Histone Deacetylase Inhibitors: A Hope for Cancer Patients

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Abstract Cancer is a disease caused by genetic and genomic alterations such as amplifications, translocations, deletions or point mutations. Also, cancer development is caused by epigenetic changes due to modifications such as post-translational histone acetylations that can alter DNA and chromatin structures without alterations in the DNA sequence. Histones are the primary protein component of chromatin. It plays an important role in the interactions between the nucleosomes and within the nucleosome itself. Histone deacetylase enzyme is found in the nucleus of the different body cells and plays a vital role in remodeling of chromatin structure and controlling gene expression. Also, it was found to play an important role in the development of cancer. Histone deacetylase inhibitors which are used mainly in psychiatry and neurology may represent a new hope for cancer therapy. They act by various mechanisms which may help in prevention and treatment of cancer. Their combination with various lines of cancer therapy may represent a new hope for cancer patients.

Keywords: histone deacetylase, hope, cancer, patients

1. Introduction

Histone deacetylase inhibitors (HDAC inhibitors, HDIs) are a group of compounds that interfere with the function of histone deacetylase enzyme. HDIs have been in common use in psychiatry and neurology as mood stabilizers and anti-epileptics [1]. Recent studies have investigated them as possible treatments for cancers, parasitic infections and inflammatory diseases [2].

Normally, histone acetyl transferases (HAT) acetylate the lysine residues in core histones of DNA leading to a less compact and more transcriptionally active chromatin [3]. On the contrary, histone deacetylases (HDAC) remove the acetyl groups from the lysine residues leading to formation of a condensed and transcriptionally silenced chromatin. Reversible modification of the terminal tails of core histones represents the major epigenetic mechanism for remodeling higher-order chromatin structure and controlling gene expression. HDAC inhibitors (HDI) block this action resulting in hyperacetylation of histones, thereby affecting gene expression [4].

Histone deacetylase inhibitors are cytostatic agents that inhibit the proliferation of tumor cells by inducing arrest of the cell cycle, differentiation and/or apoptosis. They exert their anti-tumor effects through induction of expression of tumor suppressor genes, through modulating that the acetylation/deactylation of histones and/or non-histone proteins such as transcription factors [5].Histone acetylation and deacetylation play important roles in the modulation of chromatin topology and the regulation of gene transcription. Inhibition of histone deacetylaseleads to accumulation of hyperacetylated nucleosome core histones in most regions of chromatin but affects the expression of only a small subset of genes, leading to transcriptional activation of some genes, but repression of another genes. Non-histone proteins such as transcription factors are also targets for acetylation with varying functional effects. Acetylation enhances the activity of some transcription factors such as the tumor suppressor p53 and the erythroid differentiation factor GATA-1 but may repress transcriptional activity of others including T cell factor and the co-activator ACTR. Recent studies have shown that the estrogen receptor alpha (ERalpha) can be hyperacetylated in response to histone deacetylase inhibition, suppressing ligand sensitivity and regulating transcriptional activation by histone deacetylase inhibitors [6]. Acetylation may play an important regulatory role in diverse nuclear receptor signaling functions. A number of structurally diverse histone deacetylase inhibitors have shown potent antitumor efficacy. Several compounds are currently in early phase clinical development as potential treatments for solid and hematological cancers both as monotherapy and in combination with cytotoxics and differentiation agents [7,8].

HDIs should not be considered to act only on HDACs but also act onnonhistone transcription factors and transcriptional co-regulators. HDIs can alter the degree of acetylation nonhistone effector molecules and, therefore, increase or repress the transcription of genes by this mechanism [9].

2. Classification of HDAC

Histone deacetylasescan be classified into four groups; class I which includes HDAC1, -2, -3 and -8 are related to

yeast RPD3 gene; class II which includes HDAC4, -5, -6, -7, -9 and -10 are related to yeast Hda1 gene; class III which are related to the Sir2 gene and include SIRT1-7 and class IV which contains only HDAC11 and has features of both Class I and II [10].

3. Classification of HDI

HDIs usually act on Class I and Class II HDACs by binding to the zinc-containing catalytic domain of the HDACs [11]. These HDIs include hydroxamic acids (e.g. trichostatin A), cyclic tetrapeptides (e.g.trapoxin B), depsipeptides, benzamides, electrophilic ketones, andthe aliphatic acid compounds (e.g. phenylbutyrate and valproic acid).Second-generation HDIs include the hydroxamic acids vorinostat, belinostat, LAQ824, and panobinostat and the benzamides (e.g. entinostat, mocetinostat) [12]. Also, nicotinamide, dihydrocoumarin, naphthopyranone and 2-hydroxynaphaldehydes are derivatives of NAD which have the ability to inhibit Class III HDACs [13].

4. Clinical Uses of HDIs

HDIs have a long history of use in psychiatry and neurology as mood stabilizers and anti-epileptics (e.g. valproic acid).Recently, HDIs are being studied as a mitigator for neurodegenerative diseases such as Alzheimer's disease and Huntington's disease [14]. Enhancement of memory formation is increased in mice given the HDIs sodium butyrate [15]. It was found that some cognitive deficits were restored in transgenic mice that have a model of Alzheimer's disease by nicotinamide, a competitive HDI of class III sirtuins [16].

The HDAC inhibitors are under investigation for treatment of human immunodeficiency virus (HIV). It was reported that HDIs can flush HIV from the reservoirs. After that, a separate vaccination to eliminate HIV allows the immune system to neutralize the virus. Givinostat is also under investigations for treatment of polycythemia vera, thrombocythemia and myelofibrosis. Also, HDIs are being studied for protection of the cardiac muscles in acute myocardial infarction [17].

5. HDIs and Cancer

The results of several studies reported that HDIs may have potent anticancer effect [8,18,19]. The exact mechanisms of this effect are unclear but the epigenetic pathways were proposed [20]. HDIs can induce p21 expression, a regulator of p53's tumor suppressor activity. HDACs are involved in the pathway by which the retinoblastoma protein (pRb) suppresses cell proliferation [21]. The pRb protein is a part of a complex that attracts HDACs to the chromatin so that it will deacetylate histones [22]. HDAC1 negatively regulates the cardiovascular transcription factor Kruppel-like factor 5 through direct interaction [23]. Estrogen is well-established as a mitogenic factor implicated in the tumorigenesis and progression of breast cancer via its binding to the estrogen receptor alpha (ERα). Recent data indicated that

chromatin inactivation mediated by HDAC and DNA methylation is a critical component of ERα silencing in human breast cancer cells. HDIs were licenced for treatment of cutaneous T cell lymphoma and multiple myeloma [24].

Recently, Zhu et al. [25] reported that trichostatin A (TSA) and sodium valproate (VPA), which are HDIs, significantly repressed the proliferation of chondrosarcoma cells in a concentration-dependent manner. TSA arrested the cell cycle in G2/M phase and VPA arrested the cell cycle in G1 phase. The tumor growth was markedly suppressed in mice treated with both TSA and VPA. Moreover, Pang et al. [26] found that vorinostat, an HDAC inhibitor, had a potent anticancer effect through affecting chromatin interactions at MYC/PVT1 locus. Pompo et al. [27] reported that novel HDIs induced growth arrest, apoptosis and differentiation in sarcoma cancer stem cells. When tested in human osteosarcoma, rhabdomyosarcoma, and Ewing's sarcoma stem cells, the new HDIs increased acetyl-H3 and acetyl-tubulin levels and inhibited cancer stem cells growth by apoptosis induction. At non-toxic doses, they promoted osteogenic differentiation.

6. Combination of HDIs with Other Anticancer Agents

As single agents, treatment with HDIs has demonstrated limited clinical benefit for patients with solid tumors, prompting the investigation of novel treatment combinations with other anti-cancer agents [28]. The acceptable toxicity profile associated with HDAC inhibitor treatment permits a broad integration into currently approved chemotherapy regimens [29]. One of these combinations is with DNA damage-inducing therapies. HDIs synergistically enhance the growth inhibition and apoptosis of DNA-damaging agents and irradiation. This occurs through a HDAC inhibitor-mediated increase in chromatin accessibility and downregulation of DNA repair [28]. Also, HDIs were combined to topoisomerase inhibitors. Vorinostat, which is one of HDIs, was found to enhance the effect of topetecan and SN-38 (the metabolite of ironotecan) in small-cell lung cancer and glioblastoma cells in vitro [30,31]. The cytotoxic effects of the topoisomerase I inhibitor karenitecin were enhanced by the combination with valproic acid [32]. Moreover, the combination between valproic acid and methotrexate had a beneficial effect on transplantable tumor model [8]. Raha et al. [33] reported that combined histone deacetylase inhibition and tamoxifen induced apoptosis in tamoxifen-resistant breast cancer models by reversing Bcl-2 overexpression.

HDIs combination with radiotherapy has been shown in various cancer cell lines including breast, prostate, lung, colon and cervical cancer. Preclinical studies suggested that the most effective treatment schedule requires pretreatment of cancer cells with the HDIs followed by ionizing radiation [34]. When administered before radiotherapy, treatment of colorectal xenograft models with vorinostat resulted in significantly reduced tumor volume compared with treatment with radiotherapy alone [35].

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