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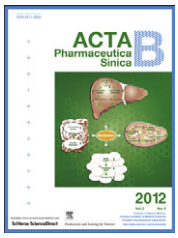

REVIEW

Histone deacetylases and their inhibitors: molecular mechanisms and therapeutic implications in diabetes mellitus

Xiaojie Wang[a], Xinbing Wei[a], Qi Pang[b], Fan Yi[a,*]

[a]*Department of Pharmacology, School of Medicine, Shandong University, Jinan 250012, China*
[b]*Department of Neurosurgery, Provincial Hospital Affiliated to Shandong University, Jinan 250021, China*

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Abstract Epigenetic mechanisms such as DNA methylation, histone modification and microRNA changes have been shown to be important for the regulation of cellular functions. Among them, histone deacetylases (HDACs) are enzymes that balance the acetylation activities of histone acetyltransferases in chromatin remodeling and play essential roles in gene transcription to regulate cell proliferation, migration and death. Recent studies indicate that HDACs are promising drug targets for a wide range of diseases including cancer, neurodegenerative and psychiatric disorders, cardiovascular dysfunction, autoimmunity and diabetes mellitus. This review highlights the role of HDACs in diabetes mellitus and outlines several important cellular and molecular mechanisms by which HDACs regulate glucose homeostasis and can be targeted for the treatment of diabetic microvascular complications. It is hoped that our understanding of the role of HDACs in diabetes mellitus will lead to the development of better diagnostic tools and the design of more potent and specific drugs targeting selective HDAC proteins for the treatment of the disease.

*Corresponding author. Tel./fax: +86 0531 88382616.
E-mail address: fanyi@sdu.edu.cn (Fan Yi).

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1. Introduction

Histone deacetylases (HDACs) are enzymes that balance the activities of histone acetyltransferases (HATs) in chromatin remodeling and thereby play an essential role in gene transcription to regulate cell proliferation, migration and apoptosis, immune pathways and angiogenesis. In the last few years, numerous studies have demonstrated the role of HDACs in cancer initiation and progression giving rise to the view that HDACs are potentially important drug targets in the treatment of cancer. Recent studies also indicate that targeting HDACs is a promising therapeutic strategy for a number of other diseases including neurodegenerative disorders, cardiovascular dysfunction, autoimmunity and diabetes mellitus. This review highlights the role of HDACs in the regulation of glucose metabolism, insulin resistance, insulin expression and secretion and the therapeutic potential of HDAC inhibitors for the treatment of diabetes mellitus. It is hoped that clarification of the pathological role of HDAC-mediated signaling pathways will aid in the development of diagnostic tools and in the design of more potent and specific drugs that target individual HDAC proteins.

2. The HDAC family: classification, location and substrates

HDACs are a family of enzymes which compete with HATs to control the acetylation of lysine residues making up the histones. The balance of acetylation and deacetylation then determines the post-translational acetylation status of histone and other non-histone proteins[1].

To date, 18 HDACs have been identified in mammals made up of four classes according to their sequence identity and catalytic activity[2]. Class I HDACs (HDAC1, 2, 3 and 8) share sequence homology with the yeast Rpd3 protein and contain a nuclear localization signal (NLS) but, with the exception of HDAC3, no nuclear export signal (NES). Accordingly, they are mainly located in the nucleus and regulate the expression of many genes[3], such as thioredoxin binding protein-2 (TBP-2), myocyte enhancer factor-2 (MEF2), NF-κB and GATA[4].

Class II HDACs (HDAC4–7, 9 and 10) are larger proteins than class I because they contain additional regulatory domains. They contain both an NLS and NES and shuttle between the cytoplasm and nucleus depending on their phosphorylation status. Class II HDACs are further subdivided into class IIa (HDAC4, 5, 7, 9) and IIb (HDAC6, 10) with class IIa having relatively low enzymatic activity compared to class I possibly to allow them to efficiently process restricted sets of specific, unknown natural substrates. Class IIb HDACs have primarily non-epigenetic functions involving the regulation of protein folding and turnover[5,6].

HDAC11 is the sole member of class IV. It is localized in the nucleus and has a catalytic domain in the N-terminal region. HDAC11 has been demonstrated to regulate the balance between immune activation and immune tolerance in $CD4^+$ T-cells[7] and to play an essential role in oligodendrocyte differentiation[8] and the regulation of OX40 ligand expression in Hodgkin lymphoma[9].

Classes I, II and IV HDACs possess a Zn^{2+}-dependent mechanism of action whereas the structurally unrelated class III HDACs comprise a family of nicotinamide adenine dinucleotide (NAD)-dependent deacetylases sharing sequence homology with the yeast Sir2 protein[10,11]. Because of this, class III HDACs are also called 'sirtuins' (SIRTs). SIRTs 1–7 target a wide range of cellular proteins in the nucleus, cytoplasm and mitochondria for post-translational modification by acetylation or ADP-ribosylation. Among them, SIRT1 and SIRT2 can shuttle between the nucleus and cytoplasm[12,13]. SIRT1, the founding member of the class, couples protein deacetylation with NAD^+ hydrolysis and links cellular energy and redox state to multiple signaling and survival pathways which positively regulate transcription factors such as NF-κB, p53 and forkhead box (FOX) proteins. In addition, SIRT1 may play a role in tumor initiation and progression as well as in the development of drug resistance by blocking senescence and apoptosis or promoting cell growth and angiogenesis. SIRT2 is mainly localized to the cytoplasm and affects α-tubulin acetylation status.

SIRTs 3, 4 and 5 are mainly localized in the mitochondria[14]. SIRT3 helps to maintain energetic cell homeostasis by positively regulating the activity of acetylcoenzyme A synthetase 2 and deacetylating complex I of the respiratory chain involved in ATP production. SIRT4 has ADP ribosylase activity which inactivates glutamate dehydrogenase and, in turn, inhibits insulin secretion in pancreatic β-cells. SIRT5 deacetylates and thereby activates carbamoyl phosphate synthetase 1 to promote ammonia detoxification. SIRTs 6 and 7 are predominantly found in the nucleus where they are involved in DNA repair and ribosomal RNA transcription, respectively.

To date, sirtuins have emerged as potential therapeutic targets for the treatment of cancer and of metabolic, cardiovascular and neurodegenerative diseases. This review focuses on the Zn^{2+}-dependent HDACs because they are the targets of small molecule HDAC inhibitors that have shown efficacy in animal models of diabetes mellitus. The classification, location, substrates, main biological functions and inhibitors of HDACs are shown in Table 1.

3. HDAC inhibitors

HDAC inhibitors are chemical compounds that inhibit Zn^{2+}-dependent HDAC enzymes and for which some 490 clinical trials have been carried out over the last 10 years. Their efficacy against malignant cells and their potent anticancer activity in pre-clinical studies have been demonstrated. They also display protective effects in animal models of various neurological and cardiovascular diseases and of diabetes mellitus[15–17].

HDAC inhibitors can be structurally grouped into hydroxamates, cyclic peptides, aliphatic acids, benzamides, boronic acid-based compounds, benzofuranone and sulfonamide containing molecules and α/β peptide structures[18]. Most of them possess a stereotypical three-part structure consisting of a zinc-binding "warhead" group which docks in the active site, a linker, and a surface recognition domain which interacts with residues near the entrance of the active site. Among them, vorinostat (suberoylanilide hydroxamic acid) and depsipeptide (Romidepsin, FK-228) were approved by the FDA in 2006 and 2009, respectively. Vorinostat is structurally related to trichostatin A (TSA) which is indicated for the treatment of relapsed and refractory cutaneous T-cell lymphoma (CTCL). The cyclic peptides are the most structurally complex group of HDAC inhibitors of which depsipeptide is one of the most important members.