EXPERIMENTAL CELL RESEARCH 318 (2012) 1229–1244

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Review Article

HDAC modulation and cell death in the clinic

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ARTICLE INFORMATION

Article Chronology:
Received 3 December 2011
Revised version received
26 January 2012
Accepted 27 January 2012
Available online 3 February 2012

Keywords:
Histone deacetylases
Histone deacetylase inhibitors
Cancer
Clinical trials

ABSTRACT

Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are two opposing classes of enzymes, which finely regulate the balance of histone acetylation affecting chromatin packaging and gene expression. Imbalanced acetylation has been associated with carcinogenesis and cancer progression. In contrast to genetic mutations, epigenetic changes are potentially reversible. This implies that epigenetic alterations are amenable to pharmacological interventions. Accordingly, some epigenetic-based drugs (epidrugs) have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for cancer treatment. Here, we focus on the biological features of HDAC inhibitors (HDACis), analyzing the mechanism(s) of action and their current use in clinical practice.

Contents

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doi:10.1016/j.yexcr.2012.01.025

Introduction

The most common mechanisms of epigenetic gene control involve modifications of DNA and/or histones, such as DNA methylation and the covalent modifications of core histones (i.e. acetylation, methylation, phosphorylation, ubiquitination, etc.). Under physiological conditions, chromatin acetylation is the result of the balanced activities of "writers" (histone acetyltransferases, HATs) and "erasers" (histone deacetylases, HDACs) enzymes.

HAT enzymes transfer an acetyl group from acetyl-CoA to the ε amino groups of lysine residues of the N-terminal regions, reducing interactions between adjacent nucleosomes. In contrast, re-establishment of the positive charge in the amino-terminal tails of core histones catalyzed by HDACs tightens the interaction between histones and DNA, thus blocking binding sites on promoters and inhibiting gene transcription. The "reading process" of ε-N-acetyl lysine (Kac) marks is performed by bromodomain-containing (BRD) proteins. These "readers" are a family of evolutionarily conserved protein-interaction modules, characterized by a four-helix bundle structure [1].

HATs and HDACs can be altered both for expression and function, establishing a dramatic pathological phenotype causing or contributing to diseases such as cancer, auto-immune disorders and neurological pathologies [2–4]. Thus, HDACs represent promising therapeutic targets given that HDACis might reverse aberrant epigenetic states associated with cancer [5,6].

Histone deacetylases

The family of HDACs comprises four classes: class I, II and IV are zinc-dependent amidohydrolases, whereas class III (the so-called Sirtuins) requires NAD+ for the deacetylation reaction. Class I consists of HDAC1, 2, 3 and 8 and is homologous to the reduced potassium dependency 3 (RPD3) yeast enzyme. This class is predominantly located in the nucleus [7]. Class II shows homology to the yeast protein hda1 [8]. It can be subdivided into class IIa (HDAC4, 5, 7 and 9) and IIb (HDAC6 and 10). The class II subtypes shuttle between cytoplasm and nucleus in response to external stimuli [9]. The only member of class IV is HDAC11 [10] (Fig. 1).

HDACs catalyze the removal of an acetyl group from the ε-amino group of lysine side chains of the core nucleosomal histones (H2A, H2B, H3, and H4), thereby reconstituting the positive charge on the lysine. The active site of HDACs consists of a cylindrical pocket, covered by hydrophobic and aromatic amino acids, where the lysine residue fits when deacetylation takes place. During deacetylation a zinc ion locates near the bottom of the cylindrical pocket and is coordinated by amino acids and a single water molecule, already activated by an Asp-His change relay system [11]. The members of class III HDACs are homologous to the *Saccharomyces cerevisiae* silencing protein Sir2 [12]. This class consists of seven NAD-dependent HDAC enzymes (SIRT1–7). Sirtuins seem to be involved in gene silencing, aging, and energy metabolism. Interestingly, SIRT1, 6 and 7 are localized in the nucleus; SIRT3, 4 and 5 in the mitochondria; and SIRT2 in the cytoplasm [12] (Fig. 1).

Role of HDACs in disease

Aberrant HDAC expression

HDACs have numerous histone and non-histone substrates involved in crucial cellular processes both in normal development and in cancer [2]. During the multistep process of tumorigenesis, individual HDAC family members contribute to the hallmarks of cancer by altering differentiation and apoptosis as well as contributing to proliferation, angiogenesis and metastasis. Strikingly, numerous clinical studies in cancer patients have established that the most prevalent alteration of HDAC function is overexpression. For example, HDAC1 and 2 are increased in gastric [13,14] and prostate cancer [15]. Interestingly, the HDAC2 gene frameshift mutation is the only genetic alteration identified in HDAC genes, leading to the loss of HDAC2 protein and activity in human microsatellite instability-high (MSI-H) endometrial and MSI colon cancer cell lines [16].

HDAC1, 2, 3 as well as HDAC6, have been implicated in modulation of estrogen-signaling pathways in human breast cancer [17,18]. Both diffuse large B-cell lymphomas (DLBCL) and peripheral T-cell lymphomas exhibit HDAC1, 2 and 6 overexpression [19], whereas classical Hodgkin's lymphomas display increased HDAC1, 2 and 3 levels [20]. In ovarian cancers, high levels of class I HDACs have been reported [21]. Elevated levels of HDAC1, 2, 3, 7 and 8 have been described in pancreatic ductal adenocarcinoma [22,23]. High expression of HDAC1 and 2 correlates with reduced patient survival in colorectal carcinomas [24,25], whereas high HDAC8 levels correlate with metastasizing and advanced stage disease with poor prognosis in neuroblastoma [26].

Only recently, deregulated miRNA expression has been attributed to aberrant HDAC expression in tumors. A miRNA targeting HDAC1, miR-449, which induces cell cycle arrest and apoptosis in prostate cancer cells has been identified [27]. In hepatocellular carcinoma, low levels of miR-22, which targets HDAC4, have been correlated with worse prognosis [28]. In Waldenstrom myeloma, the upregulation of miR-9* results in HDAC4 and 5 downmodulation, leading to increased histone-H3 and -H4 acetylation [29].

Sirtuins can also be deregulated in pathological systems. For instance, SIRT1 is overexpressed in lung cancer [30], prostate cancer [31] and leukemia [32]. On the contrary, SIRT1 has been reported to be downregulated in colon tumors [33].