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Histone deacetylases inhibitors (HDACis) as novel therapeutic application in various clinical diseases

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ABSTRACT

Accumulating evidence suggests that histone hypoacetylation which is partly mediated by histone deacetylase (HDAC), plays a causative role in the etiology of various clinical disorders such as cancer and central nervous diseases. HDAC inhibitors (HDACis) are natural or synthetic small molecules that can inhibit the activities of HDACs and restore or increase the level of histone acetylation, thus may represent the potential approach to treating a number of clinical disorders. This manuscript reviewed the progress of the most recent experimental application of HDACis as novel potential drugs or agents in a large number of clinical disorders including various brain disorders including neurodegenerative and neurodevelopmental cognitive disorders and psychiatric diseases like depression, anxiety, fear and schizophrenia, and cancer, endometriosis and cell reprogramming in somatic cell nuclear transfer in human and animal models of disease, and concluded that HDACis as potential novel therapeutic agents could be used alone or in adjunct to other pharmacological agents in various clinical diseases.

Contents

Abbreviations: HAT, histone acetyltransferases; HSP70, heat shock protein 70; GDNF, glial cell line-derived neurotrophic factor; BDNF, brain derived neurotrophic factor; SMN, survival motor neuron; FMR, fragile X mental retardation; iNOS, inducible nitric oxide synthase; MMP-9, matrix metalloproteinase-9; MIP-1, macrophage inflammatory protein-1; MCP-1, monocyte chemoattractant protein-1; IGFBP-3, insulin-like growth factors binding protein-3; PCNA, proliferating cell nuclear antigen; FADD, fas associated death domain; TRADD, tnf receptor associated death domain; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; SA-β-Gal, senescence associated-β-galactosidase; VEGF, vascular endothelial growth factor; TSA, trichostatin A; VPA, valproic acid; SAHA, suberoylanilide hydroxamic acid.

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1. Introduction of HDACi

Recent findings implicate epigenetic modifications of non-histone protein and histone, especially histone hypoacetylation, which plays a causative role in the etiology of various clinical disorders (Abel and Zukin, 2008). Histone deacetylases (HDACs), a family of 18 molecules divided in four sub-classes (Group I, IIa, IIb, III and IV) defined according to structural similarities (Hildmann et al., 2007; Yang and Seto, 2008; Colussi et al., 2010), play functional role ranging from modification of histone and non-histone protein, regulation of chromatin structure, repression or activation of gene expression and regulation of cell metabolism (Hildmann et al., 2007; Colussi et al., 2010). HDAC inhibitors (HDACis) are natural or synthetic small molecules that can inhibit the activities of HDACs and restore or increase the level of histone acetylation.

The currently available HDACis can be divided into four structural classes: the short chain fatty acids (e.g. sodium butyrate, phenylbutyrate, VPA), the hydroxamic acids (e.g. TSA and SAHA), the epoxyketones (e.g. trapoxin), and the benzamides (Fischer et al., 2010). The largest class of HDACi is the hydroxamic acids, among which TSA and SAHA are the most commonly used. However, a recent study reported that SAHA might inhibit class I HDACs more potently than class IIa HDACs (Kilgore and Fass, 2010). The most prominent members of the short fatty acid HDAC inhibitor class are sodium butyrate, VPA and phenylbutyrate. The founding member of the benzamides, MS-275 (Entinostat), is more selective than SAHA, TSA or the short fatty acid inhibitors (Hu et al., 2003; Khan et al., 2008). As described below, accumulating evidence supports that histone hypoacetylation is involved, thus HDACi currently being applied as potential drugs or agents stand-alone or combined with other agents in a large number of clinical disorders in human and animal models, including various brain disorders such as cognitive disorders including neurodegenerative and neurodevelopmental disorders and psychiatric diseases like depression, anxiety and schizophrenia, and cancer, endometriosis, cell reprogramming in somatic cell nuclear transfer (SCNT). These clinical diseases involve epigenetic modifications of a subset of interrelated genes and intervention by HDACis. Reduced histone acetylation is a final common endpoint in these clinical disorders, but could be restored or increased by HDACis via the inhibition of the activity of HDAC, regulating of the transcriptional state of the set of interrelated genes crucial to various clinical diseases such as neurodegenerative disorders, neurodevelopmental disorders, psychiatric disorders and cancer (Fig. 1). The specific mechanisms involved in these disorders will be detailed in the following section.

2. HDACi as a novel treatment for brain disorders

As described below, recent increasing body of evidence provides a strong case for the use of HDACis as a novel treatment for various brain disorders including neurodegenerative and neurodevelopmental cognitive disorders and psychiatric diseases like depression, anxiety and schizophrenia.

2.1. HDACi in cognitive disorders

Due to the effect of HDACis in the histone acetylation, an increasing number of researchers started to investigate the potential of HDACis in the improvement of various cognitive disorders. As described below, HDACis have been demonstrated to have an improvement or ameliorative effects in various neurodegenerative disorders including Stroke, Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), spinal muscular atrophy (SMA), and in various neurodevelopmental disorders like Rubinstein-Taybi syndrome (RTS) and Fragile X syndrome (FXS).

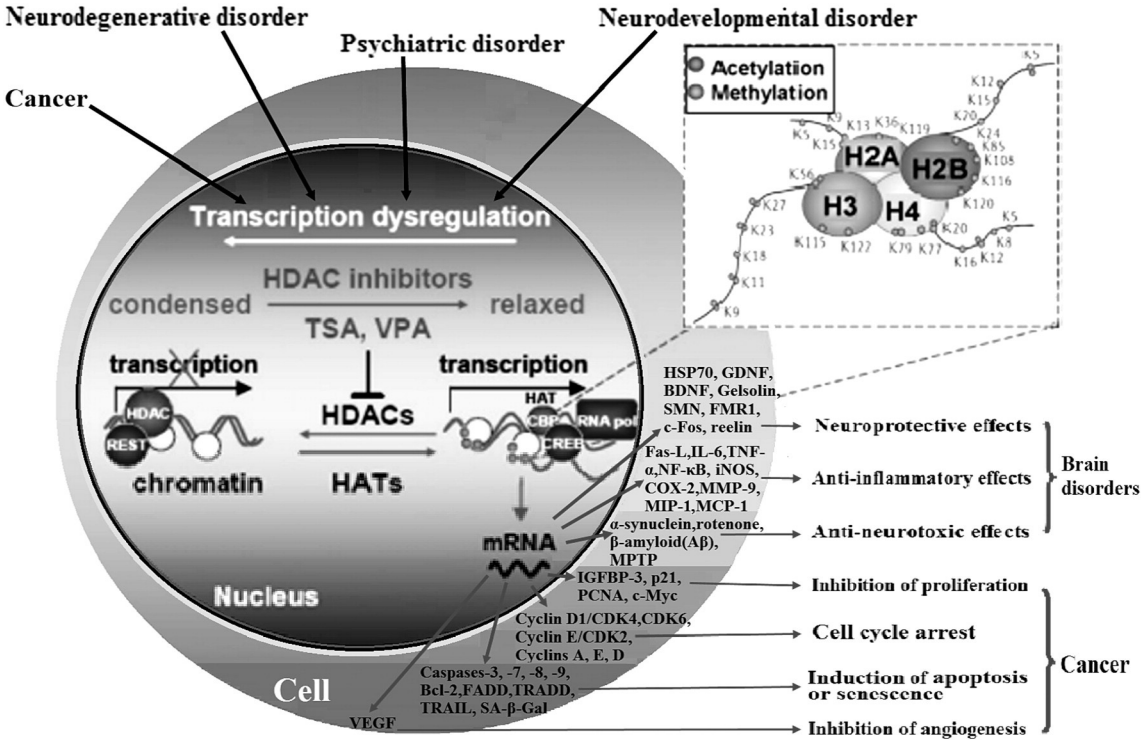

Fig. 1. Scheme showing that various clinical diseases involve epigenetic modifications of a subset of interrelated genes and intervention by HDACis. HDACis such as TSA and VPA inhibit the activity of HDACs, shifting the balance toward active transcription of the set of interrelated genes crucial to inflammation, neurotoxicity, neuroprotection involved in various barin disorders and to cell proliferation, senescence, apoptosis, cell cycle arrest and angiogenesis involved in cancer.
Adapted from Abel and Zukin (2008).