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Histone deacetylase inhibitors

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Abstract

The human genome is contained in chromatin, which is a complex macromolecular complex. It is made of DNA, histones and non-histone proteins. The structure of chromatin and the process of its rearrangement regulate the process of transcription, and hence gene expression. Deacetylase (HDAC) is a group of enzymes that catalyzes the cleavage of acetyl groups from lysine residues in histone and nonhistone proteins. This reaction is catalyzed by zinc or NAD + ions [3]. Histone deacetylases are present in the cytoplasm or nucleus of eukaryotes [4, 5]. These enzymes have been divided into 5 classes (I, IIa, IIb, III and IV) due to the similarity in structure and origin. Vorinostat is one of the most studied HDAC inhibitors. It belongs to the second generation polar-planar hydroxamic acid derivatives that inhibit class I and II histone deacetylases. Panobinostat and belinostat are HDAC inhibitors derived from hydroxamic acid that have also entered clinical trials. Valproic acid, from the group of aliphatic acids, belongs to inhibitors of class I and IIα deacetylases and is an established drug anticonvulsants. Histone deacetylase inhibitors may be useful in the treatment of neoplasms because they influence the action of factors related to cell proliferation, may cause cell cycle arrest, and coordinate the action of apoptotic factors and induce apoptosis. There are several deacetylase inhibitors available as drugs and are in different phases of clinical trials. They differ in potency and enzyme specificity. However, it is still unknown which deacetylases are essential for initiating and sustaining metabolic pathways leading to tumor development.

Key words: inhibitors, histone deacetylase, cancer

Introduction

The human genome is contained in chromatin, which is a complex macromolecular complex. It is made of DNA, histones and non-histone proteins. The structure of chromatin and the process of its rearrangement regulate the process of transcription, and hence gene expression. The main factors that regulate the chromatin structure is the process of histone acetylation and deacetylation. The process of acetylation, regulated by the enzyme histone acetyltransferase (HATs), causes the relaxation of chromatin, resulting in an increase in gene expression. The process of deacetylation led by histone deacetylase (HADs) acts in an antagonistic way, causes tight packing of chromatin and blocking of gene transcription. Histone modifications play an important role in the regulation of gene expression [1]. The imbalance between deacetylation and acetylation causes disturbances in gene expression and deregulation of cellular processes such as the cell cycle, proliferation and apoptosis. These changes may contribute to the formation of neoplastic cells, which are characterized by a lack of apoptosis and a high proliferation index [2]

Deacetylase (HDAC) is a group of enzymes that catalyzes the cleavage of acetyl groups from lysine residues in histone and nonhistone proteins. This reaction is catalyzed by zinc or NAD + ions [3]. Histone deacetylases are present in the cytoplasm or nucleus of eukaryotes [4, 5]. These enzymes have been divided into 5 classes (I, IIa, IIb, III and IV) due to the similarity in structure and origin [2]. It can be seen that the catalytic activity of class I, II and IV is closely related to the zinc ion in the active center of the enzyme. In contrast, class III requires nicotinadenine dinucleotide (NAD) as a cofactor for catalytic activity [5]. Histone deacetylases are also subject to numerous control mechanisms, protein-protein interactions and post-translational modifications that affect their functionality. The modifications that are subject to are phosphorylation, acetylation, glycosylation, ubiquitination, sumoylation and S-nitrilation [3]. Histone deacetylation changes the chromatin structure and increases its availability for transcription factors, while deacetylation of nonhistone proteins influences numerous cellular processes [3,5].

The imbalance between HDAC and HAT activity is associated with the emergence of numerous diseases and disorders, including neurodegenerative diseases, depression, schizophrenia, endometriosis and cancer [2]. Epigenetic aberration of gene expression related to histone deacetylase activity plays an important role in the development and progression of tumors. It has been shown that HDACs are deregulated in neoplasms, therefore they have been recognized as a good target of anti-cancer therapy, and their inhibitors (HDI) are a promising anti-cancer agent [2, 5].

Histone deacetylase inhibitors

Histone acetylation is an important regulatory mechanism controlling the transcription of approximately 2–10% of genes. Histone deacetylation causes chromatin condensation, while decondensation is caused by increased acetylation. Histone deacetylases are involved in various pathways and functions of telephones; nevertheless, it offers research to unveil all their cellular functions and interactions that could result in the development of more effective HDAC inhibitor therapy. HDAC inhibitors traveling to be a promising anti-cancer drug journey, especially when with other anti-cancer drugs and / or radiation therapy[8]

Histone deacetylase inhibitors may be useful in the treatment of neoplasms because they influence the action of factors related to cell proliferation, may cause cell cycle arrest, coordinate the action of apoptotic factors and induce apoptosis [2].

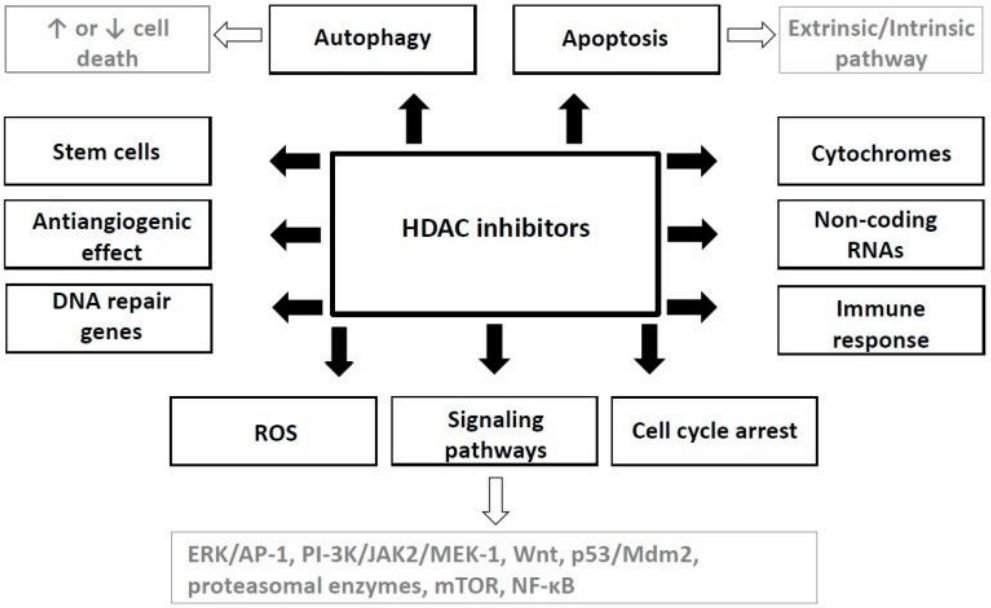

Figure 1. Mechanism of anti-tumor activity of HDAC inhibitors [8]

Vorinostat (SAHA) is one of the most studied HDAC inhibitors. It belongs to the second generation of polar-planar hydroxamic acid derivatives which inhibit class I and II histone deacetylases. The therapeutic effects of vorinostat have been studied in patients with haematological malignancies - including various types of leukemias, non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD), multiple myeloma (MM) or cutaneous T-cell lymphoma (CTCL), as well as in solid tumors, eg in papillary thyroid cancer, bladder, lung, prostate and breast cancer [6].

Panobinostat and belinostat are HDAC inhibitors derived from hydroxamic acid that have also entered clinical trials. Panobinostat, a class I, II and IV deacetylase inhibitor, was first used in the treatment of hematological cancers. The activity of belinostat does not preferentially target a selected class of deacetylases. It is used in the form of short intravenous infusions, and recently also orally in the treatment of hematological and solid tumors. [6]

Valproic acid from the group of aliphatic acids belongs to class I and IIα deacetylase inhibitors and is a recognized anticonvulsant drug. The antitumor activity of this compound has been studied both in hematological diseases and in advanced solid tumors. In the treatment of AML and MDS, the response was achieved in an average of 24% of patients, it was significantly dependent on the type of disease in relation to the WHO classification, and it occurred in 54% of MDS patients with a normal number of bone marrow blasts, but only in 6% of patients. with refractory anemia with excess blasts in 16% of patients with AML and in none of the patients with chronic myelomonocytic leukemia [7].

References

[1]. Chen P-J i inni, Epigenetic modifications by histone deacetylases: Biological implications and therapeutic potential in liver fibrosis, Biochimie, 2015 Vol.116, Pages 61-69

[2]. Qiu X i inni, Histone deacetylases inhibitors (HDACis) as novel therapeutic application in various clinical diseases, Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2017, Vol. 72

[3]. Seto E., Yoshida M., Erasers of histone acetylation: the histone deacetylase enzymes, Cold Spring Harb Perspect Biol., 2014,6(4)

[4]. Seidel C. i inni, , Histone deacetylase 6 in health and disease, Epigenomics, 2015, 7(1), 103-18

[5]. Wawruszak A i inni., Histone Deacetylase Inhibitors and Phenotypical Transformation of Cancer Cells, Cancers., 2019, 11(2), 148

[6]. Grabarska A, Dmoszyńska-Graniczka M, Nowosadzka E, Stepulak A. Inhibitory deacetylaz histonów - mechanizmy działania na poziomie molekularnym i zastosowania kliniczne [Histone deacetylase inhibitors - molecular mechanisms of actions and clinical applications]. Postepy Hig Med Dosw (Online). 2013 Aug 2;67:722-35. Polish. doi: 10.5604/17322693.1061381. PMID: 24018438.

[7]. Kuendgen A., Knipp S., Fox F., Strupp C., Hildebrandt B., Steidl C., Germing U., Haas R., Gattermann N.: Results of a phase 2 study of valproic acid alone or in combination with all-trans retinoic acid in 75 patients with myelodysplastic syndrome and relapsed or refractory acute myeloid leukemia. Ann. Hematol., 2005; 84, Suppl 1: 61-66

[8]. Eckschlager T, Plch J, Stiborova M, Hrabeta J. Histone Deacetylase Inhibitors as Anticancer Drugs. Int J Mol Sci. 2017 Jul 1;18(7):1414. doi: 10.3390/ijms18071414. PMID: 28671573; PMCID: PMC5535906.