
100. Cara JF. Insulin-Like Growth Factors, Insulin-Like Growth Factor Binding Proteins and Ovarian Androgen Production. Horm Res. 1994;42(1–2):49–54.
101. la Marca A, Egbe TO, Morgante G, Paglia T, Cianci A, De Leo V. Metformin treatment reduces ovarian cytochrome P-450c17alpha response to human chorionic gonadotrophin in women with insulin resistance-related polycystic ovary syndrome. Hum Reprod. 2000 Jan;15(1):21–3.
102. Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, et al. A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in

obese women with the polycystic ovary syndrome. J Clin Endocrinol Metab. 1991 Jan;72(1):83–9.
103. Moghetti P, Tosi F, Bonin C, Di Sarra D, Fiers T, Kaufman J-M, et al. Divergences in insulin resistance between the different phenotypes of the polycystic ovary syndrome. J Clin Endocrinol Metab. 2013 Apr;98(4):E628-37.
104. Kennedy GC, German MS, Rutter WJ. The minisatellite in the diabetes susceptibility locus IDDM2 regulates insulin transcription. Nat Genet. 1995;
105. Paquette J, Giannoukakis N, Polychronakos C, Vafiadis P, Deal C. The INS 5' variable number of tandem repeats is associated with IGF2 expression in humans. J Biol Chem. 1998;
106. Waterworth DM, Bennett ST, Gharani N, McCarthy MI, Hague S, Batty S, et al. Linkage and association of insulin gene VNTR regulatory polymorphism with polycystic ovary syndrome. Lancet. 1997;
107. Vanková M, Vrbíková J, Hill M, Cinek O, Bendlová B. Association of insulin gene VNTR polymorphism with polycystic ovary syndrome. In: Annals of the New York Academy of Sciences. 2002.
108. Yun JH, Gu BH, Kang Y Bin, Choi BC, Song S, Baek KH. Association between INS-VNTR polymorphism and polycystic ovary syndrome in a Korean population. Gynecol Endocrinol. 2012;
109. Siegel S, Futterweit W, Davies TF, Concepcion ES, Greenberg DA, Villanueva R, et al. A C/T single nucleotide polymorphism at the tyrosine kinase domain of the insulin receptor gene is associated with polycystic ovary syndrome. Fertil Steril. 2002 Dec;78(6):1240–3.
110. Shi X, Xie X, Jia Y, Li S. Associations of insulin receptor and insulin receptor substrates genetic polymorphisms with polycystic ovary syndrome: A systematic review and meta-analysis. J Obstet Gynaecol Res. 2016;
111. Tong C, Wu Y, Zhang L, Yu Y. Insulin resistance, autophagy and apoptosis in patients with polycystic ovary syndrome: Association with PI3K signaling pathway. Front Endocrinol (Lausanne). 2022;13:1091147.
112. Thangavelu M, Godla UR, Paul Solomon FD, Maddaly R. Single-nucleotide polymorphism of INS, INSR, IRS1, IRS2, PPAR-G and CAPN10 genes in the pathogenesis of polycystic ovary syndrome. J Genet. 2017 Mar;96(1):87–96.
113. Cai X, Liu C, Mou S. Association between Fat Mass- and Obesity- Associated (FTO) Gene Polymorphism and Polycystic Ovary Syndrome: A Meta-Analysis. PLoS One. 2014 Jan 22;9(1):e86972.
114. Ramos RB, Spritzer PM. FTO gene variants are not associated with polycystic ovary syndrome in women from Southern Brazil. Gene. 2015 Apr;560(1):25–9.
115. Liu AL, Xie HJ, Xie HY, Liu J, Yin J, Hu JS, et al. Association between fat mass and obesity associated (FTO) gene rs9939609 A/T polymorphism and polycystic ovary syndrome: a systematic review and meta-analysis. BMC Med Genet. 2017 Aug 21;18(1):89.
116. Ali AHA, Shkurat TP, Abbas AH. Association analysis of FTO gene polymorphisms rs9939609 and obesity risk among the adults: A systematic review and meta-analysis. Meta Gene. 2021 Feb;27:100832.
117. Jakimiuk AJ, Weitsman SR, Magoffin DA. 5alpha-reductase activity in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 1999 Jul;84(7):2414–8.

118. Goodarzi MO, Shah NA, Antoine HJ, Pall M, Guo X, Azziz R. Variants in the 5alpha-reductase type 1 and type 2 genes are associated with polycystic ovary syndrome and the severity of hirsutism in affected women. J Clin Endocrinol Metab. 2006 Oct;91(10):4085–91.
119. Graupp M, Wehr E, Schweighofer N, Pieber TR, Obermayer-Pietsch B. Association of genetic variants in the two isoforms of 5α-reductase, SRD5A1 and SRD5A2, in lean patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2011;
120. Wu C, Wei K, Jiang Z. 5α-reductase activity in women with polycystic ovary syndrome: a systematic review and meta-analysis. Reprod Biol Endocrinol. 2017 Dec 27;15(1):21.
121. Kiriakidou M, McAllister JM, Sugawara T, Strauss JF. Expression of steroidogenic acute regulatory protein (StAR) in the human ovary. J Clin Endocrinol Metab. 1996 Nov;81(11):4122–8.
122. Johnson BS, Krishna MB, Padmanabhan RA, Pillai SM, Jayakrishnan K, Laloraya M. Derailed peripheral circadian genes in polycystic ovary syndrome patients alters peripheral conversion of androgens synthesis. Hum Reprod. 2022 Jul 30;37(8):1835–55.
123. Nazouri A-S, Khosravifar M, Akhlaghi A-A, Shiva M, Afsharian P. No relationship between most polymorphisms of steroidogenic acute regulatory (StAR) gene with polycystic ovarian syndrome. Int J Reprod Biomed. 2015 Dec;13(12):771–8.
124. Matsui H, Takatsu Y, Kumano S, Matsumoto H, Ohtaki T. Peripheral administration of metastin induces marked gonadotropin release and ovulation in the rat. Biochem Biophys Res Commun. 2004 Jul;320(2):383–8.
125. Farsimadan M, Moammadzadeh Ghosi F, Takamoli S, Vaziri H. Association analysis of KISS1 polymorphisms and haplotypes with polycystic ovary syndrome. Br J Biomed Sci. 2021 Oct;78(4):201–5.
126. Varikasuvu SR, Prasad VS, Vamshika V, Satyanarayana M, Panga JR. Circulatory metastin/kisspeptin-1 in polycystic ovary syndrome: a systematic review and meta-analysis with diagnostic test accuracy. Reprod Biomed Online. 2019 Oct;39(4):685–97.
127. Voisey J, Carroll L, van Daal A. Melanocortins and their receptors and antagonists. Curr Drug Targets. 2003 Oct;4(7):586–97.
128. Hepsen S, Cakal E, Karakose M, Eyerci N, Saat H, Beysel S, et al. Melanocortin 3 receptor gene polymorphism is associated with polycystic ovary syndrome in Turkish population. Gynecol Endocrinol. 2019 Aug 3;35(8):685–90.
129. Batarfi AA, Filimban N, Bajouh OS, Dallol A, Chaudhary AG, Bakhashab S. MC4R variants rs12970134 and rs17782313 are associated with obese polycystic ovary syndrome patients in the Western region of Saudi Arabia. BMC Med Genet. 2019 Aug 20;20(1):144.
130. Chen Z-J, Zhao H, He L, Shi Y, Qin Y, Shi Y, et al. Genome-wide association study identifies susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. Nat Genet. 2011 Jan 12;43(1):55–9.
131. Shi Y, Zhao H, Shi Y, Cao Y, Yang D, Li Z, et al. Genome-wide association study identifies eight new risk loci for polycystic ovary syndrome. Nat Genet. 2012 Sep 12;44(9):1020–5.
132. Pau C, Saxena R, Welt CK. Evaluating reported candidate gene associations with polycystic ovary syndrome. Fertil Steril. 2013 May;99(6):1774–8.

133. Karakaya C, Çil AP, Bilguvar K, Çakir T, Karalok MH, Karabacak RO, et al. Further delineation of familial polycystic ovary syndrome (PCOS) via <scp>whole-exome</scp> sequencing: <scp>PCOS</scp> -related rare <scp> *FBN3* </scp> and <scp> *FN1* </scp> gene variants are identified. J Obstet Gynaecol Res. 2022 May 9;48(5):1202–11.
134. Janani DM, Ramasubramanyan S, Chellappa V, Santhanam R, Manickam R, Shameli J, et al. Whole exome and targeted sequencing reveal novel mutations associated with inherited PCOS condition in an Indian cohort. J Hum Genet. 2023 Jan;68(1):39–46.
135. Sharma P, Jain M, Halder A. An Investigation of Steroid Biosynthesis Pathway Genes in Women with Polycystic Ovary Syndrome. J Hum Reprod Sci. 2022;15(3):240–9.
136. Liu F, Tian L, Tan J, Li Z, Qin H, Xu D, et al. Identification of a novel ESR1 mutation in a Chinese PCOS woman with estrogen insensitivity in IVF treatment. Reprod Biol Endocrinol. 2022 Nov 18;20(1):157.
137. Caburet S, Fruchter RB, Legois B, Fellous M, Shalev S, Veitia RA. A homozygous mutation of GNRHR in a familial case diagnosed with polycystic ovary syndrome. Eur J Endocrinol. 2017 May;176(5):K9–14.
138. Khan MJ, Nazli R, Ahmed J, Basit S. Whole Genome Sequencing instead of Whole Exome Sequencing is required to identify the Genetic Causes of Polycystic Ovary Syndrome in Pakistani families. Pakistan J Med Sci. 2018;34(3):540–5.
139. Sahin SB, Nalkiran I, Ayaz T, Irfan Guzel A, Eldes T, Calapoglu T, et al. Genetic variations in *OLR1* gene associated with PCOS and atherosclerotic risk factors. J Investig Med. 2023 Feb 16;71(2):113–23.
140. Yang B-Y, Yu H-X, Min J, Song X-X. A novel mutation in gene of PRPS1 in a young Chinese woman with X-linked gout: a case report and review of the literature. Clin Rheumatol. 2020 Mar 26;39(3):949–56.
141. Shukla P, Mukherjee S, Patil A, Joshi B. Molecular characterization of variants in mitochondrial DNA encoded genes using next generation sequencing analysis and mitochondrial dysfunction in women with PCOS. Gene. 2023 Mar 1;855:147126.

Bölüm 8

SMA GENETİĞİ

H. Ümit LÜLEYAP[1]

GİRİŞ

Spinal müsküler atrofi olarak tanımlanan SMA, omurilikteki motor nöronların dejenerasyonu ile karakterize, ilerleyici proksimal kas zayıflığına neden olan otozomal resesif sinir-kas hastalığıdır. Motor nöronlar için hayati öneme sahip SMN1 (survival motor neuron) genindeki mutasyonlar ve özellikle delesyonlar nedeniyle SMN gen ürününün yetersizliği ve/veya işlevsizliği sonucu meydana gelen bir hastalıktır. SMA hastalığı, çocukluk çağı ölümlerinin en yaygın kalıtsal nedeni olarak dikkat çekmekte olup tahmini görülme sıklığı; 6.000 -10.000 canlı doğumda 1 olup, taşıyıcılık sıklığı 1/50 düzeyindedir.

SMN1 genindeki mutasyonlar, 4 grupta toplanan tüm SMA tiplerinin birinci derecede sorumlusudur. Yedek veya *backup* gen olarak tanımlanan SMN2 geninin kopya sayısı ise, hastalığın şiddeti konusunda belirleyici olup hangi SMA tipinin ortaya çıkacağını belirler.

SMN1 ve SMN2 genlerinin her ikisi de, hayatta kalma motor nöronu (SMN) proteini adı verilen bir proteinin yapımı için genetik bilgi sağlar. Normalde, çoğu fonksiyonel SMN proteini SMN1 geninden üretilirken, küçük bir miktar da SMN2 geninden üretilir. SMN2 geninden alternatif splayzing ile üretilen SMN proteininin birkaç farklı versiyonu bulunur, ancak yalnızca bir versiyon işlevsel fakat miktar olarak sadece %10 düzeyinde katkı sağlar. Üretilen diğer versiyonlar ise görece daha küçüktür ve çabuk bozulur. SMN proteini, motor nöronların bakımı için önemli olan, SMN kompleksi adı verilen bir grup proteinden biridir. Spinal müsküler atrofisi olan çoğu insanda, SMN protein üretimini bozan SMN1 geninin bir parçası eksiktir. SMN proteininin eksikliği, motor nöron ölümüne neden olarak beyin-kas sinyal iletimi kesintiye uğrayarak ilgili kas/kas grubunun dejenerasyonuna neden olur

[1] Prof. Dr., (PhD) Çukurova Üniversitesi Tıp Fakültesi,Tıbbi Biyoloji ve Genetik AD, ululeyap@cu.edu.tr, ORCID iD: 0000-0001-8759-1381

KAYNAKLAR

1. Werdnig G: Zwei frühinfantile hereditäre Fälle von progressive Muskelatrophie unter dem Bilde der Dystrophie, aber auf neurotischer Grundlage [Two early infantile hereditary cases of progressive muscular atrophy simulating dystrophy, but on a neural basis; in German]. Arch Psychiatr Nervenkr. 1891, 22: 437-480..
2. Hoffmann J: U" ber chronische spinale Muskelatrophie im Kindesalter, auf familiärer Basis [On chronic spinal muscular atrophy in childhood, with a familial basis; in German]. Dtsch Z Nervenheilkd. 1893, 3: 427-470..
3. Brzustowicz LM, Lehner T, Castilla LH, Penchaszadeh GK, Wilhelmsen KC, Daniels R, Davies KE, Leppert M, Ziter F, Wood D, Dubowitz V, Zerres K, Hausmanowa-Petrusewicz I, Ott J, Munsat TL, Gilliam TC: Genetic mapping of chronic childhood-onset spinal muscular atrophy to chromosome 5q11.2-13.3. Nature. 1990, 344: 540-41.
4. Lefebvre S, Burglen L, Reboullet S, Clermont O, Burlet P, Viollet L, Benichou B, Cruaud C, Millasseau P, Zeviani M, Le Paslier D, Frézal J, Cohen D, Weissenbach J, Munnich A, Melki J: Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 1995, 80: 155-65. 8-MacLeod MJ, Taylor JE, Lunt PW, Mathew CG, Robb SA: Prenatal onset spinal muscular atrophy. Eur J Paediatr Neurol. 1999, 3: 65-72.
5. Dubowitz V: Very severe spinal muscular atrophy (SMA type 0): an expanding clinical phenotype. Eur J Paediatr Neurol. 1999, 3: 49-51.
6. Felderhoff-Mueser U, Grohmann K, Harder A, Stadelmann C, Zerres K, Bührer C, Obladen M: Severe spinal muscular atrophy variant associated with congenital bone fractures. J Child Neurol.
7. Kelly TE, Amoroso K, Ferre M, Blanco J, Allinson P, Prior TW: Spinal muscular atrophy variant with congenital fractures. Am J Med Genet. 1999, 87: 65-68. -
8. Rudnik-Schöneborn S, Heller R, Berg C, Betzler C, Grimm T, Eggermann T, Eggermann K, Wirth R, Wirth B, Zerres K: Congenital heart disease is a feature of severe infantile spinal muscular atrophy. J Med Genet. 2008, 45: 635-8
9. Shababi M, Habibi J, Yang HT, Vale SM, Sewell WA, Lorson CL: Cardiac defects contribute to the pathology of spinal muscular atrophy models. Hum Mol Genet. 2010, 19: 4059-4071.
10. Messina S, Pane M, De Rose P, Vasta I, Sorleti D, Aloysius A, Sciarra F, Mangiola F, Kinali M, Bertini E, Mercuri E: Feeding problems and malnutrition in spinal muscular atrophy type II. Neuromuscul Disord. 2008, 18: 389-93.
11. Kinali M, Banks LM, Mercuri E, Manzur AY, Muntoni F: Bone mineral density in a paediatric spinal muscular atrophy population. Neuropediatrics. 2004, 35: 325-8. 17-
12. Khatri IA, Chaudhry US, Seikaly MG, Browne RH, Iannaccone ST: Low bone mineral density in spinal muscular atrophy. J Clin Neuromuscul Dis. 2008, 10: 11-7.
13. Shanmugarajan S, Tsuruga E, Swoboda KJ, Maria BL, Ries WL, Reddy SV: Bone loss in survival motor neuron (Smn(-/-) SMN2) genetic mouse model of spinal muscular atrophy. J Pathol. 2009, 219: 52-60.
14. Zerres K, Rudnik-Schöneborn S, Forrest E, Lusakowska A, Borkowska J, Hausmanowa-Petrusewicz I: A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. J Neurol Sci. 1997, 146: 67-72.

15. Vitte J, Fassier C, Tiziano FD, Dalard C, Soave S, Roblot N, Brahe C, Saugier-Veber P, Bonnefont JP, Melki J: Refined characterization of the expression and stability of the SMN gene products. Am J Pathol. 2007, 171: 1269-80.
16. Wirth B: An update of the mutation spectrum of the survival motor neuron gene (SMN1) in autosomal recessive spinal muscular atrophy (SMA). Hum Mut. 2000, 15: 228-237.
17. Gavrilov DK, Shi X, Das K, Gilliam TC, Wang CH: Differential *SMN2* expression associated with SMA severity. Nat Genet. 1998, 20: 230-31.
18. Feldkötter M, Schwarzer V, Wirth R, Wienker TF, Wirth B: Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet. 2002, 70: 358-68.
19. Rudnik-Schöneborn S, Berg C, Zerres K, Betzler C, Grimm T, Eggermann T, Eggermann K, Wirth R, Wirth B, Heller R: Genotype-phenotype studies in infantile spinal muscular atrophy (SMA) type I in Germany: implications for clinical trials and genetic counselling. Clin Genet. 2009, 76: 168-178.
20. Coovert DD, Le TT, McAndrew PE, Strasswimmer J, Crawford TO, Mendell JR, Coulson SE, Androphy EJ, Prior TW, Burghes AH: The survival motor neuron protein in spinal muscular atrophy. Hum Mol Genet. 1997, 6: 1205-1214.
21. Liu Q, Dreyfuss G: A novel nuclear structure containing the survival of motor neurons protein. EMBO J. 1996, 15: 3555-3565.
22. Schmid A, DiDonato CJ: Animal models of spinal muscular atrophy. J Child Neurol. 2007, 22: 1004-1012.
23. Monani UR, Pastore MT, Gavrilina TO, Jablonka S, Le TT, Andreassi C, DiCocco JM, Lorson C, Androphy EJ, Sendtner M, Podell M, Burghes AH: A transgene carrying an A2G missense mutation in the SMN gene modulates phenotypic severity in mice with severe (type I) spinal muscular atrophy. J Cell Biol. 2003, 160: 41-52.
24. Le TT, Pham LT, Butchbach ME, Zhang HL, Monani UR, Coovert DD, Gavrilina TO, Xing L, Bassell GJ, Burghes AH: SMNDelta7, the major product of the centromeric survival motor neuron (SMN2) gene, extends survival in mice with spinal muscular atrophy and associates with full-length SMN. Hum Mol Genet. 2005, 14: 845-857.
25. Zhang H, Xing L, Rossoll W, Wichterle H, Singer RH, Bassell GJ: Multiprotein complexes of the survival of motor neuron protein SMN with Gemins traffic to neuronal processes and growth cones of motor neurons. J Neurosci. 2006, 26: 8622-8632.
26. Lunn MR, Wang CH: Spinal muscular atrophy. Lancet. 2008, 371: 2120-2133. 10.1016/S0140-6736(08)60921-6. Review.
27. Rossoll W, Jablonka S, Andreassi C, Kröning AK, Karle K, Monani UR, Sendtner M: *Smn*, the spinal muscular atrophy-determining gene product, modulates axon growth and localization of beta-actin mRNA in growth cones of motorneurons. J Cell Biol. 2003, 163: 801-812.
28. Zhang HL, Pan F, Hong D, Shenoy SM, Singer RH, Bassell GJ: Active transport of the survival motor neuron protein and the role of exon-7 in cytoplasmic localization. J Neurosci. 2003, 23: 6627-6637.
29. McWhorter ML, Monani UR, Burghes AH, Beattie CE: Knockdown of the survival motor neuron (Smn) protein in zebrafish causes defects in motor axon outgrowth and pathfinding. J Cell Biol. 2003, 162: 919-931.

30. Lambrechts A, Braun A, Jonckheere V, Aszodi A, Lanier LM, Robbens J, Van Colen I, Vandekerckhove J, Fässler R, Ampe C: Profilin II is alternatively spliced, resulting in profilin isoforms that are differentially expressed and have distinct biochemical properties. Mol Cell Biol. 2000, 20: 8209-8219.
31. Setola V, Terao M, Locatelli D, Bassanini S, Garattini E, Battaglia G: Axonal-SMN (a-SMN), a protein isoform of the survival motor neuron gene, is specifically involved in axonogenesis. Proc Natl Acad Sci USA. 2007, 104: 1959-1964.
32. Simic G: Pathogenesis of proximal autosomal recessive spinal muscular atrophy. Acta Neuropathol. 2008, 116: 223-234.
33. Sharma A, Lambrechts A, Hao le T, Le TT, Sewry CA, Ampe C, Burghes AH, Morris GE: A role for complexes of survival of motor neurons (SMN) protein with gemins and profilin in neurite-like cytoplasmic extensions of cultured nerve cells. Exp Cell Res. 2005, 309: 185-97.
34. Mentis GZ, Blivis D, Liu W, Drobac E, Crowder ME, Kong L, Alvarez FJ, Sumner CJ, O'Donovan MJ: Early functional impairment of sensory-motor connectivity in a mouse model of spinal muscular atrophy. Neuron. 2011, 69: 453-467.
35. Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, Aloysius A, Morrison L, Main M, Crawford TO, Trela A: Participants of the International Conference on SMA Standard of Care. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol. 2007, 22: 1027-1049.
36. Cuscó I, López E, Soler-Botija C, Jesús Barceló M, Baiget M, Tizzano EF: A genetic and phenotypic analysis in Spanish spinal muscular atrophy patients with c.399_402del AGAG, the most frequently found subtle mutation in the SMN1 gene. Hum Mutat. 2003, 22: 136-43
37. Prior TW, Snyder PJ, Rink BD, Pearl DK, Pyatt RE, Mihal DC, Conlan T, Schmalz B, Montgomery L, Ziegler K, Noonan C, Hashimoto S, Garner S: Newborn and carrier screening for spinal muscular atrophy. Am J Med Genet A. 2010, 152A: 1605-1607.
38. Swoboda KJ, Prior TW, Scott CB, McNaught TP, Wride MC, Reyna SP, Bromberg MB: Natural history of denervation in SMA: Relation to age, SMN2 copy number, and function. Ann Neurol. 2005, 57: 704-712
39. Kwon DY, Motley WW, Fischbeck KH, Burnett BG. Increasing expression and decreasing degradation of SMN ameliorate the spinal muscular atrophy phenotype in mice. Hum Mol Genet 2011;20:3667-77
40. Garbes L, Riessland M, Hölker I, Heller R, Hauke J, Tränkle C, et al. LBH589 induces up to 10-fold SMN protein levels by several independent mechanisms and is effective even in cells from SMA patients non-responsive to valproate. Hum Mol Genet 2009;18:3645-58.
41. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in InfantileOnset Spinal Muscular Atrophy. N Engl J Med 2017;377:1723- 32.
42. Hoy SM. Nusinersen: First Global Approval. Drugs 2017;77:473-9.
43. Van Meerbeke JP, Gibbs RM, Plasterer HL, Miao W, Feng Z, Lin MY, et al. The DcpS inhibitor RG3039 improves motor function in SMA mice. Hum Mol Genet 2013;22:4074-83.
44. Mattis VB, Rai R, Wang J, Chang CW, Coady T, Lorson CL. Novel aminoglycosides increase SMN levels in spinal muscular atrophy fibroblasts. Hum Genet 2006;120:589-601.

45. Ross LF, Kwon JM. Spinal Muscular Atrophy: Past, Present, and Future. Neoreviews 2019;20:437-51.
46. Wirth B. Spinal Muscular Atrophy: In the Challenge Lies a Solution. Trends Neurosci 2021;44:306-22.
47. Passini MA, Bu J, Richards AM, Kinnecom C, Sardi SP, Stanek LM, Hua Y, Rigo F, Matson J, Hung G, Kaye EM, Shihabuddin LS, Krainer AR, Bennett CF, Cheng SH: Antisense oligonucleotides delivered to the mouse CNS ameliorate symptoms of severe spinal muscular atrophy. Sci Transl Med. 2011, 3: 72ra18.
48. Harper JM, Krishnan C, Darman JS, Deshpande DM, Peck S, Shats I, Backovic S, Rothstein JD, Kerr DA: Axonal growth of embryonic stem cell-derived motoneurons in vitro and in motoneuron- injured adult rats. Proc Natl Acad Sci USA. 2004, 101: 7123-7128.
49. Deshpande DM, Kim YS, Martinez T, Carmen J, Dike S, Shats I, Rubin LL, Drummond J, Krishnan C, Hoke A, Maragakis N, Shefner J, Rothstein JD, Kerr DA: Recovery from paralysis in adult rats using embryonic stem cells. Ann Neurol. 2006, 60: 32-44.
50. Corti S, Nizzardo M, Nardini M, Donadoni C, Salani S, Ronchi D, Simone C, Falcone M, Papadimitriou D, Locatelli F, Mezzina N, Gianni F, Bresolin N, Comi GP: Embryonic stem cell-derived neural stem cells improve spinal muscular atrophy phenotype in mice. Brain. 2010, 133: 465-481. 10.1093/brain/awp318.
51. Corti S, Nizzardo M, Nardini M, Donadoni C, Salani S, Del Bo R, Papadimitriou D, Locatelli F, Mezzina N, Gianni F, Bresolin N, Comi GP: Motorneuron transplantation rescues the phenotype of SMARD1 (spinal muscular atrophy with respiratory distress type 1). J Neurosci. 2009, 29: 11761-11771.
52. Dimos JT, Rodolfa KT, Niakan KK, Weisenthal LM, Mitsumoto H, Chung W, Croft GF, Saphier G, Leibel R, Goland R, Wichterle H, Henderson CE, Eggan K: Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. Science. 2008, 321: 1218-1221.

.