Am J Transl Res 2011;3(5):454-467
www.ajtr.org /ISSN:1943-8141/AJTR1109001

Review Article

Potential non-oncological applications of histone deacetylase inhibitors

Katherine Ververis[1,2], Tom C Karagiannis[1,2]

[1]Epigenomic Medicine, Baker IDI Heart and Diabetes Institute, The Alfred Medical Research and Education Precinct, Melbourne, Victoria, Australia; [2]Department of Pathology, The University of Melbourne, Parkville, Victoria, Australia

Received September 15, 2011; accepted October 2, 2011; Epub October 10, 2011; Published October 31, 2011

Abstract: Histone deacetylase inhibitors have emerged as a new class of anticancer therapeutic drugs. Their clinical utility in oncology stems from their intrinsic cytotoxic properties and combinatorial effects with other conventional cancer therapies. To date, the histone deacetylase inhibitors suberoylanilide hydroxamic acid (Vorinostat, Zolinza®) and depsipeptide (Romidepsin, Istodax®) have been approved by the US Food and Drug Administration for the treatment of refractory cutaneous T-cell lymphoma. Further, there are currently over 100 clinical trials involving the use of histone deacetylase inhibitors in a wide range of solid and hematological malignancies. The therapeutic potential of histone deacetylase inhibitors has also been investigated for numerous other diseases. For example, the cytotoxic properties of histone deacetylase inhibitors are currently being harnessed as a potential treatment for malaria, whereas the efficacy of these compounds for HIV relies on de-silencing latent virus. The anti-inflammatory properties of histone deacetylase inhibitors are the predominant mechanisms for other diseases, such as hepatitis, systemic lupus erythematosus and a wide range of neurodegenerative conditions. Additionally, histone deacetylase inhibitors have been shown to be efficacious in animal models of cardiac hypertrophy and asthma. Broad-spectrum histone deacetylase inhibitors are clinically available and have been used almost exclusively in preclinical systems to date. However, it is emerging that class- or isoform-specific compounds, which are becoming more readily available, may be more efficacious particularly for non-oncological applications. The aim of this review is to provide an overview of the effects and clinical potential of histone deacetylase inhibitors in various diseases. Apart from applications in oncology, the discussion is focused on the potential efficacy of histone deacetylase inhibitors for the treatment of neurodegenerative diseases, cardiac hypertrophy and asthma.

Keywords: Chromatin modifications, histone acetylation, histone deacetylase inhibitor, Trichostatin A, neurodegeneration, cardiac hypertrophy, asthma

Introduction

Chromatin is a dynamic structure that undergoes remodeling to facilitate metabolic processes including transcription, replication and repair [1]. These structural changes are mediated largely by DNA methylation and post-translational modifications of histones. Of the various post-translational modifications, histone acetylation is relatively well-characterized, with the first reports highlighting the importance of this modification in RNA synthesis dating to 1964 [2, 3]. Histone acetylation status is regulated by the opposing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs) [4]. HATs transfer the acetyl moiety of acetyl-coA resulting in acetylation of the ε-amino tails of lysine residues in histones [5]. This neutralizes the positive charge on histone tails, weakening the interaction between histones and negatively DNA, yielding a more open, transcriptionally permissive chromatin conformation [4, 5]. Conversely, HDACs remove acetyl groups from histones resulting in a more condensed, transcriptionally repressive chromatin conformation [6]. In addition to the core H2A, H2B, H3 and H4 histones, numerous non-histones proteins are targets for acetylation / deacetylation. These include key cell motility proteins (e.g. α-tubulin, cortactin), chaperones (e.g. HSP90, HSP70), DNA repair proteins (e.g. Ku70, Ku86) and transcription factors and co-regulators (e.g.

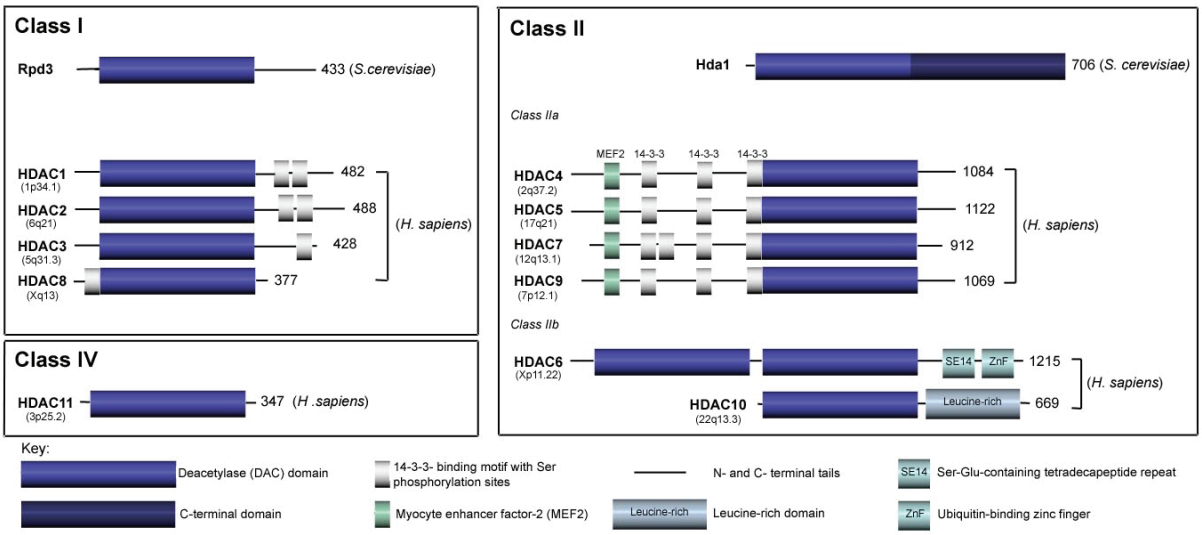

Figure 1. Schematic representation of the classical class I, II and IV mammalian histone deacetylases (HDACs). Class I enzymes are homologous with the yeast, reduced potassium dependency-3 (Rpd3) and consist of HDAC1, 2, 3 and 8. The class II HDACs are homologous to the yeast, histone deacetylase-1 (Hda1) and enzymes in this class are further subdivided into two sub-classes. Class IIa is comprised of HDAC4, 5, 7 and 9; class IIb consists of HDAC6 and 10. The HDACs have a conserved deacetylase (DAC) domain depicted as a blue cylinder with the C- and N-terminal tails represented as black lines. Green cylinders represent the myocyte enhancer factor-2 (MEF2)-binding domains and short grey cylinders depict the 14-3-3 binding motifs with Ser phosphorylation sites. The number of amino acid residues of the longest isoform of each HDAC is shown on the right and the chromosomal site of each HDAC is shown in brackets. H. sapiens, Homo sapiens; S. cerevisiae, Saccharomyces cerevisiae; SE14, Ser-Glu containing tetradecapeptide repeats; ZnF, ubiquitin-binding zinc finger domain. Adapted from [18].

p53, MyoD, c-Myc) [7-10].

The 18 mammalian HDAC enzymes identified to date are classified into two distinct families – the metal dependent enzymes which are represented by class I, II and IV HDACs and the class III sirtuins [7, 11-13]. Class III HDACs include sirtuins 1-7 which are homologous to the yeast silent information regulator 2 [14]. Deacetylation of lysine residues by sirtuins requires consumption nicotinamide adenine dinucleotide (NAD^+) [14]. The metal-dependent enzymes are typically referred to as the classical HDACs and require co-ordination of divalent metal ion for catalytic activity [15]. The 11 classical HDACs are categorized into three classes based on their homology to yeast proteins (**Figure 1**) [15-18]. Briefly, class I enzymes include HDAC1, 2, 3 and 8 and share homology with the yeast transcriptional regulator RDP3 [16, 17]. They are expressed ubiquitously, localized predominantly in the nucleus and HDACs 1-3 are part of multi-protein nuclear repressor proteins [12, 13]. Overall, it is thought that class I enzymes have a critical role in cell survival and proliferation [12, 13, 19]. Class II enzymes are related to yeast HDA1 and are further subdivided into IIa (HDACs 4, 5, 7 and 9) and IIb (HDACs 6 and 10) [20, 21]. They shuttle between the nucleus and cytoplasm and have more tissue-specific expression patterns and functions [8, 10, 12, 13]. HDAC6 is a major cytoplasmic protein with key substrates such as α-tubulin, HSP90 and the important redox regulatory proteins peroxiredoxin I and II [22, 23]. It has diverse roles in modulating cell growth, migration and cellular survival [24-26].

Histone deacetylase inhibitors: anticancer effects

HDAC enzymes have important roles in modulating proliferation, apoptosis, migration and differentiation [12, 13]. Further, aberrant HDAC expression and activity has been observed in numerous malignancies [27-33]. These provided the basis for the development of HDAC inhibitors as anticancer therapies. Indeed, the HDAC inhibitors suberoylanilide hydroxamic acid (SAHA, Vorinostat, Zolinza®) and depsipeptide

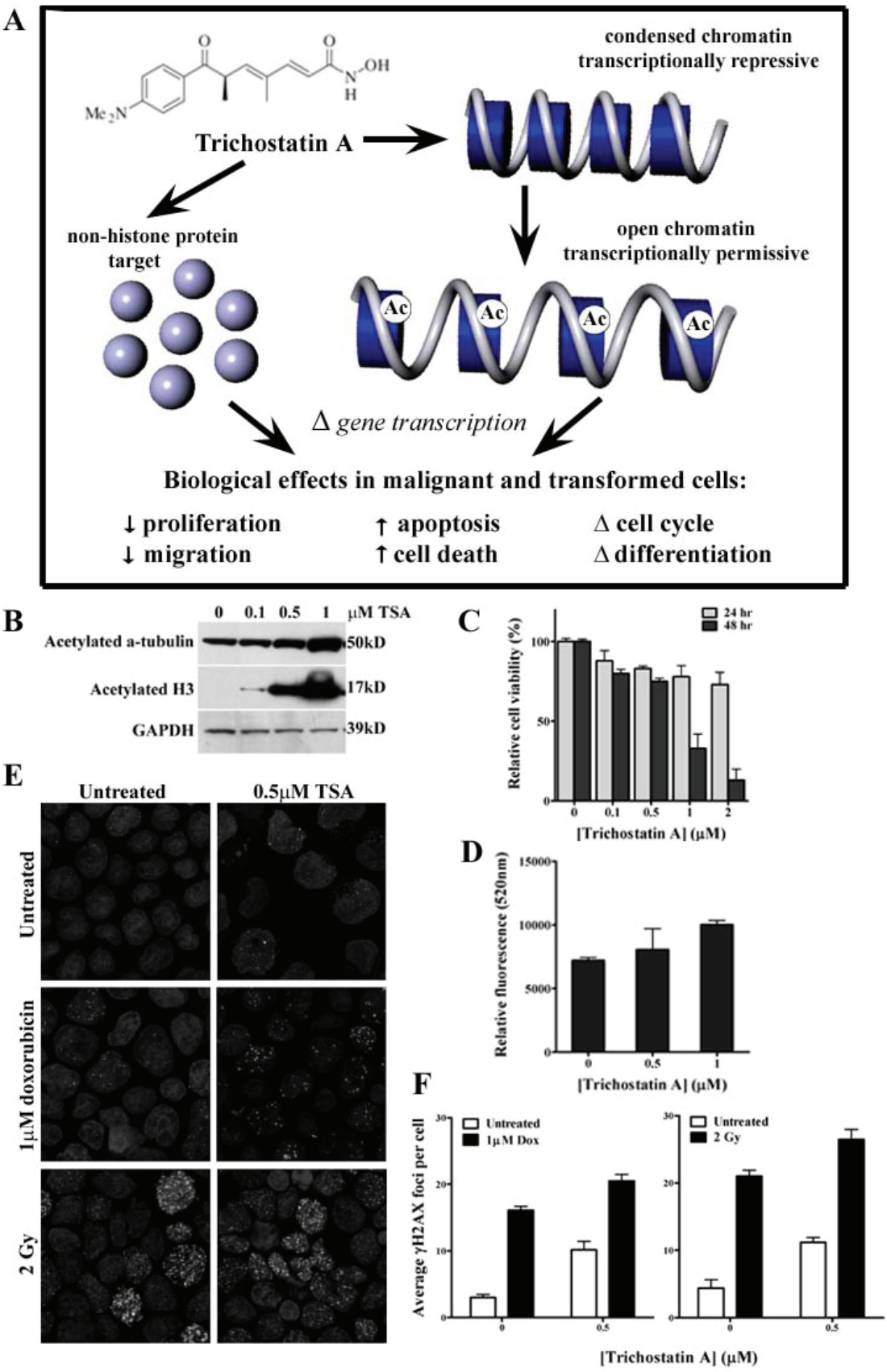
A
condensed chromatin
transcriptionally repressive
Trichostatin A
non-histone protein
target
open chromatin
transcriptionally permissive
Ac
Ac
Ac
Ac
Δ gene transcription
Biological effects in malignant and transformed cells:
↓ proliferation
↓ migration
↑ apoptosis
↑ cell death
Δ cell cycle
Δ differentiation
B
0 0.1 0.5 1 μM TSA
Acetylated a-tubulin
50kD
Acetylated H3
17kD
GAPDH
39kD
C
24 hr
48 hr
Relative cell viability (%)
[Trichostatin A] (μM)
D
Relative fluorescence (520nm)
[Trichostatin A] (μM)
E
Untreated
0.5μM TSA
Untreated
1μM doxorubicin
2 Gy
F
Untreated
1μM Dox
Untreated
2 Gy
Average γH2AX foci per cell
[Trichostatin A] (μM)

Figure 2. Summary of the biological effects of the prototypical broad-spectrum HDAC inhibitor (HDAC inhibitors) Trichostatin A (TSA). (A) TSA alters gene transcription by inhibiting histone deacetylase activity and remodelling chromatin architecture. Hyperacetylation of the core histones results in a more open, transcriptionally permissive chromatin structure. TSA also results in the deacetylation of numerous non-histone protein targets. The overall effect of TSA in malignant and transformed cells is decreased proliferation, increased cell-death, induction of apoptosis, decreased migration, cell cycle arrest (predominantly G1 arrest and G1 and G2/M arrest at higher concentrations) and differentiation. (B) TSA results in the accumulation of hyperacetylated histone H3 and α-tubulin in T-cell leukemic CEM-CCRF cells. Cells were treated with the indicated concentrations of TSA for 24 hours prior to extraction of whole cells lysates. Immunoblots of acetylated histone H3 and α-tubulin with a GAPDH loading control are shown. (C) TSA decreases the relative cell viability of CEM-CCRF cells. Cells were treated with the indicated concentrations of TSA for 24 and 48 hours and relative cell viability was measured using the Cell Titre (Promega) assay kit. (D) TSA induces apoptosis in CEM-CCRF cells. Cells were treated with the indicated concentrations of TSA for 24 hours and caspase 3/7 activity was measured using the Apo-One (Promega) assay kit. (E) TSA augments doxorubicin- and radiation-induced DNA double-strand breaks in CEM-CCRF cells. Micrographs of CEM-CCRF cells immunostained for γH2AX (depicted as white foci) are shown. (F) Cells were treated with 0.5μM TSA for 24 hours prior to one hour incubation with 1μM doxorubicin at 37°C. Cells were washed and incubated for a further 24 hours prior to staining for γH2AX. In separate experiments cells were treated with 0.5μM TSA for 24 hours prior to irradiation with 2 Gy (^{137}Cs). Cells were stained for γH2AX foci one hour following irradiation.

(Romidepsin, Istodax®) have been approved by the US Food and Drug Administration (FDA) for the treatment of refractory cutaneous T-cell lymphoma, in 2006 and 2009, respectively [34, 35].

Briefly, the main structural groups of HDAC inhibitors include the hydroxamic acids such as Trichostatin A, SAHA and Panobinostat (LBH5890) and the cyclic peptides which include depsipeptide and trapoxin [7, 12, 13, 17, 36]. These are relatively potent HDAC inhibitors with activity in the nanomolar to low micromolar range. The benzamides (e.g. Entinostat) and electrophilic ketones (e.g. α-ketomide) are also potent HDAC inhibitors [7, 36]. The short-chain fatty acids which include phenylbutyrate, sodium butyrate and valproic acid are less potent with HDAC inhibition activity in the millimolar range [7, 36]. Although these HDAC inhibitors show some selectivity in cell-free assay systems, they are typically referred to as broad-spectrum compounds as they inhibit multiple class I, II and IV HDAC enzymes. Although it is still controversial as to whether they would provide a therapeutic advantage, particularly in oncology, more class-selective and isoform-selective analogues are increasingly becoming available. Prime examples include tubacin and PC-34501 which selectively inhibit HDACs 6 and 8, respectively [23, 37-39].

In summary, HDAC inhibitors decrease proliferation, induce cell-death and apoptosis, cause differentiation and cell cycle arrest and alter migration in malignant and transformed cell lines (**Figure 2**) [12, 13, 40]. The cytotoxic effects of HDAC inhibitors are much more pronounced, in malignant and transformed cells compared to normal cells. This provides the advantageous therapeutic window in oncology. In addition to their intrinsic cytotoxic properties HDAC inhibitors have been shown to induce at least additive cytotoxic effects with other anticancer modalities (**Figure 2**). Effective combinations with HDAC inhibitors include those with conventional cancer modalities such as chemotherapy (anthracyclines and retinoic acid) and radiotherapy [8, 12, 13, 41-45]. Further, HDAC inhibitors have been shown to augment the effects ultraviolet radiation and range other biological agents such as tumor-necrosis-factor apoptosis-inducing ligand [46, 47]. The clinical potential of HDAC inhibitors in oncology is highlighted by the fact that there are currently there are over 100 clinical trials involving these compounds for a wide range of malignancies.

Non-oncological applications of histone deacetylase inhibitors

Apart from applications in oncology, the therapeutic potential of HDAC inhibitors has also been investigated for a wide range of other diseases. Examples include HIV infection where the potential of HDAC inhibitors in de-silencing latent virus was evaluated and ulcerative colitis where inhibition of NF-κB activation by butyrate was proposed to be beneficial [48, 49]. Other examples include hepatitis for which HDAC inhibitors were shown to function by inhibiting TNF-α and INFγ and similarly, downregulation of

pro-inflammatory cytokines is thought to provide the basis for the potential use of HDAC inhibitors in systemic lupus erythematosus [50, 51]. The potential of HDAC inhibitors as antimalarial agents has also been investigated. It has been shown that the mammalian HDAC inhibitors Trichostatin A and apicidin cause histone acetylation and inhibit the growth of Plasmodium falciparum, the main malarial parasite in humans [52-54]. Similarly, the mammalian HDAC inhibitors azelaic bishydroxamic acid and suberohydroxamic acid exhibit antimalarial activity against P. falciparum [55]. This prompted the development of analogues based on the structures of L-cysteine and 2-aminosuberic acid yielding compounds with greater selectivity for the protozoan HDAC enzymes [56, 57]. In addition to diseases described above, a considerable research effort has been aimed at evaluating the potential of HDAC inhibitors as therapeutics for neurodegenerative disorders, cardiac hypertrophy and more recently asthma, which will be the focus of discussion of the remaining of this review.

Histone deacetylase inhibitors for the treatment of neurodegenerative disorders

Aberrant acetylation has been associated with numerous neurodegenerative diseases; a primary example of which is Rubinstein-Taybi syndrome. Rubinstein-Taybi syndrome is a developmental disorder characterized by mental retardation and is caused by mutations in cyclic AMP response element binding protein (CREB) and p300 genes with HAT function [58]. Relevant animal models which exhibit defects in chromatin acetylation and impairment of long term-memory, such as late phase of hippocampal long-term potentiation have been used to evaluate the effects of restoration of acetylation defects [59]. It has been shown that enhancing CREB-dependent genes improves the condition of the mice. Similarly, pharmacological intervention with the broad-spectrum HDAC inhibitor Trichostatin A, partially restored long-term memory loss providing the basis for the possible use of HDAC inhibition for the treatment of Rubinstein-Taybi syndrome [60].

The potential efficacy of broad-spectrum HDAC inhibitors particularly, Trichostatin A, butyrates and valproic acid, have been investigated in a wide range of other neurodegenerative conditions [61, 62]. For example, valproic acid, Trichostatin A and phenylbutyrate have been investigated for their potential in ameliorating the effects of stroke [63-68]. Overall, the findings indicate the HDAC inhibitors may restore histone acetylation status, enhance neurogenesis and decrease neuroinflammatory responses. Similarly, restoration of acetylation status – both histone and the non-histone substrate α-tubulin–anti-inflammatory effects and decreased dopaminergic neuronal death have been shown to be responsible for the beneficial effects of HDAC inhibitors in models of Parkinson's disease [69-72]. Further, HDAC inhibition has been shown to be effective in models of Huntington's disease due to restored histone acetylation status and normalization of striatal atrophy [62, 73-76]. Suppression of motor neuron degeneration and muscle atrophy as well as increased expression of SMN2 provides the basis for the potential use of HDAC inhibitors in spinal muscular atrophy [77-84]. Valproic acid and phenylbutyrate, either alone in combination with antioxidants or lithium have also shown beneficial effects in models of amyotrophic lateral sclerosis [85-90]. Like for other neurodegenerative conditions, the beneficial effects of the HDAC inhibitors involve restored histone acetylation status, suppression of motor neuronal death and improved motor function and survival.

Alzheimer's disease is a very common neurodegenerative condition and represents a leading cause of death in industrialized countries [91]. It is characterized by progressive memory loss and ultimately dementia [91]. The main pathobiological features of Alzheimer's disease include the accumulation of insoluble β-amyloid due to aberrant cleavage of amyloid precursor protein by secretases and accumulation of neurofibrillary tangles due to hyperphosphorylation of Tau protein [92, 93]. Numerous relevant in vivo models of Alzheimer's disease have been developed and these have assisted in the understanding of the molecular basis of disease and also allowed for the evaluation of pharmacological interventions. The broad-spectrum histone deacetylase inhibitors valproic acid, sodium butyrate, phenylbutyrate and Trichostatin A have shown beneficial effects in models of Alzheimer's disease [94-96]. In general, HDAC inhibitors have been shown to restore histone acetylation status and improve synaptic plasticity. Further, HDAC inhibitors have been found to improve learning and memory and to reverse

spatial memory defects [94-96]. Additionally, findings indicate that HDAC inhibitors decrease expression of β-amyloid and phosphorylation of Tau in relevant models, providing a basis for their potential efficacy in Alzheimer's disease [94-96].

Although broad-spectrum HDAC inhibitors generally display beneficial effects in various models of neurodegenerative diseases, they do exhibit toxicity in various cell types of the central nervous system. This is not unexpected given the biological effects of HDAC inhibitors as anticancer agents. Therefore, class or isoform-selective inhibitors may provide a therapeutic advantage and studies with SAHA which predominantly inhibited class I HDAC enzymes in a model of Alzheimer's disease is a step in this direction [97]. Although HDAC2 has been shown to regulate memory formation and neuronal plasticity, the function of the different HDAC isoforms in neurodegenerative diseases is still poorly understood [98]. Therefore, it is expected that further research will be aimed at identifying the role of the different HDAC enzymes and evaluating isoform-specific HDAC inhibitors in models of neurodegenerative diseases. In this context, the detailed map of HDAC1-11 enzymes in >50 regions of the rat brain will provide a starting point for examination of the roles of specific HDAC enzymes in the brain [99]. Finally, an important study in this direction utilized pharmacological and genetic approaches to specifically inhibit HDAC6, highlighting the potential for selective inhibition as a nontoxic therapeutic strategy for protection and regeneration following injury in the central nervous system [100].

Potential of histone deacetylase inhibitors for the treatment of cardiac hypertrophy

The therapeutic potential of HDAC inhibitors in models of heart disease, including cardiac hypertrophy and myocardial ischemia-reperfusion injury, has emerged [101-106]. For example, a recent study indicates that Trichostatin A protects from load- and agonist-induced hypertrophy in vivo by suppressing autophagy [107]. Similarly, a recent study indicates that valproic acid prevents pulmonary artery banding-induced right ventricular hypertrophy in rats [108]. However, the clinical potential of HDAC inhibitors for the treatment of heart disease remains controversial. This is highlighted from another recent study which indicates, in contrast to the findings with valproic acid, that Trichostatin A worsens pulmonary artery banding-induced right ventricular dysfunction in rats [109]. It was proposed that HDAC inhibitor induced-apoptosis and antiangiogenic effects are likely to be responsible for the disadvantageous effects of Trichostatin A on the pressure-overloaded right ventricle [109]. In vitro studies from our laboratory, using doxorubicin-induced hypertrophy in rat cardiac myocytes as a model system, also suggest detrimental effects of broad-spectrum HDAC inhibitors (**Figure 3**). Firstly, our findings indicate that Trichostatin A augments doxorubicin-induced hypertrophy, at least in part, by modulating the expression of the hypertrophy-associated genes, ventricular myosin light chain -2, the alpha isoform of myosin heavy chain and atrial natriuretic peptide [110]. Further, our findings indicate that pre-treatment, but not post-treatment, of cells with the broad-spectrum HDAC inhibitors, Trichostatin A, valproic acid and sodium butyrate enhance doxorubicin-induced DNA damage as monitored with γH2AX – a molecular marker of DNA double-strand breaks [110, 111].

Evidence indicates that the uncertainty surrounding the clinical potential of HDAC inhibitors in cardiac hypertrophy stems from the disparate actions of class I and class II HDACs in this disease [112-116]. Overall, class I HDACs potentiate cardiac hypertrophy and class II HDACs are thought to suppress pro-hypertrophic responses (**Figure 3**). The role of different HDAC enzymes in regulating cardiac hypertrophy has been reviewed extensively [113-115]. Briefly, class II HDACs prevent hypertrophic responses, largely, by inactivating myocyte enhancer 2 (MEF2), a transcription factor which drives cardiac hypertrophy in response to stress [115, 117]. In addition, the activities of numerous other transcription factors involved in myocardial growth including, serum response factor, myocardin and calmodulin binding transcription activator 2, are modulated by class II HDAC enzymes [114, 118]. Although the precise mechanisms are yet to be fully elucidated, direct evidence for the function of class II HDACs in suppressing stress-induced hypertrophy comes from in vivo experiments involving mice lacking either HDAC5 or HDAC9 [115, 119]. Mice lacking HDAC5 and HDAC9, which are typically highly expressed in the heart, develop extremely enlarged hearts following cardiac stress [115, 119]. Given the differential functions of HDAC enzymes in cardiac hypertrophy it is widely an-

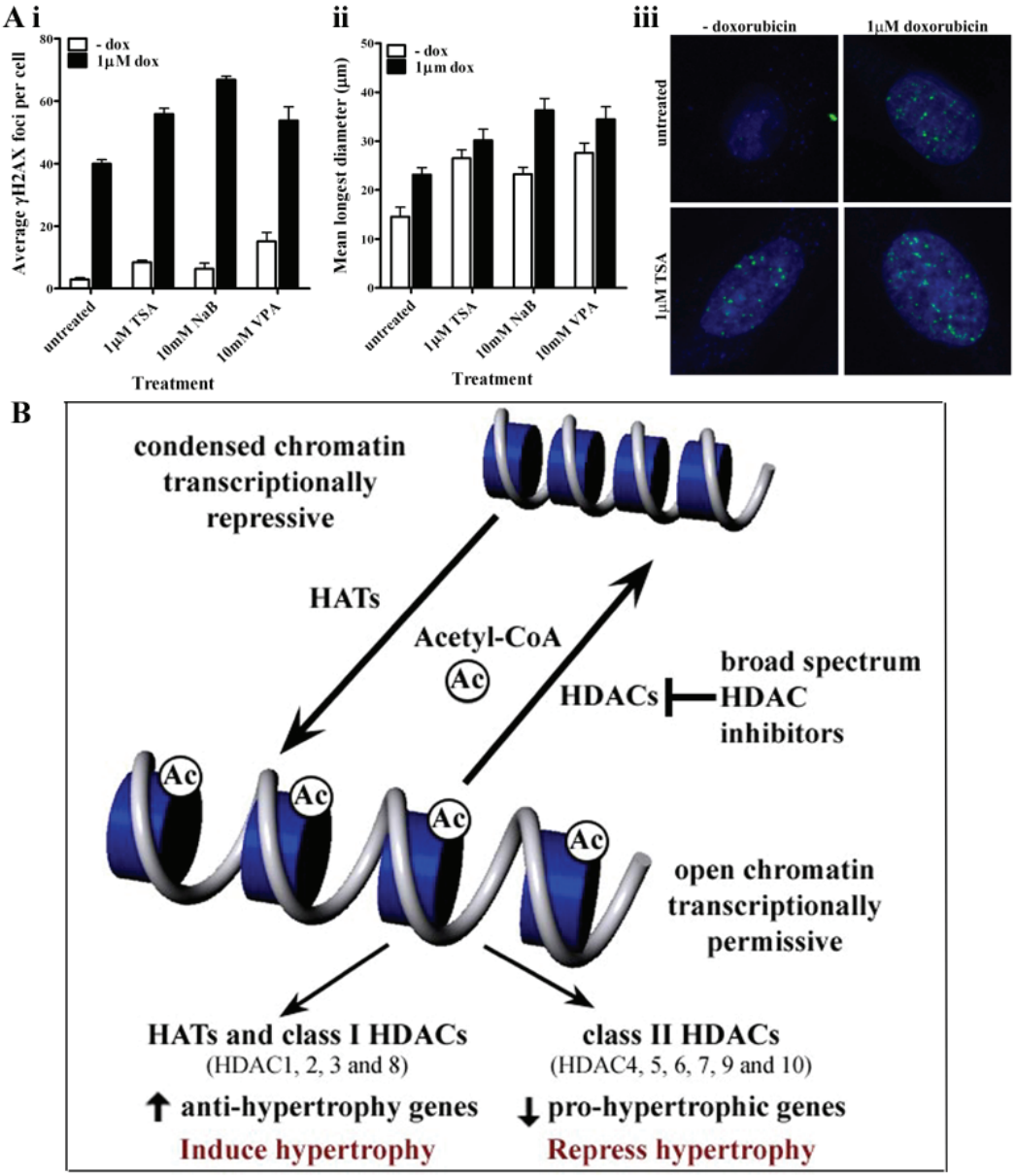

Figure 3. Histone acetylation status is regulated by the opposing actions of histone acetyltransferase (HATs) and histone deacetylases (HDACs). The precise function of HDAC enzymes in regulating cardiac hypertrophy remains unknown. Similarly, the potential of HDAC inhibitors in the treatment of cardiac hypertrophy remains controversial. A number of reports have indicated a beneficial effect of broad-spectrum HDAC inhibitors in animal models of cardiac hypertrophy. However, others have indicated the opposite effect. (A) We have shown that broad-spectrum HDAC inhibitors augment doxorubicin induced hypertrophy *in vitro*. H9c2 myoblasts were differentiated into cardiac myocytes after 7 days culture in the presence of 10 nM all-*trans* retinoic acid. (i) Cells were then treated with 1 μM Trichostatin A (TSA), 10 mM sodium butyrate (NaB) and 10 mM valproic acid (VPA) for 24 hours prior to one hour incubation with 1μM doxorubicin. Cells were washed and incubated for a further 24 hours in fresh media prior to immunostaining for γH2AX. Analysis of γH2AX foci indicates that broad-spectrum HDAC inhibitors augment doxorubicin-induced DNA double strand breaks. (ii) Cells treated with HDAC inhibitors also induced a hypertrophic response with an increase in the mean of the longest diameter of H9c2 cells. (iii) Photomicrographs of differentiated H9c2 cardiac myocytes treated with 1μM TSA and immunostained for γH2AX (depicted as white foci) are shown. (B) Recent evidence indicates that class I HDACs promote cardiac hypertrophy whereas class II enzymes inhibit pro-hypertrophic pathways which may be regulated by the myocyte enhancer factor-2 (MEF2) transcription factor. Therefore, it is anticipated that class I-specific HDAC inhibitors may be more beneficial for the potential treatment of cardiac hypertrophy.

ticipated that class I HDAC inhibitors may be more efficacious in this disease. In this context, Spiruchostatin A, a potent inhibitor with selectivity towards class I HDACs in cardiac myocytes, has been shown to abrogate the pro-hypertrophic effects of phenylephrine and urocortin [120]. Further research in this direction is expected.

Effects of histone deacetylase inhibitors in models of asthma

Like for cardiac hypertrophy, the potential clinical utility of HDAC inhibitors in asthma remains controversial. Studies indicate that aberrant HAT and HDAC expression and activity may be implicated in asthma pathogenesis. Analysis of bronchial biopsies has indicated reduced HDAC activity and reduced HDAC1 and HDAC2 protein expression is asthmatic compared to normal subjects [121]. The same study HAT activity is increased in subjects with asthma [121]. Further, it was shown that treatment with inhaled steroids reduces HAT and increases HDAC activity, providing evidence for a mechanism accounting for the increased expression of multiple inflammatory genes in asthma [121]. Similarly, it has been shown that conditional deletion of HDAC1 results in increased Th2 cytokine production and enhanced airway inflammation in an in vivo allergic airway inflammation model [122]. These findings suggest that HDAC inhibition would be contraindicated in asthma. However, paradoxical findings have shown that HDAC inhibition attenuates airway hyperresponsiveness (AHR) and inflammation in animals of inflammation and asthma [123, 124]. Of particular interest are the findings that the broad-spectrum HDAC inhibitor, Trichostatin A, improved AHR and reduced inflammation by decreasing the expression of Th2 cytokines using a mouse model of allergic airways disease [124]. More recent findings have indicated that Trichostatin A inhibits AHR but not inflammation in a mouse asthma model [125]. Incidentally, published findings from our laboratory indicate the beneficial effects of the dietary class III HDAC agonist, resveratrol, in inhibiting AHR and inflammation in a chronic ovalbumin-challenge and sensitization model of allergic airways disease [126]. In similar experiments (unpublished observations) we have found beneficial effect of both Trichostatin A and valproic acid in the chronic mouse model of allergic airways disease. Overall, the recent findings are indicating the potential for HDAC inhibition as a therapeutic modality in asthma. In this context, it will be important to systematically investigate the function of specific HDAC isoforms in asthma pathobiology. Similarly, the effects of selective HDAC inhibitors may clarify the clinical utility of this class of compounds in asthma.

Conclusions

The potential versatility of HDAC inhibitors extends beyond their current application in oncology. The efficacy of HDAC inhibitors in a wide range of conditions including neurodegenerative disorders, cardiac hypertrophy and asthma has been investigated in relevant systems. While broad-spectrum HDAC inhibitors have been evaluated almost exclusively to date, it is emerging that class- or isoform-specific compounds, which are increasingly becoming available, may be more beneficial. However, the molecular pathways regulated by different HDAC-isoforms in disease processes remain poorly understood. Given the clinical potential of HDAC inhibitors, this issue will undoubtedly be clarified by further research. Already, evidence is pointing to the importance of investigating class - or isoform-selective HDAC inhibitors as potential therapeutics for cardiac diseases, with the expectation that class I HDACs will be more efficacious.

Acknowledgements

The support of the Australian Institute of Nuclear Science and Engineering is acknowledged. TCK was the recipient of AINSE awards. Epigenomic Medicine Laboratory is supported by the National Health and Medical Research Council of Australia. KV is supported by a Baker IDI postgraduate scholarship. Supported in part by the Victorian Government's Operational Infrastructure Support Program. The authors would like to acknowledge the use of the facilities provided by Monash Micro Imaging @ AMREP and particularly, the expert assistance from Drs Stephen Cody and Iśka Carmichael.

Address correspondence to: Dr Tom Karagiannis, Epigenomic Medicine, BakerIDI Heart and Diabetes Institute, 75 Commercial Road, Melbourne, VIC, Australia Tel: +613 8532 1309; Fax: +613 8532 1100; E-mail: tom.karagiannis@bakeridi.edu.au

References

[1] Kouzarides T. Chromatin modifications and their function. Cell 2007; 128: 693-705.

[2] Allfrey VG, Faulkner R and Mirsky AE. Acetylation and Methylation of Histones and Their Possible Role in the Regulation of Rna Synthesis. Proc Natl Acad Sci USA 1964; 51: 786-794.
[3] Allfrey VG, Mirsky AE. Structural Modifications of Histones and their Possible Role in the Regulation of RNA Synthesis. Science 1964; 144: 559.
[4] Smith BC, Denu JM. Chemical mechanisms of histone lysine and arginine modifications. Biochim Biophys Acta 2009; 1789: 45-57.
[5] Roth SY, Denu JM and Allis CD. Histone acetyltransferases. Annu Rev Biochem 2001; 70: 81-120.
[6] Kuo MH, Allis CD. Roles of histone acetyltransferases and deacetylases in gene regulation. Bioessays 1998; 20: 615-626.
[7] Dokmanovic M, Marks PA. Prospects: histone deacetylase inhibitors. J Cell Biochem 2005; 96: 293-304.
[8] Minucci S, Pelicci PG. Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. Nat Rev Cancer 2006; 6: 38-51.
[9] Rosato RR, Grant S. Histone deacetylase inhibitors: insights into mechanisms of lethality. Expert Opin Ther Targets 2005; 9: 809-824.
[10] Xu WS, Parmigiani RB and Marks PA. Histone deacetylase inhibitors: molecular mechanisms of action. Oncogene 2007; 26: 5541-5552.
[11] de Ruijter AJ, van Gennip AH, Caron HN, Kemp S and van Kuilenburg AB. Histone deacetylases (HDACs): characterization of the classical HDAC family. Biochem J 2003; 370: 737-749.
[12] Marks PA. Histone deacetylase inhibitors: a chemical genetics approach to understanding cellular functions. Biochim Biophys Acta 2010; 1799: 717-725.
[13] Marks PA, Xu WS. Histone deacetylase inhibitors: Potential in cancer therapy. J Cell Biochem 2009; 107: 600-608.
[14] Tanner KG, Landry J, Sternglanz R and Denu JM. Silent information regulator 2 family of NAD- dependent histone/protein deacetylases generates a unique product, 1-O-acetyl-ADP-ribose. Proc Natl Acad Sci USA 2000; 97: 14178-14182.
[15] Gregoretti IV, Lee YM and Goodson HV. Molecular evolution of the histone deacetylase family: functional implications of phylogenetic analysis. J Mol Biol 2004; 338: 17-31.
[16] Bolden JE, Peart MJ and Johnstone RW. Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov 2006; 5: 769-784.
[17] Marks P, Rifkind RA, Richon VM, Breslow R, Miller T and Kelly WK. Histone deacetylases and cancer: causes and therapies. Nat Rev Cancer 2001; 1: 194-202.
[18] Yang XJ and Seto E. The Rpd3/Hda1 family of lysine deacetylases: from bacteria and yeast to mice and men. Nat Rev Mol Cell Biol 2008; 9: 206-218.
[19] Yang XJ and Seto E. Collaborative spirit of histone deacetylases in regulating chromatin structure and gene expression. Curr Opin Genet Dev 2003; 13: 143-153.
[20] Martin M, Kettmann R and Dequiedt F. Class IIa histone deacetylases: regulating the regulators. Oncogene 2007; 26: 5450-5467.
[21] Witt O, Deubzer HE, Milde T and Oehme I. HDAC family: What are the cancer relevant targets? Cancer Lett 2009; 277: 8-21.
[22] Kovacs JJ, Murphy PJ, Gaillard S, Zhao X, Wu JT, Nicchitta CV, Yoshida M, Toft DO, Pratt WB and Yao TP. HDAC6 regulates Hsp90 acetylation and chaperone-dependent activation of glucocorticoid receptor. Mol Cell 2005; 18: 601-607.
[23] Parmigiani RB, Xu WS, Venta-Perez G, Erdjument-Bromage H, Yaneva M, Tempst P and Marks PA. HDAC6 is a specific deacetylase of peroxiredoxins and is involved in redox regulation. Proc Natl Acad Sci USA 2008; 105: 9633-9638.
[24] Gao YS, Hubbert CC and Yao TP. The microtubule-associated histone deacetylase 6 (HDAC6) regulates epidermal growth factor receptor (EGFR) endocytic trafficking and degradation. J Biol Chem 2010; 285: 11219-11226.
[25] Hubbert C, Guardiola A, Shao R, Kawaguchi Y, Ito A, Nixon A, Yoshida M, Wang XF and Yao TP. HDAC6 is a microtubule-associated deacetylase. Nature 2002; 417: 455-458.
[26] Kawaguchi Y, Kovacs JJ, McLaurin A, Vance JM, Ito A and Yao TP. The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. Cell 2003; 115: 727-738.
[27] Chang HH, Chiang CP, Hung HC, Lin CY, Deng YT and Kuo MY. Histone deacetylase 2 expression predicts poorer prognosis in oral cancer patients. Oral Oncol 2009; 45: 610-614.
[28] Gloghini A, Buglio D, Khaskhely NM, Georgakis G, Orlowski RZ, Neelapu SS, Carbone A and Younes A. Expression of histone deacetylases in lymphoma: implication for the development of selective inhibitors. Br J Haematol 2009; 147: 515-525.
[29] Nakagawa M, Oda Y, Eguchi T, Aishima S, Yao T, Hosoi F, Basaki Y, Ono M, Kuwano M, Tanaka M and Tsuneyoshi M. Expression profile of class I histone deacetylases in human cancer tissues. Oncol Rep 2007; 18: 769-774.
[30] Ropero S, Fraga MF, Ballestar E, Hamelin R, Yamamoto H, Boix-Chornet M, Caballero R, Alaminos M, Setien F, Paz MF, Herranz M, Palacios J, Arango D, Orntoft TF, Aaltonen LA, Schwartz S, Jr and Esteller M. A truncating mutation of HDAC2 in human cancers confers resistance to histone deacetylase inhibition. Nat Genet 2006; 38: 566-569.

[31] Sjoblom T, Jones S, Wood LD, Parsons DW, Lin J, Barber TD, Mandelker D, Leary RJ, Ptak J, Silliman N, Szabo S, Buckhaults P, Farrell C, Meeh P, Markowitz SD, Willis J, Dawson D, Willson JK, Gazdar AF, Hartigan J, Wu L, Liu C, Parmigiani G, Park BH, Bachman KE, Papadopoulos N, Vogelstein B, Kinzler KW and Velculescu VE. The consensus coding sequences of human breast and colorectal cancers. Science 2006; 314: 268-274.

[32] Weichert W. HDAC expression and clinical prognosis in human malignancies. Cancer Lett 2009; 280: 168-176.

[33] Zhang Z, Yamashita H, Toyama T, Sugiura H, Ando Y, Mita K, Hamaguchi M, Hara Y, Kobayashi S and Iwase H. Quantitation of HDAC1 mRNA expression in invasive carcinoma of the breast*. Breast Cancer Res Treat 2005; 94: 11-16.

[34] Marks PA and Breslow R. Dimethyl sulfoxide to vorinostat: development of this histone deacetylase inhibitor as an anticancer drug. Nat Biotechnol 2007; 25: 84-90.

[35] Campas-Moya C. Romidepsin for the treatment of cutaneous T-cell lymphoma. Drugs Today (Barc) 2009; 45: 787-795.

[36] Dokmanovic M, Clarke C and Marks PA. Histone deacetylase inhibitors: overview and perspectives. Mol Cancer Res 2007; 5: 981-989.

[37] Haggarty SJ, Koeller KM, Wong JC, Grozinger CM and Schreiber SL. Domain-selective small-molecule inhibitor of histone deacetylase 6 (HDAC6)-mediated tubulin deacetylation. Proc Natl Acad Sci USA 2003; 100: 4389-4394.

[38] Namdar M, Perez G, Ngo L and Marks PA. Selective inhibition of histone deacetylase 6 (HDAC6) induces DNA damage and sensitizes transformed cells to anticancer agents. Proc Natl Acad Sci USA 2010; 107: 20003-20008.

[39] Tang W, Luo T, Greenberg EF, Bradner JE and Schreiber SL. Discovery of histone deacetylase 8 selective inhibitors. Bioorg Med Chem Lett 2011; 21: 2601-2605.

[40] Kwa FA, Balcerczyk A, Licciardi P, El-Osta A and Karagiannis TC. Chromatin modifying agents - the cutting edge of anticancer therapy. Drug Discov Today 2011; 16: 543-547.

[41] De los Santos M, Zambrano A and Aranda A. Combined effects of retinoic acid and histone deacetylase inhibitors on human neuroblastoma SH-SY5Y cells. Mol Cancer Ther 2007; 6: 1425-1432.

[42] Kim HJ and Bae SC. Histone deacetylase inhibitors: molecular mechanisms of action and clinical trials as anti-cancer drugs. Am J Transl Res 2011; 3: 166-179.

[43] Karagiannis TC, Harikrishnan KN and El-Osta A. The histone deacetylase inhibitor, Trichostatin A, enhances radiation sensitivity and accumulation of gammaH2A.X. Cancer Biol Ther 2005; 4: 787-793.

[44] Karagiannis TC, Harikrishnan KN and El-Osta A. Disparity of histone deacetylase inhibition on repair of radiation-induced DNA damage on euchromatin and constitutive heterochromatin compartments. Oncogene 2007; 26: 3963-3971.

[45] Sanchez-Gonzalez B, Yang H, Bueso-Ramos C, Hoshino K, Quintas-Cardama A, Richon VM and Garcia-Manero G. Antileukemia activity of the combination of an anthracycline with a histone deacetylase inhibitor. Blood 2006; 108: 1174-1182.

[46] Briggs B, Ververis K, Rodd AL, Foong LJ, Silva FM and Karagiannis TC. Photosensitization by iodinated DNA minor groove binding ligands: Evaluation of DNA double-strand break induction and repair. J Photochem Photobiol B 2011; 103: 145-152.

[47] Singh TR, Shankar S and Srivastava RK. HDAC inhibitors enhance the apoptosis-inducing potential of TRAIL in breast carcinoma. Oncogene 2005; 24: 4609-4623.

[48] Lehrman G, Hogue IB, Palmer S, Jennings C, Spina CA, Wiegand A, Landay AL, Coombs RW, Richman DD, Mellors JW, Coffin JM, Bosch RJ and Margolis DM. Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. Lancet 2005; 366: 549-555.

[49] Luhrs H, Gerke T, Muller JG, Melcher R, Schauber J, Boxberge F, Scheppach W and Menzel T. Butyrate inhibits NF-kappaB activation in lamina propria macrophages of patients with ulcerative colitis. Scand J Gastroenterol 2002; 37: 458-466.

[50] Leoni F, Fossati G, Lewis EC, Lee JK, Porro G, Pagani P, Modena D, Moras ML, Pozzi P, Reznikov LL, Siegmund B, Fantuzzi G, Dinarello CA and Mascagni P. The histone deacetylase inhibitor ITF2357 reduces production of pro-inflammatory cytokines in vitro and systemic inflammation in vivo. Mol Med 2005; 11: 1-15.

[51] Mishra N, Reilly CM, Brown DR, Ruiz P and Gilkeson GS. Histone deacetylase inhibitors modulate renal disease in the MRL-lpr/lpr mouse. J Clin Invest 2003; 111: 539-552.

[52] Colletti SL, Myers RW, Darkin-Rattray SJ, Gurnett AM, Dulski PM, Galuska S, Allocco JJ, Ayer MB, Li C, Lim J, Crumley TM, Cannova C, Schmatz DM, Wyvratt MJ, Fisher MH and Meinke PT. Broad spectrum antiprotozoal agents that inhibit histone deacetylase: structure-activity relationships of apicidin. Part 2. Bioorg Med Chem Lett 2001; 11: 113-117.

[53] Colletti SL, Myers RW, Darkin-Rattray SJ, Gurnett AM, Dulski PM, Galuska S, Allocco JJ, Ayer MB, Li C, Lim J, Crumley TM, Cannova C, Schmatz DM, Wyvratt MJ, Fisher MH and Meinke PT. Broad spectrum antiprotozoal agents that inhibit histone deacetylase: structure-activity relationships of apicidin. Part 1. Bioorg Med Chem Lett 2001; 11: 107-111.

[54] Darkin-Rattray SJ, Gurnett AM, Myers RW, Dulski PM, Crumley TM, Allocco JJ, Cannova C, Meinke PT, Colletti SL, Bednarek MA, Singh SB, Goetz MA, Dombrowski AW, Polishook JD and Schmatz DM. Apicidin: a novel antiprotozoal agent that inhibits parasite histone deacetylase. Proc Natl Acad Sci USA 1996; 93: 13143-13147.

[55] Andrews KT, Walduck A, Kelso MJ, Fairlie DP, Saul A and Parsons PG. Anti-malarial effect of histone deacetylation inhibitors and mammalian tumour cytodifferentiating agents. Int J Parasitol 2000; 30: 761-768.

[56] Andrews KT, Tran TN, Lucke AJ, Kahnberg P, Le GT, Boyle GM, Gardiner DL, Skinner-Adams TS and Fairlie DP. Potent antimalarial activity of histone deacetylase inhibitor analogues. Antimicrob Agents Chemother 2008; 52: 1454-1461.

[57] Andrews KT, Tran TN, Wheatley NC and Fairlie DP. Targeting histone deacetylase inhibitors for anti-malarial therapy. Curr Top Med Chem 2009; 9: 292-308.

[58] Petrij F, Giles RH, Dauwerse HG, Saris JJ, Hennekam RC, Masuno M, Tommerup N, van Ommen GJ, Goodman RH, Peters DJ and Breuning MH. Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP. Nature 1995; 376: 348-351.

[59] Barco A. The Rubinstein-Taybi syndrome: modeling mental impairment in the mouse. Genes Brain Behav 2007; 6 Suppl 1: 32-39.

[60] Vecsey CG, Hawk JD, Lattal KM, Stein JM, Fabian SA, Attner MA, Cabrera SM, McDonough CB, Brindle PK, Abel T and Wood MA. Histone deacetylase inhibitors enhance memory and synaptic plasticity via CREB:CBP-dependent transcriptional activation. J Neurosci 2007; 27: 6128-6140.

[61] Kazantsev AG, Thompson LM. Therapeutic application of histone deacetylase inhibitors for central nervous system disorders. Nat Rev Drug Discov 2008; 7: 854-868.

[62] Chuang DM, Leng Y, Marinova Z, Kim HJ and Chiu CT. Multiple roles of HDAC inhibition in neurodegenerative conditions. Trends Neurosci 2009; 32: 591-601.

[63] Zhong Y, Zhou LJ, Ren WJ, Xin WJ, Li YY, Zhang T and Liu XG. The direction of synaptic plasticity mediated by C-fibers in spinal dorsal horn is decided by Src-family kinases in microglia: the role of tumor necrosis factor-alpha. Brain Behav Immun 2010; 24: 874-880.

[64] Kim HJ, Rowe M, Ren M, Hong JS, Chen PS and Chuang DM. Histone deacetylase inhibitors exhibit anti-inflammatory and neuroprotective effects in a rat permanent ischemic model of stroke: multiple mechanisms of action. J Pharmacol Exp Ther 2007; 321: 892-901.

[65] Faraco G, Pancani T, Formentini L, Mascagni P, Fossati G, Leoni F, Moroni F and Chiarugi A. Pharmacological inhibition of histone deacetylases by suberoylanilide hydroxamic acid specifically alters gene expression and reduces ischemic injury in the mouse brain. Mol Pharmacol 2006; 70: 1876-1884.

[66] Kim HJ, Leeds P and Chuang DM. The HDAC inhibitor, sodium butyrate, stimulates neurogenesis in the ischemic brain. J Neurochem 2009; 110: 1226-1240.

[67] Qi X, Hosoi T, Okuma Y, Kaneko M and Nomura Y. Sodium 4-phenylbutyrate protects against cerebral ischemic injury. Mol Pharmacol 2004; 66: 899-908.

[68] Sinn DI, Kim SJ, Chu K, Jung KH, Lee ST, Song EC, Kim JM, Park DK, Kun Lee S, Kim M and Roh JK. Valproic acid-mediated neuroprotection in intracerebral hemorrhage via histone deacetylase inhibition and transcriptional activation. Neurobiol Dis 2007; 26: 464-472.

[69] Kontopoulos E, Parvin JD and Feany MB. Alpha-synuclein acts in the nucleus to inhibit histone acetylation and promote neurotoxicity. Hum Mol Genet 2006; 15: 3012-3023.

[70] Chen PS, Peng GS, Li G, Yang S, Wu X, Wang CC, Wilson B, Lu RB, Gean PW, Chuang DM and Hong JS. Valproate protects dopaminergic neurons in midbrain neuron/glia cultures by stimulating the release of neurotrophic factors from astrocytes. Mol Psychiatry 2006; 11: 1116-1125.

[71] Wu X, Chen PS, Dallas S, Wilson B, Block ML, Wang CC, Kinyamu H, Lu N, Gao X, Leng Y, Chuang DM, Zhang W, Lu RB and Hong JS. Histone deacetylase inhibitors up-regulate astrocyte GDNF and BDNF gene transcription and protect dopaminergic neurons. Int J Neuropsychopharmacol 2008; 11: 1123-1134.

[72] Gardian G, Yang L, Cleren C, Calingasan NY, Klivenyi P and Beal MF. Neuroprotective effects of phenylbutyrate against MPTP neurotoxicity. Neuromolecular Med 2004; 5: 235-241.

[73] Hockly E, Richon VM, Woodman B, Smith DL, Zhou X, Rosa E, Sathasivam K, Ghazi-Noori S, Mahal A, Lowden PA, Steffan JS, Marsh JL, Thompson LM, Lewis CM, Marks PA and Bates GP. Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. Proc Natl Acad Sci USA 2003; 100: 2041-2046.

[74] Pallos J, Bodai L, Lukacsovich T, Purcell JM, Steffan JS, Thompson LM and Marsh JL. Inhibition of specific HDACs and sirtuins suppresses pathogenesis in a Drosophila model of Huntington's disease. Hum Mol Genet 2008; 17: 3767-3775.

[75] Gardian G, Browne SE, Choi DK, Klivenyi P, Gregorio J, Kubilus JK, Ryu H, Langley B, Ratan RR, Ferrante RJ and Beal MF. Neuroprotective effects of phenylbutyrate in the N171-82Q transgenic mouse model of Huntington's

disease. J Biol Chem 2005; 280: 556-563.
[76] Dompierre JP, Godin JD, Charrin BC, Cordelieres FP, King SJ, Humbert S and Saudou F. Histone deacetylase 6 inhibition compensates for the transport deficit in Huntington's disease by increasing tubulin acetylation. J Neurosci 2007; 27: 3571-3583.
[77] Chang JG, Hsieh-Li HM, Jong YJ, Wang NM, Tsai CH and Li H. Treatment of spinal muscular atrophy by sodium butyrate. Proc Natl Acad Sci USA 2001; 98: 9808-9813.
[78] Andreassi C, Angelozzi C, Tiziano FD, Vitali T, De Vincenzi E, Boninsegna A, Villanova M, Bertini E, Pini A, Neri G and Brahe C. Phenylbutyrate increases SMN expression in vitro: relevance for treatment of spinal muscular atrophy. Eur J Hum Genet 2004; 12: 59-65.
[79] Brichta L, Hofmann Y, Hahnen E, Siebzehnrubl FA, Raschke H, Blumcke I, Eyupoglu IY and Wirth B. Valproic acid increases the SMN2 protein level: a well-known drug as a potential therapy for spinal muscular atrophy. Hum Mol Genet 2003; 12: 2481-2489.
[80] Hauke J, Riessland M, Lunke S, Eyupoglu IY, Blumcke I, El-Osta A, Wirth B and Hahnen E. Survival motor neuron gene 2 silencing by DNA methylation correlates with spinal muscular atrophy disease severity and can be bypassed by histone deacetylase inhibition. Hum Mol Genet 2009; 18: 304-317.
[81] Avila AM, Burnett BG, Taye AA, Gabanella F, Knight MA, Hartenstein P, Cizman Z, Di Prospero NA, Pellizzoni L, Fischbeck KH and Sumner CJ. Trichostatin A increases SMN expression and survival in a mouse model of spinal muscular atrophy. J Clin Invest 2007; 117: 659-671.
[82] Tsai LK, Tsai MS, Ting CH and Li H. Multiple therapeutic effects of valproic acid in spinal muscular atrophy model mice. J Mol Med (Berl) 2008; 86: 1243-1254.
[83] Mercuri E, Bertini E, Messina S, Pelliccioni M, D'Amico A, Colitto F, Mirabella M, Tiziano FD, Vitali T, Angelozzi C, Kinali M, Main M and Brahe C. Pilot trial of phenylbutyrate in spinal muscular atrophy. Neuromuscul Disord 2004; 14: 130-135.
[84] Brahe C, Vitali T, Tiziano FD, Angelozzi C, Pinto AM, Borgo F, Moscato U, Bertini E, Mercuri E and Neri G. Phenylbutyrate increases SMN gene expression in spinal muscular atrophy patients. Eur J Hum Genet 2005; 13: 256-259.
[85] Ryu H, Smith K, Camelo SI, Carreras I, Lee J, Iglesias AH, Dangond F, Cormier KA, Cudkowicz ME, Brown RH, Jr and Ferrante RJ. Sodium phenylbutyrate prolongs survival and regulates expression of anti-apoptotic genes in transgenic amyotrophic lateral sclerosis mice. J Neurochem 2005; 93: 1087-1098.
[86] Del Signore SJ, Amante DJ, Kim J, Stack EC, Goodrich S, Cormier K, Smith K, Cudkowicz ME and Ferrante RJ. Combined riluzole and sodium phenylbutyrate therapy in transgenic amyotrophic lateral sclerosis mice. Amyotroph Lateral Scler 2009; 10: 85-94.
[87] Petri S, Kiaei M, Kipiani K, Chen J, Calingasan NY, Crow JP and Beal MF. Additive neuroprotective effects of a histone deacetylase inhibitor and a catalytic antioxidant in a transgenic mouse model of amyotrophic lateral sclerosis. Neurobiol Dis 2006; 22: 40-49.
[88] Sugai F, Yamamoto Y, Miyaguchi K, Zhou Z, Sumi H, Hamasaki T, Goto M and Sakoda S. Benefit of valproic acid in suppressing disease progression of ALS model mice. Eur J Neurosci 2004; 20: 3179-3183.
[89] Rouaux C, Panteleeva I, Rene F, Gonzalez de Aguilar JL, Echaniz-Laguna A, Dupuis L, Menger Y, Boutillier AL and Loeffler JP. Sodium valproate exerts neuroprotective effects in vivo through CREB-binding protein-dependent mechanisms but does not improve survival in an amyotrophic lateral sclerosis mouse model. J Neurosci 2007; 27: 5535-5545.
[90] Feng HL, Leng Y, Ma CH, Zhang J, Ren M and Chuang DM. Combined lithium and valproate treatment delays disease onset, reduces neurological deficits and prolongs survival in an amyotrophic lateral sclerosis mouse model. Neuroscience 2008; 155: 567-572.
[91] Cummings JL. Alzheimer's disease. N Engl J Med 2004; 351: 56-67.
[92] Alonso AC, Grundke-Iqbal I and Iqbal K. Alzheimer's disease hyperphosphorylated tau sequesters normal tau into tangles of filaments and disassembles microtubules. Nat Med 1996; 2: 783-787.
[93] Karran E, Mercken M and Strooper BD. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. Nat Rev Drug Discov 2011; 10: 698-712.
[94] Ricobaraza A, Cuadrado-Tejedor M, Perez-Mediavilla A, Frechilla D, Del Rio J and Garcia-Osta A. Phenylbutyrate ameliorates cognitive deficit and reduces tau pathology in an Alzheimer's disease mouse model. Neuropsychopharmacology 2009; 34: 1721-1732.
[95] Qing H, He G, Ly PT, Fox CJ, Staufenbiel M, Cai F, Zhang Z, Wei S, Sun X, Chen CH, Zhou W, Wang K and Song W. Valproic acid inhibits Abeta production, neuritic plaque formation, and behavioral deficits in Alzheimer's disease mouse models. J Exp Med 2008; 205: 2781-2789.
[96] Francis YI, Fa M, Ashraf H, Zhang H, Staniszewski A, Latchman DS and Arancio O. Dysregulation of histone acetylation in the APP/PS1 mouse model of Alzheimer's disease. J Alzheimers Dis 2009; 18: 131-139.
[97] Kilgore M, Miller CA, Fass DM, Hennig KM, Haggarty SJ, Sweatt JD and Rumbaugh G.

Inhibitors of class 1 histone deacetylases reverse contextual memory deficits in a mouse model of Alzheimer's disease. Neuropsychopharmacology 2010; 35: 870-880.
[98] Guan JS, Haggarty SJ, Giacometti E, Dannenberg JH, Joseph N, Gao J, Nieland TJ, Zhou Y, Wang X, Mazitschek R, Bradner JE, DePinho RA, Jaenisch R and Tsai LH. HDAC2 negatively regulates memory formation and synaptic plasticity. Nature 2009; 459: 55-60.
[99] Broide RS, Redwine JM, Aftahi N, Young W, Bloom FE and Winrow CJ. Distribution of histone deacetylases 1-11 in the rat brain. J Mol Neurosci 2007; 31: 47-58.
[100] Rivieccio MA, Brochier C, Willis DE, Walker BA, D'Annibale MA, McLaughlin K, Siddiq A, Kozikowski AP, Jaffrey SR, Twiss JL, Ratan RR and Langley B. HDAC6 is a target for protection and regeneration following injury in the nervous system. Proc Natl Acad Sci USA 2009; 106: 19599-19604.
[101] Kook H, Lepore JJ, Gitler AD, Lu MM, Wing-Man Yung W, Mackay J, Zhou R, Ferrari V, Gruber P and Epstein JA. Cardiac hypertrophy and histone deacetylase-dependent transcriptional repression mediated by the atypical homeodomain protein Hop. J Clin Invest 2003; 112: 863-871.
[102] Kong Y, Tannous P, Lu G, Berenji K, Rothermel BA, Olson EN and Hill JA. Suppression of class I and II histone deacetylases blunts pressure-overload cardiac hypertrophy. Circulation 2006; 113: 2579-2588.
[103] Kee HJ, Sohn IS, Nam KI, Park JE, Qian YR, Yin Z, Ahn Y, Jeong MH, Bang YJ, Kim N, Kim JK, Kim KK, Epstein JA and Kook H. Inhibition of histone deacetylation blocks cardiac hypertrophy induced by angiotensin II infusion and aortic banding. Circulation 2006; 113: 51-59.
[104] Berry JM, Cao DJ, Rothermel BA and Hill JA. Histone deacetylase inhibition in the treatment of heart disease. Expert Opin Drug Saf 2008; 7: 53-67.
[105] Granger A, Abdullah I, Huebner F, Stout A, Wang T, Huebner T, Epstein JA and Gruber PJ. Histone deacetylase inhibition reduces myocardial ischemia-reperfusion injury in mice. FASEB J 2008; 22: 3549-3560.
[106] Antos CL, McKinsey TA, Dreitz M, Hollingsworth LM, Zhang CL, Schreiber K, Rindt H, Gorczynski RJ and Olson EN. Dose-dependent blockade to cardiomyocyte hypertrophy by histone deacetylase inhibitors. J Biol Chem 2003; 278: 28930-28937.
[107] Cao DJ, Wang ZV, Battiprolu PK, Jiang N, Morales CR, Kong Y, Rothermel BA, Gillette TG and Hill JA. Histone deacetylase (HDAC) inhibitors attenuate cardiac hypertrophy by suppressing autophagy. Proc Natl Acad Sci USA 2011; 108: 4123-4128.
[108] Cho YK, Eom GH, Kee HJ, Kim HS, Choi WY, Nam KI, Ma JS and Kook H. Sodium valproate, a histone deacetylase inhibitor, but not captopril, prevents right ventricular hypertrophy in rats. Circ J 2010; 74: 760-770.
[109] Bogaard HJ, Mizuno S, Hussaini AA, Toldo S, Abbate A, Kraskauskas D, Kasper M, Natarajan R and Voelkel NF. Suppression of histone deacetylases worsens right ventricular dysfunction after pulmonary artery banding in rats. Am J Respir Crit Care Med 2011; 183: 1402-1410.
[110] Karagiannis TC, Lin AJ, Ververis K, Chang L, Tang MM, Okabe J and El-Osta A. Trichostatin A accentuates doxorubicin-induced hypertrophy in cardiac myocytes. Aging (Albany NY) 2010; 2: 659-668.
[111] Ververis K, Rodd AL, Tang MM, El-Osta A and Karagiannis TC. Histone deacetylase inhibitors augment doxorubicin-induced DNA damage in cardiomyocytes. Cell Mol Life Sci 2011.
[112] McKinsey TA and Olson EN. Dual roles of histone deacetylases in the control of cardiac growth. Novartis Found Symp 2004; 259: 132 -141; discussion 141-135, 163-139.
[113] Backs J, Olson EN. Control of cardiac growth by histone acetylation/deacetylation. Circ Res 2006; 98: 15-24.
[114] Haberland M, Montgomery RL and Olson EN. The many roles of histone deacetylases in development and physiology: implications for disease and therapy. Nat Rev Genet 2009; 10: 32-42.
[115] Zhang CL, McKinsey TA, Chang S, Antos CL, Hill JA and Olson EN. Class II histone deacetylases act as signal-responsive repressors of cardiac hypertrophy. Cell 2002; 110: 479-488.
[116] Olson EN, Backs J and McKinsey TA. Control of cardiac hypertrophy and heart failure by histone acetylation/deacetylation. Novartis Found Symp 2006; 274: 3-12; discussion 13-19, 152-155, 272-156.
[117] Kolodziejczyk SM, Wang L, Balazsi K, DeRepentigny Y, Kothary R and Megeney LA. MEF2 is upregulated during cardiac hypertrophy and is required for normal post-natal growth of the myocardium. Curr Biol 1999; 9: 1203-1206.
[118] Song K, Backs J, McAnally J, Qi X, Gerard RD, Richardson JA, Hill JA, Bassel-Duby R and Olson EN. The transcriptional coactivator CAMTA2 stimulates cardiac growth by opposing class II histone deacetylases. Cell 2006; 125: 453-466.
[119] Chang S, McKinsey TA, Zhang CL, Richardson JA, Hill JA and Olson EN. Histone deacetylases 5 and 9 govern responsiveness of the heart to a subset of stress signals and play redundant roles in heart development. Mol Cell Biol 2004; 24: 8467-8476.
[120] Davidson SM, Townsend PA, Carroll C, Yurek-George A, Balasubramanyam K, Kundu TK, Stephanou A, Packham G, Ganesan A and Latchman DS. The transcriptional coactivator

p300 plays a critical role in the hypertrophic and protective pathways induced by phenylephrine in cardiac cells but is specific to the hypertrophic effect of urocortin. Chembiochem 2005; 6: 162-170.

[121] Ito K, Caramori G, Lim S, Oates T, Chung KF, Barnes PJ and Adcock IM. Expression and activity of histone deacetylases in human asthmatic airways. Am J Respir Crit Care Med 2002; 166: 392-396.

[122] Grausenburger R, Bilic I, Boucheron N, Zupkovitz G, El-Housseiny L, Tschismarov R, Zhang Y, Rembold M, Gaisberger M, Hartl A, Epstein MM, Matthias P, Seiser C and Ellmeier W. Conditional deletion of histone deacetylase 1 in T cells leads to enhanced airway inflammation and increased Th2 cytokine production. J Immunol 2010; 185: 3489-3497.

[123] Assem el SK, Peh KH, Wan BY, Middleton BJ, Dines J and Marson CM. Effects of a selection of histone deacetylase inhibitors on mast cell activation and airway and colonic smooth muscle contraction. Int Immunopharmacol 2008; 8: 1793-1801.

[124] Choi JH, Oh SW, Kang MS, Kwon HJ, Oh GT and Kim DY. Trichostatin A attenuates airway inflammation in mouse asthma model. Clin Exp Allergy 2005; 35: 89-96.

[125] Banerjee A, Trivedi CM, Damera G, Jiang M, Jester W, Hoshi T, Epstein JA and Panettieri Jr RA. Trichostatin A Abrogates Airway Constriction, but not Inflammation in Mouse and Human Asthma Models. Am J Respir Cell Mol Biol 2011.

[126] Royce SG, Dang W, Gao Y, Tran J, El-Osta A, Karagiannis TC and Tang LKM. Resveratrol has protective effects against airway remodeling and airway inflammation in a murine model of allergic airways disease. Pathobiology of Aging & Age-related Diseases 2011; 1: 7134.