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

Dario Tomas and Duc P Do*

Department of Pharmaceutical Sciences, College of Pharmacy, Chicago State University, Chicago, IL, USA

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, ubiquinatored, 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 understood. Therefore, HDACIs are currently not being used for the treatment of many cancers. The mechanisms of action of HDACIs and the role of their effects are still being investigated. While HDACIs have shown promise in clinical trials, more research is needed to fully understand their potential for cancer treatment.

*Corresponding author: Duc P Do, College of Pharmacy, Chicago State University, 9501 S King Drive, Douglas Hall 206, Chicago, IL 60628, USA, Tel: 773-821-2597, Fax: 773-821-2595, E-mail: ddo@csu.edu

Received May 24, 2014; Accepted May 25, 2014; Published May 31, 2014


Copyright: © 2014 Tomas D, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
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 HDACs interact with both histone and non-histone proteins [2,3,7,8,10-12,14-20]. These therapeutic mechanisms of action: Emerging insights. Pharmacol Ther. 124: 30-39.


Table 1: Examples of some clinical trials of combination therapies using HDACIs in breast cancers (obtained from www.ClinicalTrials.gov in May 2014) [24].
and signaling events triggered by the isothiocyanates, sulforaphane and phenethyl isothiocyanate, in multiple myeloma. Haematologica 96: 1170-1179.


