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Histone Deacetylase Inhibitors (HDACIs): Untapped Therapeutic Potential in Cancer Treatment

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Introduction

Epigenetics is the study of changes in phenotype without the corresponding changes in genotype, and historically it includes all the "inexplicable" changes in heritability of phenotype from a single cell to an organism [1]. More recently, a branch of epigenetics examines non-genetic tumor genesis and progression. This branch stems from the notion that not all cancers are generated by genetic alterations, rather epigenetic changes that lead to silencing of certain genes, while allowing transcription machinery access to other genes, resulting in divergence from the parent cell line, loss of cell regulation, and cell immortalization [2-8].

A group of key players in transcriptional regulation are histone acetyltransferases (HATs) and histone deacetylases (HDACs) (Figure 1). These two classes of enzymes work in opposing direction by either catalyzing the transfer of acetyl groups from acetyl coenzyme A (HATs) or by removing acetyl groups (HDACs) from lysine residues of histone tails [2,3,5-11]. Besides acetylation, histones are capable of being methylated, phosphorylated, ubiquinated, sumoylated, poly-ADP ribosylated, carbonylated and glycosylated [2,12].

Mechanisms of action of HDACIs

In eukaryotic cells, DNA wraps around histone proteins, creating complexes called nucleosomes that are packaged inside the nucleus. How tightly the negatively charged DNA is wrapped around the histones partly depends on the acetylation state on histone lysine residues, particularly on histones H3 and H4 [1,8,13]. HATs add an acetyl group from acetyl coenzyme A to the lysine ε-amino group, which reduces the positive charge on the histones. When histones are acetylated, the DNA is more loosely wrapped, thus leading to gene activation. HDACs, on the other hand, cause deacetylation, resulting in positively charged histones that are more tightly wrapped by DNA [1,6,8]. Histone deacetylation is correlated with gene repression. The mechanism of action of HDACI in cancer therapy seems to be multifaceted. HDACIs are thought to reduce the deacetylation levels of histone proteins that are overexpressed in cancerous cells. HAT/HDAC enzymes are capable of regulating both histone and non-histone proteins; therefore, HDACIs are able to exert their therapeutic activity through both histone and non-histone pathways [2,3,7,8,10-12,14-20].

Epigenetic therapy

On the market: Although HDACIs have been investigated against many different types of cancers in both *in vitro* and *in vivo* systems, the clinical understanding and applications of these therapeutic agents have been limited. More success was noted with liquid tumors but there is a shift towards examining the potential use of HDACIs in solid tumors [3,6,8,10,11,13,14,16,21-23]. Fewer studies in solid tumors have reached the clinical trial phase of development (www.ClinicalTrials.gov). On the market, only two HDACIs have been approved by the FDA, namely vorinostat (Zolinza, approved 2006) and romidepsin (Istodax, approved 2009) for the treatment of cutaneous T-cell lymphoma (CTCL) [3,10,11]. Both of these HDACIs bind to the zinc-finger motif of histone deacetylases, resulting in the acetylation of histones. Vorinostat is considered a pan-inhibitor while romidepsin inhibits HDAC Classes I and II, with significantly increased affinity [2,9].

In clinical trials: Several HDACIs, including valproic acid (an antiepileptic drug), vorinostat, entinostat, and panobinostat, are presently examined in clinical trials for various types of cancers [24]. In a Phase I clinical trial study, the bioavailability of vorinostat ranged from approximately 35% to 52% in patients with advanced cancers [25]. Several clinical trials showed the oral bioavailability of vorinostat and belinostat (PXD101) to be about 33% [26,27]. Valproic acid shows good oral bioavailability [28]. It is currently tested for the treatment of breast, thyroid, lung, ovarian, bladder, head and neck, pancreatic, brain and leukemia cancers. Panobinostat (LBH589) is an HDACI that is similar to vorinostat in its mechanism of action but was found to be more potent [3,5,8,9,11]. It is being tested against Hodgkin's lymphoma and cutaneous T-cell lymphoma as well as other types of cancers [24]. Additionally, there are a number of studies examining the enhanced therapeutic efficacy of using HDACIs with conventional cancer treatment strategies. Table 1 shows examples of some current clinical trials involving HDACIs in breast cancers, as found from www.ClinicalTrials.gov [24].

Challenges and future outlook: The clinical use of HDACIs for cancer therapy is limited. HDACIs have a broad range of applications and can reverse the aberrant epigenetic changes in cancers. The mechanisms by which HDACIs exert their effects are not completely

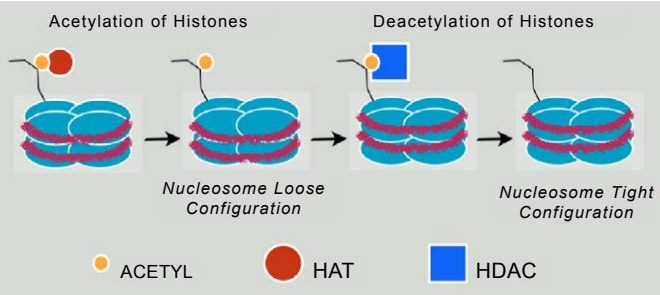

Figure 1: The role of histone acetyltransferases (HATs) and deacetylase (HDACs) in nucleosome configuration.

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HDACI	Study	Phase	Identifier Number
Entinostat (SNDX-275)	Azacitidine and Entinostat in Treating Patients With Advanced Breast Cancer	II	NCT01349959
Entinostat	Exemestane With or Without Entinostat in Treating Postmenopausal Patients With Recurrent Hormone Receptor-Positive Breast Cancer That is Locally Advanced or Metastatic	III	NCT02115282
Entinostat	Entinostat, Lapatinib Ditosylate and Trastuzumab in Patients With Locally Recurrent or Distant Relapsed Metastatic Breast Cancer Previously Treated With Trastuzumab Only	I	NCT01434303
Panobinostat (LBH589)	Re-expression of Estrogen Receptor (ER) in Triple Negative Breast Cancers	I/II	NCT01194908
Vorinostat	Vorinostat in Treating Patients With Stage IV Breast Cancer Receiving Hormone Therapy	Pilot	NCT01720602
Vorinostat	Vorinostat, Paclitaxel, and Bevacizumab in Treating Patients With Metastatic Breast Cancer and/or Breast Cancer That Has Recurred in the Chest Wall and Cannot be Removed by Surgery	I/II	NCT00368875
Vorinostat	Ixabepilone and Vorinostat in Treating Patients With Metastatic Breast Cancer	I	NCT01084057

Table 1: Examples of some clinical trials of combination therapies using HDACIs in breast cancers (obtained from www.ClinicalTrials.gov in May 2014) [24].

understood. Interestingly, HDACIs have been shown to sensitize tumors to their respective therapies [14-16,22,23,29]. Potentially, this approach may lead to improving the treatment of therapy resistant cancers. Studies have shown that HDACIs interact with both histone and non-histone proteins [2,3,7,8,10-12,14-20]. These therapeutic agents cause no or little damage to normal cells [5,19], which is highly desired. Additionally, a major advantage to using HDACIs is that at therapeutic doses, they do not show any major side effects [30]. More recent efforts are focused on examining the enhanced efficacy of HDACIs in combination therapy with conventional cancer treatment approaches [3,8,10,11,15,16,20-23,29]. Additionally, promising results have been shown for using HDACIs as chemopreventive agents [1,3,5,13,15,31-35]. Although additional studies are warranted, epigenetic therapy using HDACIs appears as a novel and effective treatment approach for cancers.

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