Trends in Pharmacological Sciences

CellPress

Review

Targeting Class I Histone Deacetylases in a "Complex" Environment

Christopher J. Millard,[1,2] Peter J. Watson,[1,2] Louise Fairall,[1,2] and John W.R. Schwabe[1,*]

Histone deacetylase (HDAC) inhibitors are proven anticancer therapeutics and have potential in the treatment of many other diseases including HIV infection, Alzheimer's disease, and Friedreich's ataxia. A problem with the currently available HDAC inhibitors is that they have limited specificity and target multiple deacetylases. Designing isoform-selective inhibitors has proven challenging due to similarities in the structure and chemistry of HDAC active sites. However, the fact that HDACs 1, 2, and 3 are recruited to several large multisubunit complexes, each with particular biological functions, raises the possibility of specifically inhibiting individual complexes. This may be assisted by recent structural and functional information about the assembly of these complexes. Here, we review the available structural information and discuss potential targeting strategies.

Trends

All currently licenced HDAC drugs (HDAC inhibitors) are pan-inhibitors that work by targeting the active-site zinc.

HDAC inhibitors are used in the clinic as anticancer therapeutics, but due to their nonselective nature, many patients experience significant side effects.

The focus within the field is turning to the development of isoform-selective HDAC inhibitors to reduce off-target effects experienced by patients.

HDACs 1, 2, and 3 are of particular interest as they are recruited to multiprotein complexes to mediate gene transcription. As part of these complexes, the HDACs become maximally activated, and are targeted to specific genes.

The recruitment of class I HDACs into multiprotein assemblies opens up the possibility of using alternative strategies to develop complex-specific HDAC inhibitors.

Targeting HDAC Enzymes

Therapeutics that target HDAC enzymes are actively used in the clinic for the treatment of haematological malignancies and have recently been suggested to be useful in the treatment of other diseases including HIV infection [1–8]. However, all currently licenced HDAC inhibitors are pan-inhibitors, that is, drugs that have little or no selectively for the 11 known zinc-dependent HDACs. More selective inhibitors are actively being investigated but have not yet been licenced for use in the clinic. The lack of specificity of licenced drugs may explain why patients often experience significant undesirable side effects when taking HDAC inhibitors – probably due to the result of widespread perturbation of normal cell homeostasis [9].

Arguably, of the zinc-dependent HDACs, the most promising drug targets are HDACs 1, 2, and 3, which play important roles in regulating gene expression through removing acetyl groups on lysine residues within histone tails [10]. While high-resolution structures of these three enzymes have been determined, developing truly isoform-selective HDAC inhibitors has proven challenging due to the structural similarity of the active sites of these enzymes [11,12].

A further challenge with targeting HDACs 1, 2, and 3 is that each enzyme forms the catalytic subunit of a number of discrete gene-regulatory complexes. Thus, multiple complexes can contain the same HDAC enzyme yet have distinct functions and biological roles. Furthermore, even if we are successful in designing isoform-specific inhibitors, these would still target multiple complexes and hence multiple biological activities. However, as we learn more about these complexes, there emerges the possibility of designing novel HDAC inhibitors that target individual complexes. In this review, we explore our knowledge of the assembly of class I HDAC

[1]Henry Wellcome Laboratories of Structural Biology, Department of Molecular and Cell Biology, University of Leicester, Lancaster Road, Leicester LE1 9HN, UK
[2]These authors contributed equally to this work.

*Correspondence:
john.schwabe@le.ac.uk
(John W.R. Schwabe).

complexes and potential strategies towards designing and developing complex-specific HDAC inhibitors.

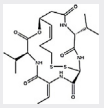
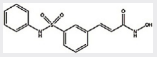
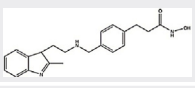
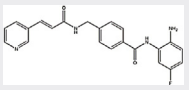
Current HDAC Inhibitors

The major clinical application of HDAC inhibitors has been in the treatment of cancer, where they cause terminal differentiation and apoptosis of cancer cells. Class I HDACs are overexpressed in many different cancers including gastric, breast, colorectal, prostate, and liver cancer, as well as Hodgkin's lymphoma [13]. The first HDAC inhibitor drug vorinostat (SAHA) was licensed by the US FDA in 2006 for the treatment of cutaneous T cell lymphoma [8,14]. Four further drugs have also been licensed for other haematological malignancies [7,15–17] (Table 1) and another 138 HDAC inhibitors are in clinical trials (http://clinicaltrials.gov). While the current HDAC inhibitors are effective against various haematological malignancies, they are less effective against solid tumours [18]. HDACs have also been targeted for the treatment of other diseases including, Alzheimer's disease [1], muscular dystrophy [2], Friedreich's ataxia [3], heart disease [4], and HIV infection [5]. Beyond the treatment of cancer, givinostat has been granted orphan drug status for the treatment of polycythaemia vera and Duchenne and Becker muscular dystrophies. HDAC inhibitors have also been shown to have synergistic effects when used in combination with proteasome inhibitors [19] and DNA methyltransferase inhibitors [20].

Current HDAC inhibitors act by targeting the active site of the enzyme and can be grouped into four main categories: hydroxamic acids, cyclic peptides, benzamides, and aliphatic acids. Significant challenges remain in the development of truly isoform-specific HDAC inhibitors [21]. The benzamide class of HDAC inhibitors show some selectivity towards the class I enzymes [22,23]. Chidamide is one such benzamide inhibitor that has been licenced for clinical use [7]. Another HDAC inhibitor that shows some selectivity is the compound RGFP966, developed by Repligen Corporation, which preferentially targets HDAC3 over HDAC1 and HDAC2 [24].

Importantly, the benzamide inhibitors have binding kinetics that differ markedly from those of hydroxamic acid inhibitors such as SAHA and TSA (trichostatin A). Both association and dissociation rates are much slower, resulting in much longer residence times. The slow binding kinetics can be explained by the need for structural rearrangements of the active site to allow benzamide binding [25].

Table 1. Current HDAC inhibitors licenced for clinical use.

HDAC inhibitor	Structure	HDAC inhibitor type	Indication	Licensing body	Year licensed	Refs
Vorinostat (Zolinza)		Hydroxamic acid	Cutaneous T cell lymphoma	FDA	2006	[14]
Romidepsin (Isodax)		Macrocyclic peptide	Cutaneous T cell lymphoma	FDA	2009	[15]
Belinostat (Beleodaq)		Hydroxamic acid	Peripheral T cell lymphoma	FDA	2014	[16]
Panbinostat (Farydak)		Hydroxamic acid	Multiple myeloma	FDA/EMA	2015	[6,17]
Chidamide (Epidaza)		Benzamide	Peripheral T cell lymphoma	Chinese FDA	2015	[7]

EMA, European Medicines Agency; (US) FDA, Food and Drugs Administration.