Review Article

Recent Advances in Histone Deacetylase Targeted Cancer Therapy

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Abstract
Epigenetic regulators such as histone acetyltransferases (HATs) and histone deacetylases (HDACs) are known to play an important role in gene expression. Of these enzymes, HDACs have been shown to be commonly associated with many types of cancers and to affect cancer development. Consequently, HDACs have been considered as promising targets for cancer therapy. In addition, the inhibition of HDACs by histone deacetylase inhibitors (HDACIs) shifts the balance between the deacetylating activity of HDACs and the acetylating activity of HATs in the regulation of gene expression. Therefore, HDACIs are an exciting new addition in cancer therapies. Numerous HDACIs have been identified and some have recently been used in clinical trials for cancer treatment, although the mechanisms underlying the anticancer effects of HDACIs remain unclear. In this review, we examine the most recent developments in HDACIs and various aspects of HDAC-targeted cancer treatment.

Key words Histone deacetylase inhibitor · Molecular targeted therapy · Cancer therapy

Introduction
Tumorigenesis is considered to be a multiple-step change in the normal regulation of gene expression.1-3 Epigenetic modulations are important for the understanding of the regulation of genetic information.4-6 Epigenetic phenomena, including histone acetylation and deacetylation, provide additional mechanisms for controlling gene expression at the chromatin level.7-9 The balance of acetylation by histone acetyltransferases (HATs) and deacetylation by histone deacetylases (HDACs) prevents full acetylation of DNA, thereby creating a default underacetylated state. Acetylated histone tails and other chromosome-associated proteins have been identified in nucleosomes and have been shown to be important in regulating gene expression.10,11 Histone acetylation is often associated with the transcription of genes characteristic of the differentiated state. By contrast, histone deacetylation correlates with transcriptional silencing and, specifically, with the down-regulation of the expression of proapoptotic genes, especially in cancer cells.12,13 The acetylation of lysine residues in the tails of histone proteins induces an open structure of the chromatin and accentuates the ability of the protein to interact with both DNA and other protein structures. This open conformation allows the transcriptional factors to access their promoters, thus facilitating the process of gene expression (Fig. 1). The histone deacetylase inhibitors (HDACIs) were mainly thought to act by modulating the gene expression patterns, including genes associated with cell cycle arrest and apoptosis, by inhibiting the activity of HDAC.14-17 The induction of apoptosis by HDACIs via cell death pathways mediated by TRAIL, Fas, Bid, and p53 has also been reported.18-22 However, the details of how these activities occur remain unknown. This review focuses on the molecular and pharmacological characteristics of HDACIs and the current ongoing clinical trials in solid malignant tumors.

Aberrant Expression of Histone Deacetylases in Solid Tumors
As mentioned above, an imbalance in histone acetylation manipulates the chromatin structure and affects the transcription of genes involved in the regulation of the cell cycle, differentiation, and apoptosis. In addition, the aberrant deacetylation of histones by enhanced...
HDAC activity in human tumors has been shown to lead to an imbalance in histone acetylation.23–28 Toh et al. showed that esophageal squamous cancer patients with a higher level of histone H4 acetylation had a better prognosis, and suggested that the metastasis-associated protein MTA1 may be involved in the alteration of chromatin structure and transcription repression. Indeed, immunostaining patterns of MTA1 and acetylated histone H4 were inversely correlated.29,30

Recently, at least 18 isoenzymes of HDACs were identified in humans, and were divided into four different classes.31,32 On the molecular level, class III HDACs are distinct from class I and II HDACs in that they require cofactors to activate their function. Class I HDACs include HDACs 1, 2, 3, and 8. Class II HDACs are subdivided into two subclasses, IIa (HDAC 4, 5, 7, 9) and IIb (HDAC 6, 10), based on their sequence homology and domain organization (Fig. 2).33,34 The class I isoforms are known to represent a target for new HDACI therapeutics. The efficacies of some HDACIs have been shown to correlate with a reduction in the class I HDAC activities. Indeed, several studies have so far reported a functional link between specific class I HDACs and the development of malignant solid tumors.23–28 On the other hand, the correlation between class II HDACs and cancer development has been reported less frequently. In particular, some benzene meta-substituted compounds that emerged as highly class II-selective HDAC inhibitors did not produce any effect on apoptosis in human acute myeloid leukemia cells.35 However, mutations in HDAC4 have been identified in breast cancer tissue specimens.36 Therefore, while the class II HDACs currently seem to be less suitable targets for cancer therapy than the class I HDACs, further studies are needed in other cancer types.

Fig. 1. The regulation of gene expression by histone deacetylase (HDAC) and histone acetyltransferase (HAT). In the chromatin structure, the DNA (spiral curve) is wrapped around the histone protein (cylinder). The acetylation of lysine residues (spheres) by HAT induces a negative charge, acting to neutralize the positive charge on the histones. As a result, the condensed chromatin is transformed into a more relaxed structure, which is associated with greater levels of gene transcription (active form). This relaxation can be reversed by the HDAC activity (inactive form).

Development of Histone Deacetylase Inhibitors

The development of synthetic HDACIs as anticancer drugs was first started from a simple chemical, dimethyl sulfoxide (DMSO).37 To date, several structurally distinct classes of HDACIs have been developed, and the HDACI include both natural and synthetic compounds. Usually HDACIs are classified into six groups, including short-chain fatty acids, hydroxamic acids, cyclic peptides, benzamides, electrophilic ketones, and hybrid molecules (Fig. 3 and Table 1).38

Short-chain fatty acids (such as butyrate, phenylbutyrate, and valproic acid) have become a preferred research topic in the cancer field because they are thought to be produced upon bacterial fermentation of dietary fiber, and might protect against colon cancer.39 The compounds included in this class are well-tolerated in patients, and are currently undergoing investigation in numerous clinical trials for various cancers.40–44 On the other hand, the compounds in this class are thought to be metabolized easily in vivo, and their half-life in plasma is shorter than that of the molecules in other classes of HDACIs. For this reason, high doses are required to obtain adequate therapeutic effects.45

Hydroxamic acids (such as trichostatin A, suberoyl anilide hydroxamic acid [SAHA], and suberoyl bis-hydroxamic acid [SBHA]) have a high efficacy, with nanomolar potency against both class I and II HDACs.46 The natural product trichostatin A was the first agent identified in this class of HDACIs, but is not in clinical use due to toxicity.47 More recently, synthetic hydroxamic acids such as SAHA and SBHA have been synthesized,