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Commentary

HDAC inhibitors: Clinical update and mechanism-based potential

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ABSTRACT

Recently, the role of transcriptional repression through epigenetic modulation in carcinogenesis has been clinically validated with several inhibitors of histone deacetylases and DNA methyltransferases. It has long been recognized that epigenetic alterations of tumor suppressor genes was one of the contributing factors in carcinogenesis. Inhibitors of histone deacetylase (HDAC) de-repress genes that subsequently result in growth inhibition, differentiation and apoptosis of cancer cells. Vorinostat (SAHA), romidepsin (depsipeptide, FK-228), belinostat (PXD101) and LAQ824/LBH589 have demonstrated therapeutic benefit as monotherapy in cutaneous T-cell lymphoma (CTCL) and have also demonstrated some therapeutic benefit in other malignancies. The approval of the HDAC inhibitor vorinostat (Zolinza™) was based on the inherent sensitivity of this type of lymphoma to alterations in acetylation patterns that resulted in the induction of repressed apoptotic pathways. However, the full potential of these inhibitors (epigenetic modulators) is still on the horizon, as the true breadth of their utility as anti-cancer agents will be determined by the careful analysis of gene expression changes generated by these inhibitors and then combined with conventional chemotherapy to synergistically improve response and toxicity for an overall enhanced therapeutic benefit to the patient. The question that must be considered is whether the current HDACIs are being utilized to their fullest potential in clinical trials based on their mechanism-based alterations in disease processes.

1. Histone deacetylase inhibitors

The role of gene regulation by physical alterations of either DNA or the structural components of chromatin has recently been highlighted as a major process in neoplastic transformation and maintenance of the malignant phenotype. The discovery that chromatin contains a dynamic group of nuclear proteins that regulate transcription of many genes and especially some tumor suppressor genes came about with the discovery that the histone deacetylases (HDACs) were the target for a potent natural product that induced differentiation of neoplastic cells [1]. Several other compounds were initially discovered as inducers of differentiation and as mimetics of growth factor pathways (TGFβ) that were subsequently shown to have a mechanism of action that involved inhibition of histone deacetylase enzymes [2–7]. Recently, there have been several excellent reviews of the HDAC field both preclinical characterization of histone deacetylase inhibitors (HDACIs) and clinical development of HDACIs [8–11]. A brief overview of the mechanism of HDACIs and their road to the clinic is warranted here.

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Regulation of gene transcription occurs by various mechanisms including (1) DNA methylation, (2) post-translational histone modifications (primarily acetylation but also includes methylation, phosphorylation, poly-ADP-ribosylation, ubiquitinylation, sumoylation, carbonylation and glycosylation), and (3) RNA-associated silencing [8,10]. It has long been recognized that neoplastic cells exhibit aberrant gene expression; therefore, strategies have been investigated to correct these genetic perturbations through pharmacological manipulation of the epigenome, namely, modulation of DNA methylation and histone acetylation. As the most promising clinical data have emerged from modulation of histone acetylation the focus here will be on this unique balance that maintains nucleosomal DNA in either an active (open, acetylated) or inactive (closed, deacetylated) form. This balance is controlled by the reciprocal activities of the acetylating enzymes, histone acetyltransferases (HATs) and deacetylating enzymes, histone deacetylases (HDACs). Epigenetic alterations are crucial to the onset and progression of cancer, and HDACIs have been demonstrated to reverse some of the aberrant epigenetic states associated with cancer through induction of hyperacetylation of nucleosomal histones resulting in expression of repressed genes that produce growth arrest, terminal differentiation, and/or apoptosis in carcinoma cells.

HDACs were first identified as the target of a natural product, trapoxin, which caused differentiation of cancer cells and was used as an affinity ligand to pull out the target, HDAC1, from the cell lysate [1]. Other various differentiation assays or promoter/reporter construct assays for the TGFβ pathway identified other compounds whose mechanism of action was later elucidated to be inhibition of HDACs. The biological activity of compounds such as the spiruchostatins A and B [6], diheteropeptin [7,12], scriptaid, and A-161906 were all discovered using these assays and subsequently, the mechanism of action of all these compounds was determined to be inhibition of HDACs. These observations emphasize the prominent role of HDACs in the signaling pathways regulated by TGFβ and how modulation of chromatin structure can produce desired pharmacological effects.

1.1. *Deacetylase enzymes—the HDAC family*

The HDACs can be divided into two families, (1) the Zn^{+2}-dependent HDAC family composed of class I (HDACs 1, 2, 3 and 8), class II a/b (HDACs 4, 5, 6, 7, 9 and 10), and class IV (HDAC 11) and (2) Zn^{+2}-independent NAD-dependent class III SIRT enzymes (Table 1). The class I HDACs, apparently the ''true'' histone deacetylases, are localized to the nucleus of cells. The classes II a/b deacetylases have both histones and non-histone proteins as substrates and are primarily localized to the cytoplasm but are known to shuttle in and out of the nucleus through association with 14-3-3 proteins. The class II enzymes are characterized by either a large N-terminal domain or a second catalytic domain (e.g., HDAC 6 which contains both a histone and a tubulin deacetylase catalytic domain). The class III SIRTs are NAD^{+}-dependent deacetylases with non-histone proteins as substrates (in mammalian cells) and have been linked to regulation of caloric utilization of cells (only in yeast are the SIR proteins known to be histone deacetylases) [8]. HDACs do not function independently but rather in concert with multi-protein complexes (e.g., NCoR, SMRT, MEF, MeCP2, Sin3A, etc. [13]) that are recruited to specific regions of the genome that in turn generate the unique spectrum of expressed and silenced genes that are characteristic of the expression profile(s) responsible for the malignant phenotype of cancer cells.

Table 1 – HDACs

HDAC	~MW[a] human	~MW[a] murine	AAs[b] human	AAs[b] murine	%Similarity to human (nucleic acid/amino acid)
Zn^{+2}-dependent					
Class I					
1	55,103	55,076	482	482	90.8/99.4[c]
2	55,364	55,331	488	488	91.1/98.6[c]
3	48,848	48,821	428	428	92.5/99.6[c]
8	41,758	41,772	377	377	90.9/96.3[c]
Class IIA					
4	119,070	118,562	1084	1076	86.3/94.2
5	121,992	120,941	1122	1113	91.1/95.6
7	102,927	101,286	952	938	86.8/90.3
9	111,297	65,631	1011	588	90.394.8
Class IIb					
6	131,431	125,703	1215	1149	81.1/78.7[d]
10	71,445	72,111	669	666	78.1/76.4[d]
Class IV					
11	39,183	39,157	347	347	87.3/91.9

[a] Estimated molecular weight based on amino acid sequence, may be different than observed molecular weight on SDS-PAGE gels.
[b] AAs—number of amino acids in the open reading frame.
[c] Class of HDACs with the greatest similarity between murine and human species.
[d] Class of HDACs with the greatest difference between human and murine species.