

KANSER TEDAVİSİNDE KULLANILAN İLAÇLARIN MOLEKÜLER ETKİ MEKANİZMALARI

B Ö L Ü M

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ÖZET

Bir hastalık olarak kanser, her geçen gün daha büyük bir sağlık problemi haline gelmektedir. Son 20 yılda, insan kanserlerinin moleküler mekanizmaları ve patofizyolojisi hakkındaki bilgimizde muazzam bir artış olmuştur. Bu mekanizmaların birçoğu, halihazırda kullanılan ilaçlar ile karşılaştırıldığında hastaya daha az toksisite ile daha fazla antitümör aktiviteye sahip olacakları umuduyla ilaç geliştirme için yeni hedefler olarak geliştirilmiştir. Moleküler hedefli ajanların hızlı gelişimi ve klinik uygulamaları sayesinde kanserin sistemik tedavisinde de önemli bir ilerleme olmuştur. Çoklu genetik, epigenetik ve kromozomal anormallikler içeren bazı kanser tiplerinin hem kötü fenotip hem de hücre sağkalımı açısından bir veya birkaç gene “bağımlı” olduğunu açıklamak için “onkojen bağımlılığı” kavramı ortaya koyulmuştur. Bu anormalliklerin sadece bir veya birkaçının tersine çevrilmesi, kanser hücresi büyümesini inhibe edebilir ve bazı durumlarda gelişmiş sağkalım oranlarını düşürebilir. Bu derleme, kanserin hücresel mekanizmalarındaki farklılıkları, tedavi için güncel deneysel ve klinik kanıtları özetlemekte ve moleküler mekanizmaları tanımlamaktadır. Ayrıca, bu derlemede tedavi tiplerini optimize edebilmek ve hastalık tekrarını önleyecek bakış açılarını belirlemek için bir strateji olarak antikanser ajanların moleküler hedefli ajanlar ile ortak kullanımı da tartışılmaktadır.

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KAYNAKLAR

1. Parkin, D.M., F.I. Bray, and S.S. Devesa, "Cancer burden in the year 2000. The global picture" (vol 37, pg 54, 2001). *European Journal of Cancer*, 2003. **39**(6): p. 848-848.
2. Weinberg, R.A., *Cancer Biology and Therapy: the road ahead*. *Cancer Biol Ther*, 2002. **1**(1): p. 3.
3. Hanahan, D. and R.A. Weinberg, *Hallmarks of cancer: the next generation*. *Cell*, 2011. **144**(5): p. 646-74.
4. Bhowmick, N.A., E.G. Neilson, and H.L. Moses, *Stromal fibroblasts in cancer initiation and progression*. *Nature*, 2004. **432**(7015): p. 332-7.
5. Coleman, M.P., et al., *Cancer survival in five continents: a worldwide population-based study (CONCORD)*. *Lancet Oncol*, 2008. **9**(8): p. 730-56.
6. Colotta, F., *Anticancer drug discovery and development*. *Adv Exp Med Biol*, 2008. **610**: p. 19-42.
7. Karnofsky, D.A., *Meaningful clinical classification of therapeutic responses to anti-cancer drugs*. *Clin Pharmacol Ther*, 1961. **2**: p. 709-12.
8. Sawyers, C., *Targeted cancer therapy*. *Nature*, 2004. **432**(7015): p. 294-7.
9. Dasari, S. and P.B. Tchounwou, *Cisplatin in cancer therapy: molecular mechanisms of action*. *Eur J Pharmacol*, 2014. **740**: p. 364-78.
10. Florea, A.M. and D. Busselberg, *Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects*. *Cancers (Basel)*, 2011. **3**(1): p. 1351-71.
11. Zamble, D.B. and S.J. Lippard, *Cisplatin and DNA repair in cancer chemotherapy*. *Trends Biochem Sci*, 1995. **20**(10): p. 435-9.
12. Zhang, W. and C.H. Tung, *Cisplatin Cross-Linked Multifunctional Nanodrugplexes for Combination Therapy*. *ACS Appl Mater Interfaces*, 2017. **9**(10): p. 8547-8555.
13. Song, W., et al., *Polypeptide-based combination of paclitaxel and cisplatin for enhanced chemotherapy efficacy and reduced side-effects*. *Acta Biomater*, 2014. **10**(3): p. 1392-402.
14. Chen, S.C., P.M. Chang, and M.H. Yang, *Cisplatin/Tegafur/Uracil/Irinotecan Triple Combination Therapy for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma: A Phase I/II Clinical Study*. *Oncologist*, 2016. **21**(5): p. 537-8.
15. Wu, H., et al., *Synergistic Cisplatin/Doxorubicin Combination Chemotherapy for Multidrug-Resistant Cancer via Polymeric Nanogels Targeting Delivery*. *ACS Appl Mater Interfaces*, 2017. **9**(11): p. 9426-9436.
16. Colucci, G., et al., *Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study*. *J Clin Oncol*, 2010. **28**(10): p. 1645-51.
17. Khalil, D.N., et al., *The future of cancer treatment: immunomodulation, CARs and combination immunotherapy*. *Nat Rev Clin Oncol*, 2016. **13**(6): p. 394.
18. Sathyanarayanan, V. and S.S. Neelapu, *Cancer immunotherapy: Strategies for personalization and combinatorial approaches*. *Mol Oncol*, 2015. **9**(10): p. 2043-53.
19. Duffy, A., et al., *Autophagy modulation: a target for cancer treatment development*. *Cancer Chemother Pharmacol*, 2015. **75**(3): p. 439-47.
20. Nagelkerke, A., et al., *Therapeutic targeting of autophagy in cancer. Part II: pharmacological modulation of treatment-induced autophagy*. *Semin Cancer Biol*, 2015. **31**: p. 99-105.

21. Galluzzi, L., et al., *Pharmacological modulation of autophagy: therapeutic potential and persisting obstacles*. Nat Rev Drug Discov, 2017. **16**(7): p. 487-511.
22. Martini, M., et al., *PI3K/AKT signaling pathway and cancer: an updated review*. Ann Med, 2014. **46**(6): p. 372-83.
23. Polivka, J., Jr. and F. Janku, *Molecular targets for cancer therapy in the PI3K/AKT/mTOR pathway*. Pharmacol Ther, 2014. **142**(2): p. 164-75.
24. Ciruelos Gil, E.M., *Targeting the PI3K/AKT/mTOR pathway in estrogen receptor-positive breast cancer*. Cancer Treat Rev, 2014. **40**(7): p. 862-71.
25. Babina, I.S. and N.C. Turner, *Advances and challenges in targeting FGFR signalling in cancer*. Nat Rev Cancer, 2017. **17**(5): p. 318-332.
26. Touat, M., et al., *Targeting FGFR Signaling in Cancer*. Clin Cancer Res, 2015. **21**(12): p. 2684-94.
27. Chae, Y.K., et al., *Inhibition of the fibroblast growth factor receptor (FGFR) pathway: the current landscape and barriers to clinical application*. Oncotarget, 2017. **8**(9): p. 16052-16074.
28. Tabernero, J., et al., *Phase I Dose-Escalation Study of JNJ-42756493, an Oral Pan-Fibroblast Growth Factor Receptor Inhibitor, in Patients With Advanced Solid Tumors*. J Clin Oncol, 2015. **33**(30): p. 3401-8.
29. Yuan, X., et al., *Notch signaling: an emerging therapeutic target for cancer treatment*. Cancer Lett, 2015. **369**(1): p. 20-7.
30. Radtke, F. and K. Raj, *The role of Notch in tumorigenesis: oncogene or tumour suppressor?* Nat Rev Cancer, 2003. **3**(10): p. 756-67.
31. Zhang, Z., et al., *Activation of the AXL kinase causes resistance to EGFR-targeted therapy in lung cancer*. Nat Genet, 2012. **44**(8): p. 852-60.
32. Wu, Y., et al., *Therapeutic antibody targeting of individual Notch receptors*. Nature, 2010. **464**(7291): p. 1052-7.
33. Previs, R.A., et al., *Molecular pathways: translational and therapeutic implications of the Notch signaling pathway in cancer*. Clin Cancer Res, 2015. **21**(5): p. 955-61.
34. Nickoloff, B.J., B.A. Osborne, and L. Miele, *Notch signaling as a therapeutic target in cancer: a new approach to the development of cell fate modifying agents*. Oncogene, 2003. **22**(42): p. 6598-6608.
35. Shih Ie, M. and T.L. Wang, *Notch signaling, gamma-secretase inhibitors, and cancer therapy*. Cancer Res, 2007. **67**(5): p. 1879-82.
36. Johnstone, R.W., A.J. Frew, and M.J. Smyth, *The TRAIL apoptotic pathway in cancer onset, progression and therapy*. Nat Rev Cancer, 2008. **8**(10): p. 782-98.
37. Bellail, A.C., et al., *TRAIL agonists on clinical trials for cancer therapy: the promises and the challenges*. Rev Recent Clin Trials, 2009. **4**(1): p. 34-41.
38. Dolan, D.E. and S. Gupta, *PD-1 Pathway Inhibitors: Changing the Landscape of Cancer Immunotherapy*. Cancer Control, 2014. **21**(3): p. 231-237.
39. Zou, W., J.D. Wolchok, and L. Chen, *PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations*. Sci Transl Med, 2016. **8**(328): p. 328rv4.
40. Serrano, M., G.J. Hannon, and D. Beach, *A new regulatory motif in cell-cycle control causing specific inhibition of cyclin D/CDK4*. Nature, 1993. **366**(6456): p. 704-7.
41. Vidula, N. and H.S. Rugo, *Cyclin-Dependent Kinase 4/6 Inhibitors for the Treatment of Breast Cancer: A Review of Preclinical and Clinical Data*. Clin Breast Cancer, 2016. **16**(1): p. 8-17.

42. Lyko, F. and R. Brown, *DNA methyltransferase inhibitors and the development of epigenetic cancer therapies*. J Natl Cancer Inst, 2005. **97**(20): p. 1498-506.
43. Stresemann, C., et al., *Functional diversity of DNA methyltransferase inhibitors in human cancer cell lines*. Cancer Res, 2006. **66**(5): p. 2794-800.
44. Koensgen, D., et al., *Cold Atmospheric Plasma (CAP) and CAP-Stimulated Cell Culture Media Suppress Ovarian Cancer Cell Growth - A Putative Treatment Option in Ovarian Cancer Therapy*. Anticancer Res, 2017. **37**(12): p. 6739-6744.
45. Vandamme, M., et al., *ROS implication in a new antitumor strategy based on non-thermal plasma*. Int J Cancer, 2012. **130**(9): p. 2185-94.
46. Keidar, M., et al., *Cold atmospheric plasma in cancer therapy*. Physics of Plasmas, 2013. **20**(5).
47. West, A.C. and R.W. Johnstone, *New and emerging HDAC inhibitors for cancer treatment*. J Clin Invest, 2014. **124**(1): p. 30-9.
48. Khan, O. and N.B. La Thangue, *HDAC inhibitors in cancer biology: emerging mechanisms and clinical applications*. Immunol Cell Biol, 2012. **90**(1): p. 85-94.
49. Mottamal, M., et al., *Histone Deacetylase Inhibitors in Clinical Studies as Templates for New Anticancer Agents*. Molecules, 2015. **20**(3): p. 3898-3941.
50. Arpicco, S., et al., *Hyaluronic Acid Conjugates as Vectors for the Active Targeting of Drugs, Genes and Nanocomposites in Cancer Treatment*. Molecules, 2014. **19**(3): p. 3193-3230.
51. Luo, Y., M.R. Ziebell, and G.D. Prestwich, *A hyaluronic acid-taxol antitumor bioconjugate targeted to cancer cells*. Biomacromolecules, 2000. **1**(2): p. 208-18.
52. Cho, H.J., et al., *Polyethylene glycol-conjugated hyaluronic acid-ceramide self-assembled nanoparticles for targeted delivery of doxorubicin*. Biomaterials, 2012. **33**(4): p. 1190-200.
53. Taetz, S., et al., *Hyaluronic acid-modified DOTAP/DOPE liposomes for the targeted delivery of anti-telomerase siRNA to CD44-expressing lung cancer cells*. Oligonucleotides, 2009. **19**(2): p. 103-16.
54. Senter, P.D., *Potent antibody drug conjugates for cancer therapy*. Curr Opin Chem Biol, 2009. **13**(3): p. 235-44.
55. Green, J.R., *Bisphosphonates in cancer therapy*. Curr Opin Oncol, 2002. **14**(6): p. 609-15.
56. Wilkes, G.M., *Eribulin, a microtubule inhibitor for metastatic breast cancer*. Oncology (Williston Park), 2011. **25**(2 Suppl Nurse Ed): p. 46-8.
57. Wilson, L., et al., *Effects of eribulin on microtubule binding and dynamic instability are strengthened in the absence of the betaIII tubulin isotype*. Biochemistry, 2015. **54**(42): p. 6482-9.