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Review

Histone Deacetylase Inhibitors in Cancer Treatment

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ABSTRACT

Histone deacetylases (HDACs) are enzymes that play a critical role in regulating biological processes. Histone deacetylase inhibitors can halt the growth of cancer cells and induce apoptosis by preventing the dysregulated activities of these enzymes. Studies conducted on normal tissues, primary tumors, and human cancer cell lines have shown that the loss of acetylated Lys16 (K16-H4) and trimethylated Lys20 (K20-H4) in histone H4 is a common occurrence. These losses occur in the early stages of cancer development and may contribute to tumor invasion and metastasis. This review provides a comprehensive analysis of the roles of HDACs in cancer and the therapeutic potential of HDAC inhibitors.

Keywords: Apoptosis, cancer, cancer treatment, HDAC inhibitors, sirtuin.

Cancer is a disease characterized by the uncontrolled proliferation of cells, mutations in oncogenes, loss of function in tumor suppressor genes, and epigenetic alterations. Globally, lung cancer is one of the leading causes of cancer-related mortality, resulting in the deaths of approximately 1.5 million people annually. This disease accounts for 28% of cancer cases in men and 26% in women.[1]

Histone deacetylase inhibitors (HDACIs) have emerged as promising cancer therapies due to their ability to promote differentiation, arrest the cell cycle, and induce apoptosis (programmed cell death) in cancer cells.[2]

Histone deacetylases are transcriptional co-repressors and chromatin-modifying enzymes. They play a role in post-translational modifications of both histone and non-histone proteins, as well as in chromatin condensation, which regulates cell proliferation and the cell cycle.[3]

In humans, there are 18 HDAC enzymes classified into four classes based on sequence homology and mechanism of action. Class I HDACs (HDAC1, HDAC2, HDAC3, and HDAC8) share similarities with the yeast RPD3 protein. Class II HDACs (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10) resemble the yeast HDA1 protein. Class III HDACs, known as sirtuins, include SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7. Additionally, there is a class IV isoform known as HDAC11. Class III and IV enzymes are structurally distinct from classes I and II, with class III enzymes uniquely requiring nicotinamide adenine dinucleotide (NAD+) as a cofactor for their enzymatic activity. The dynamic regulation of histone acetylation by these different classes of HDAC enzymes plays a crucial role in modulating gene expression patterns and cellular processes. Disruption of this balance is believed to contribute to the development of diseases, particularly cancer.[4]

Histone deacetylase inhibitors exert anticancer effects by promoting the acetylation of both histone and non-histone protein substrates. The effects of HDACIs on gene transcription are complex; they induce cell cycle arrest, inhibit DNA repair, trigger apoptosis, and acetylate non-histone proteins that lead to changes in gene expression. Histone deacetylase inhibitors represent a diverse group of compounds that vary in structure, biological activity, and specificity. They typically consist of a zinc-binding

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domain, a cap group, and a straight-chain linker that connects these two regions. Histone deacetylase inhibitors are classified into four main categories: short-chain fatty acids, hydroxamic acids, cyclic peptides, and synthetic benzamides.[5]

BIOLOGICAL FUNCTIONS OF HISTONE DEACETYLASES

Transcriptional Regulation

Transcription factors (TFs) can directly target DNA or undergo various post-translational modifications (PTMs) to alter gene expression. In this way, HDACs negatively regulate gene expression by forming complexes with TFs or directly modulating the transcription of TFs. For example, v-myc avian myelocytomatosis viral oncogene homolog (Myc) is a well-known proto-oncogene that promotes tumor formation. Myc regulates gene expression by recruiting and interacting with HDACs. Additionally, the acetylation of Myc is also directly or indirectly regulated by HDACs. For instance, SIRT2 stabilizes N-Myc and c-Myc proteins by deacetylating and repressing NEDD4, which facilitates the ubiquitination and degradation of Myc. The SIRT2-specific inhibitor thiomyristoyl promotes Myc ubiquitination and degradation. Histone deacetylase inhibitors such as suberoylanilide hydroxamic acid (SAHA) and entinostat (also known as MS-275) induce acetylation of Myc at K323, downregulate Myc, and are associated with the activation of tumor necrosis factor-related apoptosis-inducing ligand. Therapeutic regimens combining HDACI with DNA demethylation reagents may have a significant impact on non-small cell lung cancer by activating the immune system. p53 is a crucial tumor suppressor gene that regulates gene expression. Its activity is controlled by various PTMs. Histone deacetylases and SIRTs reduce p53 activity to support the survival of cancer cells under oxidative stress conditions. The HDAC1, HDAC2, and HDAC3 suppress p53-mediated apoptosis by deacetylating p53. Additionally, HDAC2 regulates p53's transcriptional activity by influencing its binding to DNA. When p53 is acetylated at positions K373/K382 by the p300 enzyme, it binds to DNA. The HDAC inhibitor depsipeptide recruits p300, increasing acetylation at the K373/K382 positions, which promotes the expression of p21 Cip1/Waf1 (encoded by CDKN1A, a cyclin-dependent kinase inhibitor 1A). Compared to wild-type p53, HDAC deficiency reduces mutant p53 (mtp53) expression at both the mRNA and protein levels.[6]

The HDACI promotes the preferential degradation of mutant p53 (mtp53) by inhibiting HDAC6 and downregulating heat shock protein 90 (HSP90). This occurs through the carboxy-terminal HSP90 interaction protein, which interacts with E3 ligases that suppress p53 protein degradation, including mouse double minute 2 and heat shock protein 70.[7]

Histone deacetylases regulate the activity of TFs as well as super-enhancers. Enhancer RNAs (eRNAs) are short, non-coding RNA molecules that work with promoters to alter the transcription of target genes. Trichostatin A (TSA) and SAHA reduce eRNA synthesis by inhibiting HSP90.[6]

The MEF2D and HDAC4/9 form a corepressor complex to recognize intergenic regions. In cells lacking HDAC4/9, H3K27ac levels increase around gene transcription start sites, exhibiting characteristics of active enhancers in topologically associated domains.[8]

The class I HDAC inhibitor 4SC-202 increases both H3K27ac and H3K4me3 levels around gene transcription start sites (TSS), but reduces the occupancy near the TSS of genes such as SMAD6 and E2F8. Panobinostat and romidepsin alter the super-enhancer (SE) topology at PAX8, affecting H3K27 acetylation status. Largazole, in particular, leads to the disruption of SE-driven transcripts associated with oncogenic activities.[6]

Transcriptional Activation

Although HDACs generally function in gene silencing, they can also activate transcription. This activation occurs through HDACs' involvement in the modulation of RNA polymerase II (RNAPII). Histone deacetylases play a role in the cross-interaction between acetylation and phosphorylation of the C-terminal domain of RNAPII.[6] SIRT6 assembles SMARCC2/BAF170 (SWI/SNF-related, matrix-associated, actin-dependent regulator) to create active chromatin at the oxygenase-1 enhancer and recruits RNAPII through mono-ADP-ribosylation.[9]

SIRT6 can interact with p53 to efficiently recruit RNAPII to local promoters.[6]

The SIRT6 deficiency triggers the activation of cyclin-dependent kinase 9 and phosphorylates the negative elongation factor (NELF), leading to the release of NELF from RNAPII. This process facilitates the accumulation of TFs and elongation factors associated with RNAPII, promoting the elongation of transcription for specific gene sets.[10]

Consistently, TSA and SAHA increase the interaction between RNAPII and NELF, thereby inhibiting RNAPII-mediated transcriptional elongation.[11]

Metabolism

Various kinases and metabolic pathways create a complex network with epigenetic co-repressors to regulate metabolic flux and enzyme activity. Disruptions in these processes can lead to tumor formation and cancer progression. Metabolism can affect protein acetylation by altering NAD+ and acetyl-CoA levels. Additionally, HDACs also regulate metabolic reprogramming in cancer cells.[12]

Cancer cells are typically recognized for their high glycolytic activity, and these cells prioritize aerobic glycolysis for their energy metabolism.[13]

Increased glycolysis is associated with abnormal regulation of glycolytic enzymes and glucose metabolism pathways. Class II HDACs, through their association with HDAC3, prevent the transport of gluconeogenic enzymes from the cytoplasm to the nucleus and facilitate the deacetylation and activation of the forkhead box class O (FoxO) family in the nucleus.[14] The SIRT2 enhances the enzymatic activity of isocitrate dehydrogenase 1 (IDH1) by deacetylating it at the K224 position. Hypoacetylated IDH1 converts isocitrate to α-ketoglutarate in the tricarboxylic acid cycle, inhibiting liver metastasis in colorectal cancer.[15]

Pyruvate kinase M2 (PKM2) promotes tumor formation by activating the proliferation pathway through HDAC3 and regulating oncogene expression. SIRT6 interacts with PKM2 and deacetylates it, leading to its nuclear export via exportin 4, thereby suppressing PKM2's oncogenic functions. Additionally, SIRT3 and SIRT6 act as tumor suppressors by inhibiting aerobic glycolysis in cancer cells through the destabilization of hypoxia-inducible factor 1 alpha and the inhibition of glycolytic kinases.[6] The p53 regulates gluconeogenesis by directly binding to and activating SIRT6, which leads to the deacetylation and nuclear exclusion of FoxO1.[16]

Redox and Oxidative Stress

Histone deacetylase inhibitor therapy is often associated with DNA damage caused by oxidative stress, primarily resulting from the generation of reactive oxygen species (ROS).[17] There are two redox systems in mammalian cells that respond to oxidative stress: the thioredoxin (Trx) and glutathione-glutaredoxin (Grx) systems. In response to nitric oxide, HDAC2 undergoes S-nitrosylation at Cys 262 and Cys 274, which triggers chromatin remodeling to enhance gene expression.[18]

Redox-sensitive cysteine residues (Cys-667/Cys-669) in HDAC4 respond to oxidative stress by forming intramolecular disulfide bonds. Compared to normal cells, tumor cells are enriched in the antioxidant thioredoxin reductase (TrxR), which could make them a therapeutic target. Depsipeptide inhibits TrxR and increases ROS production, leading to significant DNA damage and apoptosis. HDAC5 reduces mitochondrial ROS production, and HDAC5 deficiency enhances transcription associated with NRF2.[6]

Y-box binding protein 1 (YB-1) interacts with NRF2 under oxidative stress conditions. Entinostat increases the acetylation of YB-1, which prevents its binding to NRF2, thereby reducing NRF2 production in sarcoma cells and increasing ROS levels.[19]

DNA Damage Response

DNA damage response (DDR) is a vital mechanism that protects genomic DNA from various types of damage. Different stimuli, such as UV radiation and chemical agents like ROS and reactive nitrogen species, can cause DNA damage. Double-strand breaks (DSBs) are the most severe form of DNA damage and are repaired by homologous recombination or non-homologous end-joining pathways. Histone deacetylases (HDAC1/2) and SIRT1 play a critical role in chromatin regulation and DNA repair. DNA damage response is controlled by kinases such as ATM, ATR, and DNA-PKcs. In response to DNA damage, the interaction between HDAC1 and ATM enhances chromatin condensation. SIRT1 induces p53 activation and plays a significant role in DNA repair. Additionally, SIRT6 and SIRT7 play critical roles in DDR as well. The DNA-PKcs are recruited to DSB regions by the Ku family, and SIRT1 and SIRT3 act as protective factors under oxidative stress. SIRT6 and SIRT7 play important roles in regulating DNA repair. SIRT6 has been identified as a new sensor that initiates DDR. Poly ADP-ribose polymerases (PARPs) play a central role in the activation of DNA repair mechanisms, such as single-strand DNA breaks. Both SIRTs and PARPs require NAD+, but PARP1 consumes NAD+, which can affect SIRT activity. Cancer cells can overcome DNA damage through pathways such as base excision repair (BER), nucleotide excision repair (NER), and mismatch repair. The combined use of HDAC and PARP inhibitors may be beneficial in treating malignancies with BRCA1/2 deficiencies.[6]

THE ROLE OF HISTONE DEACETYLASES IN CANCER

One of the characteristic features of human cancer is the dysregulation of post-translational histone modifications, such as histone acetylation, which significantly impact DNA methylation and gene transcription regulation. Studies conducted on normal tissues, primary tumors, and human cancer cell lines have shown that the loss of acetylated Lys16 on histone H4 (K16-H4) and trimethylated Lys20 on histone H4 (K20-H4) is common. Additionally, this loss is associated with hypomethylation of repetitive sequences. These alterations occur during the early stages of multi-step skin cancer tumorigenesis in mice, indicating that the overall loss of monoacetylated and trimethylated forms of histone H4 is a critical event in cancer development.[20] Another study on gastrointestinal tumors concluded that the reduction in histone acetylation affects both tumorigenesis and tumor invasion and metastasis.[21]

The mechanisms of histone hypoacetylation are still largely unknown. These changes can be explained by a reduction in HAT activity or an increase in HDAC activity associated with mutations or chromosomal translocations observed in leukemias. It is known that HDACs function through multiple mechanisms in cancer development. Current studies show that HDACs are abnormally recruited to specific promoters through interaction with fusion proteins formed as a result of chromosomal translocations. Acute promyelocytic leukemia is an example of this. The genetic feature of this disease involves chromosomal translocations that produce the RAR-PML and RAR-PLZF fusion proteins. These proteins bind to retinoic acid response elements, activating the HDAC repressive complex, blocking retinoic acid binding, and suppressing the expression of genes that regulate normal differentiation and proliferation of myeloid cells.[22]

Although there are no definitive data on HDAC expression in human cancers, various studies have shown altered expression of certain HDACs in tumor samples. For instance, HDAC1 expression has been increased in stomach, prostate, colon, and breast cancers. Overexpression of HDAC2 has been found in cervical and stomach cancers, as well as in colorectal carcinoma with loss of APC expression. Additionally, high levels of HDAC3 and HDAC6 expression have been reported in colon and breast cancer samples.[23]

The findings mentioned above suggest that the overexpression and abnormal involvement of HDACs could be a common phenomenon in the transcriptional repression of tumor suppressor genes. A typical example is the cyclin-dependent kinase inhibitor p21 WAF1, which inhibits the cell cycle and is often lost in many tumors. In some cancers, p21 WAF1 is epigenetically inactivated through hypoacetylation. Treatment with HDAC inhibitors inhibits tumor cell growth and increases the acetylation of the promoter, thereby enhancing gene expression.[24]

The Snail transcription factor recruits HDAC1, HDAC2, and the corepressor complex mSin3A to mediate the repression of the E-cadherin promoter.[25]

The reduction in expression or loss of function of E-cadherin contributes to the invasive potential of carcinomas. Therefore, the abnormal involvement of HDACs in this promoter may play a critical role in tumor invasion and metastasis. In recent years, class III HDACs, or sirtuins, have gained significant attention. These HDACs play key roles in regulating various processes such as gene expression, apoptosis, stress responses, DNA repair, the cell cycle, and genomic stability. This indicates that sirtuins are essential regulators of normal cell growth and proliferation. Specifically, SIRT1 regulates histone acetylation levels (particularly at K16-H4 and K9-H3 positions) as well as the acetylation of TFs such as p53, p300 histone acetyltransferase, E2F1, Ku70, nuclear factor kappa-light-chain-enhancer of activated B cells, and the androgen receptor. Therefore, dysregulation of sirtuins is clearly important in cancer development. There are several reports indicating the upregulation or downregulation of SIRT genes in cancer. For instance, SIRT1 has been found to be upregulated in human lung cancer, prostate cancer, and leukemia, while downregulated in colon tumors. Additionally, acetylation levels of histone substrates K16-H4 and K9-H3, which are regulated by SIRT1, have been shown to vary across different tumor types. Studies have indicated that the loss of monoacetylated K16-H4 is a common event in human cancer and occurs early in cancer development. Treatment with SIRT1 inhibitors leads to re-expression of tumor suppressor genes, accompanied by an increase in acetylation levels of K16-H4 and K9-H3 in breast and colon cancer cell lines.[23,26]

In conclusion, the roles of HDACs in cancer development and progression, along with the therapeutic potential of HDAC inhibitors, represent an important area of research. The use of HDAC inhibitors in cancer treatment has shown promising results by halting tumor cell growth, preventing metastasis, and promoting apoptosis. Therefore,

understanding the potential of HDAC inhibitors in cancer therapy could contribute to the development of new and effective treatment strategies.

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REFERENCES

1. Ramaiah MJ, Tangutur AD, Manyam RR. Epigenetic modulation and understanding of HDAC inhibitors in cancer therapy. Life Sci. 2021 Jul 15;277:119504.
2. Patel R, Modi A, Vekariya H. Discovery and Development of HDAC Inhibitors: Approaches for the Treatment of Cancer a Mini-review. Curr Drug Discov Technol. 2024;21:e230224227378.
3. Singh T, Kaur P, Singh P, Singh S, Munshi A. Differential molecular mechanistic behavior of HDACs in cancer progression. Med Oncol. 2022 Aug 16;39:171.
4. Cheng B, Pan W, Xiao Y, Ding Z, Zhou Y, Fei X, et al. HDAC-targeting epigenetic modulators for cancer immunotherapy. Eur J Med Chem. 2024 Feb 5;265:116129.
5. Lakshmaiah KC, Jacob LA, Aparna S, Lokanatha D, Saldanha SC. Epigenetic therapy of cancer with histone deacetylase inhibitors. J Cancer Res Ther. 2014 Jul-Sep;10:469-78.
6. Li G, Tian Y, Zhu WG. The Roles of Histone Deacetylases and Their Inhibitors in Cancer Therapy. Front Cell Dev Biol. 2020 Sep 29;8:576946.
7. Li D, Marchenko ND, Moll UM. SAHA shows preferential cytotoxicity in mutant p53 cancer cells by destabilizing mutant p53 through inhibition of the HDAC6-Hsp90 chaperone axis. Cell Death Differ. 2011 Dec;18:1904-13.
8. Di Giorgio E, Dalla E, Franforte E, Paluvai H, Minisini M, Trevisanut M, et al. Different class IIa HDACs repressive complexes regulate specific epigenetic responses related to cell survival in leiomyosarcoma cells. Nucleic Acids Res. 2020 Jan 24;48:646-64.
9. Rezazadeh S, Yang D, Tombline G, Simon M, Regan SP, Seluanov A, et al. SIRT6 promotes transcription of a subset of NRF2 targets by mono-ADP-ribosylating BAF170. Nucleic Acids Res. 2019 Sep 5;47:7914-28.
10. Etchegaray JP, Zhong L, Li C, Henriques T, Ablondi E, Nakadai T, et al. The Histone Deacetylase SIRT6 Restrains Transcription Elongation via Promoter-Proximal Pausing. Mol Cell. 2019 Aug 22;75:683-99.e7.
11. Greer CB, Tanaka Y, Kim YJ, Xie P, Zhang MQ, Park IH, et al. Histone Deacetylases Positively Regulate Transcription through the Elongation Machinery. Cell Rep. 2015 Nov 17;13:1444-55.
12. Verdin E, Ott M. 50 years of protein acetylation: from gene regulation to epigenetics, metabolism and beyond. Nat Rev Mol Cell Biol. 2015 Apr;16:258-64.
13. WEINHOUSE S. On respiratory impairment in cancer cells. Science. 1956 Aug 10;124:267-9.
14. Mihaylova MM, Vasquez DS, Ravnskjaer K, Denechaud PD, Yu RT, Alvarez JG, et al. Class IIa histone deacetylases are hormone-activated regulators of FOXO and mammalian glucose homeostasis. Cell. 2011 May 13;145:607-21.
15. Wang B, Ye Y, Yang X, Liu B, Wang Z, Chen S, et al. SIRT2-dependent IDH1 deacetylation inhibits colorectal cancer and liver metastases. EMBO Rep. 2020 Apr 3;21:e48183.
16. Zhang P, Tu B, Wang H, Cao Z, Tang M, Zhang C, et al. Tumor suppressor p53 cooperates with SIRT6 to regulate gluconeogenesis by promoting FoxO1 nuclear exclusion. Proc Natl Acad Sci U S A. 2014 Jul 22;111:10684-9.
17. Xu W, Ngo L, Perez G, Dokmanovic M, Marks PA. Intrinsic apoptotic and thioredoxin pathways in human prostate cancer cell response to histone deacetylase inhibitor. Proc Natl Acad Sci U S A. 2006 Oct 17;103:15540-5.
18. Nott A, Watson PM, Robinson JD, Crepaldi L, Riccio A. S-Nitrosylation of histone deacetylase 2 induces chromatin remodelling in neurons. Nature. 2008 Sep 18;455:411-5.
19. El-Naggar AM, Somasekharan SP, Wang Y, Cheng H, Negri GL, Pan M, et al. Class I HDAC inhibitors enhance YB-1 acetylation and oxidative stress to block sarcoma metastasis. EMBO Rep. 2019 Dec 5;20:e48375.
20. Fraga MF, Ballestar E, Villar-Garea A, Boix-Chornet M, Espada J, Schotta G, 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;37:391-400.
21. Yasui W, Oue N, Ono S, Mitani Y, Ito R, Nakayama H. Histone acetylation and gastrointestinal carcinogenesis. Ann N Y Acad Sci. 2003 Mar;983:220-31.
22. Lin RJ, Sternsdorf T, Tini M, Evans RM. Transcriptional regulation in acute promyelocytic leukemia. Oncogene. 2001 Oct 29;20:7204-15.
23. Ropero S, Esteller M. The role of histone deacetylases (HDACs) in human cancer. Mol Oncol. 2007 Jun;1:19-25.
24. 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 Feb 3;101:1241-6.
25. Peinado H, Ballestar E, Esteller M, Cano A. Snail mediates E-cadherin repression by the recruitment of the Sin3A/histone deacetylase 1 (HDAC1)/HDAC2 complex. Mol Cell Biol. 2004 Jan;24:306-19.
26. Aykan K, Altuntaş İ, Erbaş O. DNA repair mechanisms: DNA repair defects and related diseases. D J Med Sci 2022;8:130-40.