BÖLÜM 20

HİSTON DEASETİLAZ İNHİBİTÖRLERİ

Ahmet KAYA[1]

GİRİŞ

Kanser kemoterapisinde, son birkaç yılda önemli gelişmeler olmuştur. Bununla birlikte, kullanılan ilaçlar dar bir terapötik indekse sahiptir ve genellikle sadece palyatiftir. Bu tür ilaçlar, belirli biyomakromoleküllere yönelik olmasına rağmen, hızla bölünen malign olmayan hücreler ile kanser hücreleri arasında ayrım yapmaz. Buna karşılık, son yıllarda popüler olan hedefe yönelik tedavi, kansere özgü hedeflere ve sinyal yollarına yöneliktir ve daha sınırlı spesifik mekanizmalara sahiptir.Epigenetik mekanizmaların kanser gelişiminde çok önemli rolü bir dizi çalışma ile gösterilmiştir. Karsinojenez sadece genetik değişikliklerle açıklanamaz, aynı zamanda epigenetik süreçleri de içerir (DNA metilasyonu, histon modifikasyonları ve kodlamayan RNA deregülasyonu). Histon modifikasyonları, kromatin yoğunlaşmasına yol açan H3 ve H4 histonlarının lizin deasetilasyonunu içerir(1). Bu değişiklikler, çeşitli antionkogenlerin ve DNA onarım genlerinin gen transkripsiyonunu etkiler(2). Bu nedenle, epigenetik süreçler çok sayıda araştırmada yeni terapötik hedefler olarak ortaya çıkmıştır.Bu epigenetik modifikasyonlardan asetilasyon, hücre farklılaşması, proliferasyon, anjiyogenez ve apoptoz gibi normal hücresel süreçlerin düzenlenmesinde önemli roller oynayan en yaygın olanıdır. Asetilasyonun düzensizliği, kanser patolojilerinde çeşitli hücresel olaylarla ilişkilendirilmiştir. H4'ün global hipoasetilasyonu, tümörlerin böyle yaygın bir özelliğidir(3).Histonların ve histon olmayan proteinlerin asetilasyon seviyesi, iki antagonistik enzim ailesi tarafından yönetilir: histon deasetilazlar (HDAC'ler) ve histon asetiltransferazlar (HAT'ler). HDAC'ler, bakteri, mantar, bitki ve hayvanlarda bulunan ve çekirdek histonlarda ve birçok histon olmayan proteinde bulunan lizin kalıntılarının ε-amino gruplarından bir asetil grubunu çıkarabilen

[1] Uzm. Dr., İnönü Üniversitesi Turgut Özal Tıp Merkezi Erişkin Hematoloji Bölümü, doktorahmetkaya@hotmail.com

ve hipomagnezemi gibi elektrolit bozukluklarına bağlıdır. HDACI ile tedaviden önce serum potasyum ve magnezyum seviyeleri izlenmeli ve herhangi bir eksiklik düzeltilmelidir. QT uzamasına neden olan ilaçların birlikte uygulanmasından kaçınılmalıdır. Lökopeni, granülositopeni ve trombositopeni genellikle geçicidir ve hızla geri dönüşümlüdür. Kısa zincirli yağ asitleri ile yapılan uygulamalarda konfüzyon, oryantasyon bozukluğu, ataksi, vertigo ve somnolans gibi nöropsikolojik yan etkiler kaydedilmiştir. Nadiren, öksürük ve nefes darlığı gibi pulmoner yan etkiler kaydedilmiştir (46). Serum kreatinininde yükselmeler ve/veya hipokalsemi ve hipofosfatemi gibi elektrolit dengesizlikleri olabilmektedir. Hayvanlarla yapılan klinik öncesi çalışmalarda, HDACI'ler fetal toksisite göstermiştir ve fetal büyüme geriliğine ve iskelet anormalliklerine neden olabilir ve hamile kadınlarda kaçınılmalıdır(47). Bu ajanlar viral enfeksiyonları yeniden aktive etme potansiyeline sahip olduğundan, HIV ve hepatitli hastalarda yakın gözlem gereklidir(48,49).

KAYNAKLAR

1. Li G., Margueron R., Hu G., Stokes D., Wang Y.H., Reinberg D. Highly compacted chromatin formed in vitro reflects the dynamics of transcription activation in vivo. *Mol. Cell.* 2010;38:41–53.
2. Perri F., Longo F., Giuliano M., Sabbatino F., Favia G., Ionna F., Addeo R., Scarpati G.D.V., Di Lorenzo G., Pisconti S. Epigenetic control of gene expression: Potential implications for cancer treatment. *Crit. Rev. Oncol. Hematol.* 2017;111:166–172.
3. Fraga MF, Ballestar E, Villar-Garea A, Boix-Chornet M, Espada J, Schotta G, Bonaldi T et al. Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer. Nat Genet. 2005 Apr;37(4):391-400.
4. Ropero S, Esteller M. The role of histone deacetylases (HDACs) in human cancer. Mol Oncol. 2007 Jun;1(1):19-25.
5. Zhang L, Han Y, Jiang Q, Wang C, Chen X, Li X, et al. Trend of histone deacetylase inhibitors in cancer therapy: isoform selectivity or multitargeted strategy. Med Res Rev. 2015 Jan;35(1):63-84.
6. Paris M, Porcelloni M, Binaschi M, Fattori D. Histone deacetylase inhibitors: from bench to clinic. J Med Chem. 2008 Mar 27;51(6):1505-29.
7. Jonsson KL, Tolstrup M, Vad-Nielsen J, Kjær K, Laustsen A, Andersen MNet al.Histone deacetylase inhibitor romidepsin inhibits de novo HIV-1 infections. Antimicrob Agents Chemother. 2015 Jul;59(7):3984-94.
8. Schiattarella GG, Sannino A, Toscano E, Cattaneo F, Trimarco B, Esposito G et al.Cardiovascular effects of histone deacetylase inhibitors epigenetic therapies: Systematic review of 62 studies and new hypotheses for future research. Int J Cardiol. 2016 Sep 15;219:396-403.
9. Yu CW, Chang PT, Hsin LW, Chern JW. Quinazolin-4-one derivatives as selective histone deacetylase-6 inhibitors for the treatment of Alzheimer's disease. J Med Chem. 2013 Sep 12;56(17):6775-91.
10. Roth S.Y., Allis C.D. Histone acetylation and chromatin assembly: A single escort, multiple dances? *Cell.* 1996;87:5–8.
11. Kazanets A., Shorstova T., Hilmi K., Marques M., Witcher M. Epigenetic silencing of tumor suppressor genes: Paradigms, puzzles, and potential. *Biochim. Biophys. Acta Rev. Cancer.*

2016;1865:275–288.
12. Bolden J.E., Peart M.M.J., Johnstone R.R.W. Anticancer activities of histone deacetylase inhibitors. *Nat. Rev. Drug Discov.* 2006;5:769–784.
13. Spange S., Wagner T., Heinzel T., Krämer O.H. Acetylation of non-histone proteins modulates cellular signalling at multiple levels. *Int. J. Biochem. Cell Biol.* 2009;41:185–198.
14. Hull E.E., Montgomery M.R., Leyva K.J. HDAC Inhibitors as epigenetic regulators of the immune system: Impacts on cancer therapy and inflammatory diseases. *BioMed Res. Int.* 2016;2016:8797206.
15. Tang J., Yan H., Zhuang S. Histone deacetylases as targets for treatment of multiple diseases. *Clin. Sci.* 2013;124:651–662.
16. innin M.S., Donigian J.R., Cohen A., Richon V.M., Rifkind R.A., Marks P.A., Breslow R., Pavletich N.P. Structures of a histone deacetylase homologue bound to the TSA and SAHA inhibitors. *Nature.* 1999;401:188–193.
17. Trapp J., Jung M. The role of NAD^+ dependent histone deacetylases (sirtuins) in ageing. *Curr. Drug Targets.* 2006;7:1553–1560.
18. Mariadason J.M., Corner G.A., Augenlicht L.H. Genetic reprogramming in pathways of colonic cell maturation induced by short chain fatty acids: Comparison with trichostatin A, sulindac, and curcumin and implications for chemoprevention of colon cancer. *Cancer Res.* 2000;60:4561–4572.
19. Li G., Margueron R., Hu G., Stokes D., Wang Y.H., Reinberg D. Highly compacted chromatin formed in vitro reflects the dynamics of transcription activation in vivo. *Mol. Cell.* 2010;38:41–53.
20. Hull E.E., Montgomery M.R., Leyva K.J. HDAC Inhibitors as epigenetic regulators of the immune system: Impacts on cancer therapy and inflammatory diseases. *BioMed Res. Int.* 2016;2016:8797206.
21. Ocker M. Deacetylase inhibitors-focus on non-histone targets and effects. World J Biol Chem 2010;1:55-61.
22. Spange S, Wagner T, Heinzel T, Krämer OH. Acetylation of non-histone proteins modulates cellular signalling at multiple levels. Int J Biochem Cell Biol 2009;41:185-98
23. Gui CY, Ngo L, Xu WS, Richon VM, Marks PA. Histone deacetylase (HDAC) inhibitor activation of p21WAF1 involves changes in promoter-associated proteins, including HDAC1. Proc Natl Acad Sci U S A 2004;101:1241-6
24. Rosato RR, Maggio SC, Almenara JA, Payne SG, Atadja P, Spiegel S, *et al*. The histone deacetylase inhibitor LAQ824 induces human leukemia cell death through a process involving XIAP down-regulation, oxidative injury, and the acid sphingomyelinase-dependent generation of ceramide. Mol Pharmacol 2006;69:216-25.
25. Fuino L, Bali P, Wittmann S, Donapaty S, Guo F, Yamaguchi H, *et al*. Histone deacetylase inhibitor LAQ824 down-regulates Her-2 and sensitizes human breast cancer cells to trastuzumab, taxotere, gemcitabine, and epothilone B. Mol Cancer Ther 2003;2:971-84
26. Adimoolam S, Sirisawad M, Chen J, Thiemann P, Ford JM, Buggy JJ. HDAC inhibitor PCI-24781 decreases RAD51 expression and inhibits homologous recombination. Proc Natl Acad Sci USA 2007;104:19482-7.
27. Kwon SH, Ahn SH, Kim YK, Bae GU, Yoon JW, Hong S, *et al*. Apicidin, a histone deacetylase inhibitor, induces apoptosis and Fas/Fas ligand expression in human acute promyelocytic leukemia cells. J Biol Chem 2002;277:2073-80.
28. Chen S, Dai Y, Pei XY, Grant S. Bim upregulation by histone deacetylase inhibitors mediates interactions with the Bcl-2 antagonist ABT-737: Evidence for distinct roles for Bcl-2, Bcl-xL, and Mcl-1. Mol Cell Biol 2009;29:6149-69.
29. Deroanne CF, Bonjean K, Servotte S, Devy L, Colige A, Clausse N, *et al*. Histone deacetylases inhibitors as anti-angiogenic agents altering vascular endothelial growth factor signaling. Oncogene 2002;21:427-36
30. Bots M, Johnstone RW. Rational combinations using (HDAC) inhibitors. Clin Cancer Res

2009;15:3970-7.
31. Drappatz J, Lee EQ, Hammond S, Grimm SA, Norden AD, Beroukhim R, *et al*. Phase I study of panobinostat in combination with bevacizumab for recurrent high-grade glioma. J Neurooncol 2012;107:133-8.
32. Kawaguchi Y, Kovacs JJ, McLaurin A, Vance JM, Ito A, Yao TP. The deacetylase (HDAC6) regulates aggresome formation and cell viability in response to misfolded protein stress. Cell 2003;115:727-38.
33. Nawrocki ST, Carew JS, Pino MS, Highshaw RA, Andtbacka RH, Dunner K Jr, *et al*. Aggresome disruption: A novel strategy to enhance bortezomib-induced apoptosis in pancreatic cancer cells. Cancer Res 2006;66:3773-81.
34. Marks PA, Xu WS. Histone deacetylase inhibitors: Potential in cancer therapy. J Cell Biochem 2009;107:600-8.
35. Al-Yacoub N, Fecker LF, Möbs M, Plötz M, Braun FK, Sterry W et al. Apoptosis induction by SAHA in cutaneous T-cell lymphoma cells is related to downregulation of c-FLIP and enhanced TRAIL signaling. J Invest Dermatol. 2012 Sep;132(9):2263-74.
36. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH et al.International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood. 2015 Jul 16;126(3):291-9.
37. Schaefer EW, Loaiza-Bonilla A, Juckett M, DiPersio JF, Roy V, Slack J, Wu W et al. A phase 2 study of vorinostat in acute myeloid leukemia. Haematologica. 2009 Oct;94(10):1375-82.
38. Sandor V, Bakke S, Robey RW, Kang MH, Blagosklonny MV, Bender J etal. Phase I trial of the histone deacetylase inhibitor, depsipeptide (FR901228, NSC 630176), in patients with refractory neoplasms. Clin Cancer Res. 2002 Mar;8(3):718-28.
39. Steele NL, Plumb JA, Vidal L, Tjørnelund J, Knoblauch P, Rasmussen A et al. A phase 1 pharmacokinetic and pharmacodynamic study of the histone deacetylase inhibitor belinostat in patients with advanced solid tumors. Clin Cancer Res. 2008 Feb 1;14(3):804-10.
40. Jones SF, Bendell JC, Infante JR, Spigel DR, Thompson DS, Yardley DA et al. A phase I study of panobinostat in combination with gemcitabine in the treatment of solid tumors. Clin Adv Hematol Oncol. 2011 Mar;9(3):225-30.
41. Ryan QC, Headlee D, Acharya M, Sparreboom A, Trepel JB, Ye J et al. Phase I and pharmacokinetic study of MS-275, a histone deacetylase inhibitor, in patients with advanced and refractory solid tumors or lymphoma. J Clin Oncol. 2005 Jun 10;23(17):3912-22.
42. Dizon DS, Blessing JA, Penson RT, Drake RD, Walker JL, Johnston CM et al. A phase II evaluation of belinostat and carboplatin in the treatment of recurrent or persistent platinum-resistant ovarian, fallopian tube, or primary peritoneal carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2012 May;125(2):367-71.
43. Rodríguez-Paredes M, Esteller M. A combined epigenetic therapy equals the efficacy of conventional chemotherapy in refractory advanced non-small cell lung cancer. Cancer Discov. 2011 Dec;1(7):557-9.
44. Beck J, Fischer T, George D, Huber C, Calvo E, Atadja P, *et al*. Phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of ORAL LBH589B: A novel histone deacetylase (HDAC) inhibitor. J Clin Oncol (Meet Abstr) 2005;23:3148
45. Fischer T, Patnaik A, Bhalla K, Beck J, Morganroth J, Laird GH, *et al*. Results of cardiac monitoring during phase I trials of a novel histone deacetylase (HDAC) inhibitor LBH589 in patients with advanced solid tumors and hematologic malignancies. J Clin Oncol (Meet Abstr) 2005;23:3106.
46. Zain JM, Foss F, Kelly WK, DeBono D, Petrylak A, Narwal E, *et al*. Final results of a phase I study of oral belinostat (PXD101) in patients with lymphoma. J Clin Oncol (Meet Abstr) 2009;27:8580.
47. Wise LD, Turner KJ, Kerr JS. Assessment of developmental toxicity of vorinostat, a histone deacetylase inhibitor, in Sprague-Dawley rats and Dutch Belted rabbits. Birth Defects Res B Dev Reprod Toxicol 2007;80:57-68.

48. Ritchie D, Piekarz RL, Blombery P, Karai LJ, Pittaluga S, Jaffe ES, *et al*. Reactivation of DNA viruses in association with histone deacetylase inhibitor therapy: A case series report. Haematologica 2009;94:1618-22.
49. Edelstein LC, Micheva-Viteva S, Phelan BD, Dougherty JP. Short communication: Activation of latent HIV type 1 gene expression by suberoylanilide hydroxamic acid (SAHA), an HDAC inhibitor approved for use to treat cutaneous T cell lymphoma. AIDS Res Hum Retroviruses 2009;25:883-7.