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Review Article

HYDROXAMIC ACID BASED HISTONE DEACETYLASE INHIBITORS: PRESENT AND FUTURE PROSPECTIVES AS ANTICANCER AGENT

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ABSTRACT

Histone deacetylases are set of enzymes that have been of interest in drug discovery for the last more than 3 decades. They are responsible for cleaving of acetyl groups from acetyl-lysine residues in histones and various non-histone proteins. Histone deacetylase inhibition is a contemporary, clinically validated therapeutic tactic for cancer treatment. Hydroxamic acid derivatives are among the first compounds to be identified as histone deacetylase inhibitors, comprising of three structural units namely, the surface recognition domain generally a hydrophobic group, linker domain consist of linear or cyclic structures and zinc binding group. In the present review, we are focusing on vital aspects of histone deacetylases, their classification and importance of hydroxamic acid based histone deacetylase inhibitor as anticancer agent.

Keywords: Histone deacetylases, Hydroxamic acid, Anticancer agent, Epigenetics.

INTRODUCTION

Histone deacetylases (HDACs) is identified as one of the promising goal for cancer treatment as many histone deacetylase inhibitors (HDACi) have passed into clinical trials for all tumors. Pursuing the completion of the human genome project, epigenetics has come out as a crucial area to understand how the genome translates its information. Two mechanisms have been distinguished to show important roles in the epigenetic regulation of gene transcription, namely histone modifications and DNA methylation [1]. These genomic modifications influence patterns of genetic regulation without varying the nucleotide sequence of the underlying DNA and are transferable from one cell generation to the next. Moreover, these active processes provide a mechanism by which an organism can react to environmental signals through changes in gene expression during cell growth and differentiation. Accumulating evidence indicates that deregulation of these epigenetic processes causes transcriptional repression of a subset of genes, which underlies the pathogenesis of many human diseases. In the past decade, considerable advancement has been made in understanding the causative relationship between aberrant epigenetic modification and tumorigenesis, which has resulted in to the Phase I and II clinical evaluation of HDACi [2-7] and too a smaller extent, DNA methyl transferase inhibitors [8] in solid tumors and hematological malignancies.

HDACi hinder angiogenesis, arrest cell growth and lead to differentiation and apoptosis in cancer cells. HDACs catalyze the deletion of the acetyl group from the ε-amino groups in histone lysine residues. The acetylation and deacetylation plays an imperative role in transcriptional regulation of eukaryotic cells [9, 10]. The acetylation state of the lysine residues is regulated by the action of two counteracting enzymes, the HDACs and the histone acetyl transferases (HATs) [2, 11-13]. HATs transfer an acetyl group from acetyl CoA to the ε-amino groups of a lysine residue of histones, while HDACs catalyze the hydrolysis of these acetamides by the removal of the acetyl group from the ε-amino groups of the lysine side-chains [14-16].

HDAC CLASSIFICATION

Till date, 18 different members of HDACs have been recognized and divided into four different classes, Class I, Class II, Class III, and Class IV [17,18]. Class I with its subtypes HDAC1, 2, 3, and 8 are related to yeast RPD3 deacetylase are generally localized to the nucleus and are ubiquitously expressed in many human cell lines and tissues [19]. Class II includes six subtypes, which are divided into two subclasses, class IIa with HDAC4, 5, 7, 9, and class IIb with HDAC6 and 10. Both subclasses show homology to HDA1. Class III, also known as the sirtuins are related to the Sir2 gene and include SIRT1-7, and Class IV, which contains only HDAC11 has features of both Class I and II [20, 21].

HDAC INHIBITORS

A broad range of natural and synthetic derivatives have been identified to inhibit the activity of HDACs. The term HDACi is commonly used for compounds that target the classical HDACs (Class I, II, and IV), whereas the inhibitors of Class III HDAC are referred as sirtuins inhibitors. SIRTs are virtually unaffected by compounds that inhibit Class I, II, and IV HDACs [22-24]. HDACi causes growth arrest, differentiation and apoptosis in cancer cells. As these processes are affected by malignant transformation, HDACi are currently in various stages in clinical development as antineoplastic drugs [15, 16, 23, 25]. HDACi share some common features to interact with different portions of the catalytic channel of the enzyme. The structural details of the HDACi enzyme interactions have been determined in studies of a homolog of HDAC (histone deacetylase like protein (HDLP) with the HDACi trichostatin A and suberoylanilide hydroxamic acid [26]. According to X-ray crystallographic findings and the SAR of the various inhibitor classes, it was suggested that HDACi pharmacophore comprises of:

(a) A metal-binding domain, which interacts with the active site,

(b) A surface recognition domain, which interacts with residues on the rim of the active site

(c) A linker domain, connecting metal binding domain and surface recognition domain [27]

HDACi can be divided into several structural classes including hydroxamic acids, cyclic peptides, aliphatic acids, benzamides and electrophilic ketones.

Hydroxamic Acid Analogues

Hydroxamic acid agents are among the first compound to be identified as HDACi. A hydroxamic acid is a class of chemical compounds sharing the same functional group in which a hydroxylamine is inserted into a carboxylic acid. Its general structure is R-CO-NH-OH, with an R as an

organic residue, a CO as a carbonyl group, and a hydroxylamine as NH_2-OH. They are employed as metal chelators [28, 29]. In industry, e.g. benzohydroxamic acid and others in the reprocessing of irradiated fuel [30].

This structural design for HDACi has been derived from the X-ray crystal structure of a bacterial HDAC homologue (HDLP) with bound TSA (Figure 1). It has been put forwarded that the active site consists of a narrow tubular pocket with a zinc atom inside. Based on these examinations, it has been consistent that modifications of the connection unit and hydrophobic group, which are assumed to interact with the entrance area of the catalytic pocket, will provide prospects for discovering potent and possibly selective HDACi [31].

The proposed mechanism of the hydrolysis of acetyl-lysine by the class I/II HDAC enzymes is based on the studies that the HDLP active site has features of both metallo and serine protease active sites. Several studies confirmed that both SAHA and TSA make contact with the same residues in the edge channel and active site regions of the protein. In addition, hydrogen bonding between the hydroxamic acid inhibitor functionality and the imidazole groups in the histidine (H131, H132), aspartate (D166, D173) salt bridges, along with hydrogen bonding of the active site tyrosine (Y297) to the hydroxamate carbonyl, present additional rationale for the potent inhibitory activity [32].

Trichostatin A (TSA) was the first hydroxamate natural product discovered to inhibit HDACs directly [33]. TSA and trichostatin C were isolated as fungistatic antibiotics from Streptomyces hygroscopicus [34]. Trichostatic acid, the corresponding carboxylate was shown to be ineffective as an HDACi, indicating that the hydroxamate is prerequisite for activity.

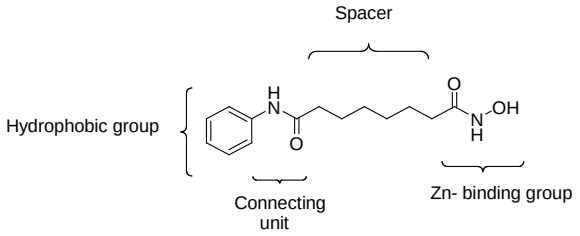

Fig.1: The essential structural feature of SAHA, an US FDA approved HDACi

SAHA (vorinostat) is the one of most clinically advanced HDACi [35-37]. A large number of preclinical studies demonstrated that SAHA could induce growth arrest, differentiation and apoptosis in a wide range of cancer cell lines [35, 38]. Vorinostat was approved by the US FDA in 2006 for the therapy of the cutaneous manifestations in patients with advanced refractory cutaneous T-cell lymphoma [37]. PXD-101 also known as Bellinostat is currently in phase II trial evaluation and is undergoing further studies with an oral preparation [39]. PXD-101 and NVP-LAQ824, identified by Novartis are proved to be effective HDACi in nanomolar concentrations. Other significant hydroxamic acids as anticancer agent include oxamflatin, scriptaid, LBH, PCI-24781 (Figure-2).

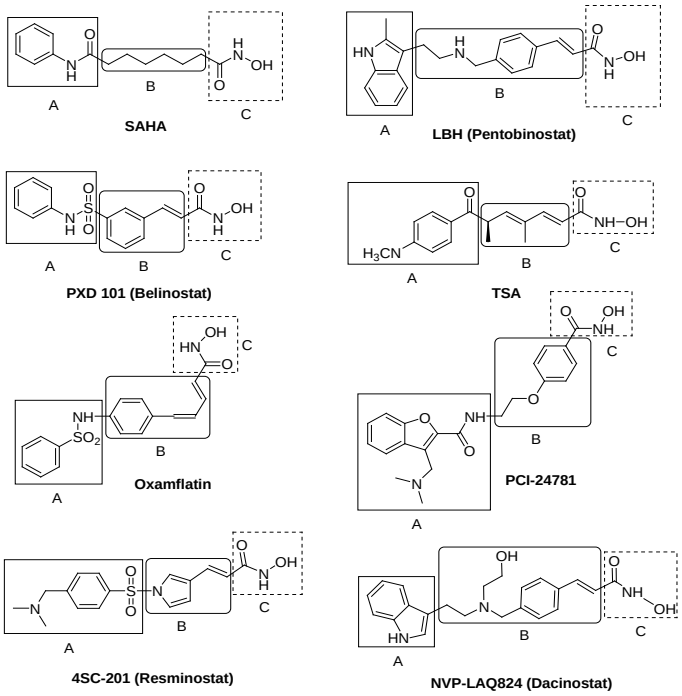

Fig. 2: Presence of vital structural features in clinically tested hydroxamic acid based HDAC Inhibitors. A = surface recognition; B = linker, and C = metal binding group

CONCLUSION

As motivated by the assumed translational potential of HDACi in cancer therapy, how these agents facilitate their anticancer action has been the emphasis of several contemporary studies. However, still a major challenge is lack of in-depth understanding of the biological function of the structurally diverse HDAC isoforms and their participation in the process of tumorigenesis. Hydroxamic acid analogues have exhibited greater inhibitory activity against the several HDACs. There are lots of possibilities to discover the novel HDACi by optimization of surface recognition moieties. A number of hydroxamic acid based HDACi are in various phases of clinical trial. It can be anticipated that these scientific endeavor will result in discovery of novel hydroxamic acid based HDACi as anticancer agent in the years to come.

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