

## Bölüm 3

# CircRNA'LARIN KANSER PATOGENEZİNDEKİ İŞLEVİ VE ÖNEMİ

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### 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 molekülleridir [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 görecekları 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

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## 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/FOXO1 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., *circ-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 BAMP, 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.