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Histone deacetylases as targets for treatment of multiple diseases

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Abstract

HDACs (histone deacetylases) are a group of enzymes that deacetylate histones as well as non-histone proteins. They are known as modulators of gene transcription and are associated with proliferation and differentiation of a variety of cell types and the pathogenesis of some diseases. Recently, HDACs have come to be considered crucial targets in various diseases, including cancer, interstitial fibrosis, autoimmune and inflammatory diseases, and metabolic disorders. Pharmacological inhibitors of HDACs have been used or tested to treat those diseases. In the present review, we will examine the application of HDAC inhibitors in a variety of diseases with the focus on their effects of anti-cancer, fibrosis, anti-inflammatory, immunomodulatory activity and regulating metabolic disorders.

Keywords

acetylation; cancer; fibrosis; histone deacetylase; immunomodulation; inflammation; metabolic disorder

INTRODUCTION

Epigenetics refers to the regulation of gene expression via posttranslational modification of protein complexes associated with DNA without alterations in the DNA sequence [1,2]. The fundamental structure of chromatin consists of the nucleosome, which is composed of 146 bp of DNA surrounding an octamer of core histones (two H2A/H2B dimers and a H3/H4 tetramer) [2]. Remodelling of chromatin between relatively ‘open’ and ‘closed’ forms has a key role in epigenetic regulation of gene expression [3]. Post-translational modifications of the N-terminal tails of histones are involved in this remodelling process, including acetylation, methylation, phosphorylation, ubiquitinylation, sumoylation, carbonylation and glycosylation [3,4].

Acetylation and deacetylation are regulated by two groups of enzymes: HATs (histone acetyltransferases) and HDACs (histone deacetylases). The reverse activities of HATs and

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HDACs regulate gene expression through chromatin modification [5,6]. HDACs are a class of deacetylating enzymes that remove acetyl groups from ε-amino groups of lysine residues of histones, as well as non-histone proteins, causing the condensation of chromatin structure and thereby repressing gene expression [5,6]. On the basis of their homology with respective yeast orthologues, HDACs are classified into four groups: class I HDACs (HDAC1– 3 and 8), which are related to yeast Rpd3 (reduced potassium dependency 3) [7]; class II HDACs, which are divided into two subclasses, class IIa (HDAC4, 5, 7, and 9) and class IIb (HDAC6 and 10), both homologous with the yeast gene Hda1 (histone deacetylase 1) [8]; class III, which consist SIRT1–7, also known as sirtuins, are homologous with yeast Sir2 (silent information regulator 2) [9,10]; and class IV (HDAC11), which contains conserved residues in catalytic regions shared by both class I and II HDAC enzymes [11]. Class I and II are referred to as ‘classical’ HDACs.

It has been widely demonstrated that HDACs are promising targets for therapeutic interventions in cancer and other diseases. Classical HDACs are mainly involved in the development of cancer. Increased expression of class I HDACs (HDAC1–3) is associated with nodal spread and is an independent prognostic marker for gastric cancer [12]. High expression of some of the class II HDACs, such as HDAC6, is correlated with tumour invasion in breast cancer [13], and low expression of class II HDACs genes (HDAC5 and HDAC10) is associated with poor prognosis in lung cancer patients [14]. In addition to cancers, HDACs have been shown to be involved in other diseases, including tissue fibrosis, autoimmune and inflammatory diseases, and metabolic disorders. Since HDACs are considered as crucial targets of multiple diseases, HDACIs (HDAC inhibitors) have been evaluated in basic experiments and clinical trials. In the present review, we will evaluate the application of HDACIs in these diseases, with a focus on their effects on cancer, fibrosis, inflammation and immunomodulation and metabolic disorders (Table 1).

HDAC INHIBITORS

HDACIs are compounds that have the ability to prevent the deacetylation of lysine residues within the N-terminal tails of histone proteins. On the basis of their chemical structure, HDACIs are categorized into the six groups: (i) hydroxamates, such as TSA (trichostatin A) and SAHA (suberoylanilide hydroxamic acid); (ii) short-chain fatty acids, such as butyric acid and valproic acid; (iii) cyclic tetrapeptides, such as CHAP31 (cyclic hydroxamic-acid-containing peptide 31) and romidepsin (FK- 228); (iv) benzamides, such as entinostat (MS-275), tacedinaline (CI-994) and chidamide (CS-055); (v) electrophilic ketones, such as trifluoromethylketone; and (vi) miscellaneous compounds, such as MGCD0103. They may also be classified according to their specificity for HDACs [1]. SAHA, TSA, panobinostat, belinostat and resminostat are pan-deacetylase inhibitors. Butyrate and valproate inhibit class I and IIa HDACs, whereas romidepsin, MS-275 and mocetinostat are considered to be class I-specific [1]. Tubacin is specific to inhibit HDAC6 [15]. The ‘classical’ HDACIs are specific to the Zn^{2+} -dependent class I and class II HDACs and act by binding to the Zn^{2+} -containing catalytic domain of the HDACs.

The mechanism of action of HDACIs involves inhibiting the deacetylation of histones. Hyperacetylation results in an increase in the space between the nucleosome and the DNA

that is wrapped around it. The opening of chromatin structure subsequently provides the access for gene transcription. HDACIs target gene expression without changing DNA sequence. A study in colon carcinoma cells showed that 7% of genes were modulated by sodium butyrate treatment (256 genes elevated and 333 genes repressed of 8063 genes) [16]. Another study in bladder carcinoma and breast carcinoma cells demonstrated that approximately 8–10% of genes are regulated on the Affymetrix 6800 gene chips by various HDACIs [17]. Post-TSA treatment results in differential gene expression of various enzymes and transcription factors involved in apoptosis, cell-cycle regulation, extracellular matrix regulation, signal transduction, immune response and metabolism pathways [18].

Besides histones, HDACIs also have effects on non-histone proteins which include proteins involved in the regulation of gene expression, pathways of extrinsic and intrinsic apoptosis, cellcycle progression, redox pathways, mitotic division, DNA repair, cell migration and angiogenesis [19-26]. A large number of nonhistone transcription factors and transcriptional co-regulators are known to be modified by acetylation. HDACIs can alter the degree of acetylation of these molecules and, therefore, increase or repress their activity. For example, the inducible transcription factor NF-κB (nuclear factor κB) is deregulated in a large number of diseases, and application of HDACIs has been shown to repress NF-κB signalling and expression of several NF-κB target genes [27,28]. Therefore HDACIs might have an effect on immune responses, inflammation, cell survival, differentiation and proliferation. The tumour suppressor p53 is a key player in cellular signalling. HDACIs, including TSA, SAHA and MS- 275, dominantly up-regulate the gene expression of p53 [17,29], which may partly be responsible for the anti-cancer effect of HDACIs. STAT3 (signal transducer and activator of transcription 3) is a transcriptional factor required for the development and progression of tissue fibrosis in multiple organs, including kidney, skin and lung. The administration of TSA can suppress transcriptional activation of STAT3 [30], which might be one of the possible mechanisms of the anti-fibrotic effects of HDACIs.

Therefore HDACIs can induce acetylation of histone, as well as non-histone proteins, which affect a variety of physiological and pathological processes, controlling apoptosis/ autophagy, cell cycle, fibrogenesis, immune response, inflammation and metabolism through its downstream molecular targets (Figure 1).

HDACs AND CANCERS

Traditionally, cancer has been considered to originate from genetic alteration, such as gene mutations, deletions, rearrangements and chromosomal abnormalities, leading to aberrant expression of tumour suppressor genes and oncogenes [31,32]. However, growing evidence suggests that epigenetic modulation also plays a crucial role in the initiation and progression of cancers [33,34]. Different from genetic defects, epigenetic changes are reversible and therefore considered as a promising newmechanistic class of anti-cancer therapy. It has been shown that a global loss of monoacetylation of histone H4 is a common hallmark of human tumour cells [35]. Changes in histone H4 acetylation occur early during the tumorigenic process [35]. The aberrant recruitment of HDACs to promoters through their physical association with oncogenic DNA-binding fusion proteins results from chromosomal translocations or overexpression of repressive transcription factors that physically interact

with HDACs [3]. For example, the oncogenic PML-RARα (promyelocytic leukaemia-retinoic acid receptor α), PLZF-RARα (promyelocytic leukaemia zinc fingerretinoic acid receptor α) and AML-1 (acute myeloid leukaemia-1) transcription factors and the AML1-ETO (eight-twenty-one) corepressor fusion proteins induce leukaemogenesis by recruiting HDAC-containing repressor complexes to constitutively repress expression of specific target genes [36,37]. Inhibition of HDAC activity increased the transcriptional activity of the oncogenic fusion protein and transcription factor EWS-FLI1 by increasing its DNA binding activity in Ewing sarcoma (EWS) [38]. Individual HDACs, including HDAC1, HDAC2, HDAC3 and HDAC6, are overexpressed in a number of tumours [39-42]. siRNA (small interfering RNA)-mediated knockdown of individual HDACs in certain tumour cell lines suppresses tumour cell growth and survival [42,43], indicating the critical role of HDACs in the development and progression of tumours and as anticancer therapeutic targets.

HDACIs inhibit the dynamic turnover of acetylation, resulting in hyperacetylation of target proteins [44]. This can affect a wide range of cellular functions, and promote cytostatic and cytotoxic effects in a wide range of tumour cell types, but has little effect on normal cells [44]. The molecular mechanisms underlying the anticancer effects of HDACIs remain to be fully elaborated. Genomic effects on gene transcription may be responsible for the anticancer effects of HDACIs. In several models of cancer, HDACIs, including TSA, SAHA and MS-275, up-regulate tumour suppressing genes {p53, p21, pRb (retinoblastoma protein), tob1, Hep 27, Cbp (C-terminal Src kinase-binding protein)/PAG1 (phosphoprotein associated with glycosphingolipid-enriched microdomains 1), IRF [IFN (interferon) regulatory factor]-8} and down-regulate oncogenes [Src, HIF1α (hypoxia-inducible factor 1α) and HER2 (human epidermal growth factor receptor 2)] [17,45-48], therefore inhibiting the development and progression of tumours. HDACIs can cause cell-cycle arrest in a p53-independent manner due to induction of p21 and/or tob1 byHDACIs through a direct effect on the Sp1 site in the p21 promoter [49,50]. Since most cancer cells have lost p53 or pRb or both, resulting in loss of the G_1/S DNA damage checkpoint, the induction of p21, p27Kip1 and/or tob1 by HDACIs produces an aberrant cell-cycle arrest (checkpoint), leading to apoptosis [17]. HDACIs can also increase the sensitivity of carcinoma cells to TRAIL [TNF (tumour necrosis factor)-related apoptosis-inducing ligand] and down-regulate c-FLIP [cellular Fas-associated death domainlike IL (interleukin)-1β-converting enzyme-inhibitory protein], resulting in activation of extrinsic apoptosis pathways and inducing apoptosis of tumour cells [51]. Besides apoptosis, HDACIs also induce caspase-independent autophagic cell death in tumour cells [52]. Furthermore, HDACIs have anti-angiogenic effects, associating with decreased expression of pro-angiogenic genes such as VEGF (vascular endothelial growth factor), bFGF (basic fibroblast growth factor), HIF1α, angiopoietin 2, TIE2 (tunica intima endothelial kinase 2), survivin and eNOS [endothelial NOS (nitric oxide synthase)] [53-57]. Inhibition of angiogenesis by HDACIs affects the nutrient supply to the primary tumour [3]. HDACIs are also reported to sensitize cancer cells to chemotherapies. TS (thymidylate synthase) is the target of the chemotherapeutic agent 5-FU (5-fluorouracil), which is associated with drug resistance. Initial gene expression studies with HDACIs recognized that TS was one of the HDACI gene targets [17]. HDACI treatment enhanced the sensitivity of cancer cells to 5-FU via down-regulation of TS expression [58,59]. In

summary, HDACI-regulated gene expression can contribute to cell-cycle arrest, apoptosis and angiogenesis inhibition.

Currently, HDACIs have been successfully used as therapies for the treatment of haematological malignancies. In particular, SAHA and romidepsin (FK-228) have been approved by the United States FDA (Food and Drug Administration) for the treatment of CTCL (cutaneous T-cell lymphoma). A single dose of HDACIs demonstrated limited clinical benefit against solid tumours. However, HDACIs in combination with other anticancer agents have shown a synergistic effect. For example, SAHA enhanced sensitivity of non-small-cell lung cancer cells to 5- FU/S-1 [58]. VPA (valproic acid) can augment the antitumour effects of 5-FU in a human pancreas cancer cell line and a cholangiocarcinoma cell line [60]. HDACIs are also used as radiosensitizers in the treatment of solid tumours. The combination of an HDACI, H6CAHA, with γ-radiation completely blocked the growth of human prostate cancer tumour xenografts over 60 days [61]. Moreover, adding SAHA to capecitabine-based chemoradiotherapy enhanced the radiosensitivity of xenografts in terms of inhibiting colorectal carcinoma growth [62]. VPN was shown to augment radiation-induced cytotoxicity in human oesophageal squamous cell carcinoma by chromatin decondensation with histone hyperacetylation and down-regulation of Rad51 [63]. Therefore HDACIs can serve as a promising therapy for cancers.

HDACs AND INTERSTITIAL FIBROSIS

Recent studies have shown that the HDACs play an important role in the development of multiple tissue fibrosis, including skin, kidney, liver, heart and lung. Activation of fibroblasts is critically involved in the development of interstitial fibrosis of a variety of organs. The activated fibroblast, termed a myofibroblast, demonstrates specific phenotypic changes, including the expression of α-SMA (α-smooth muscle actin) and increased production of ECM (extracellular matrix) components, including collagen and fibronectin [30]. Glenisson et al. [64] examined the role of HDACs in TGF-β1 (transforming growth factor β1)-induced myofibroblastic differentiation, a process involved in tissue fibrosis. They found that among the eight HDACs (HDAC1–HDAC8) tested, silencing of HDAC4, HDAC6 and HDAC8 expression impaired TGF-β1-induced α-SMA expression. HDAC4 silencing efficiently abrogated α-SMA expression and prevented TGF-β1-mediated morphological changes. Intervention by TSA prevented α-SMA transcript and protein expression and morphological changes mediated by TGF-β1 in cultured human skin fibroblasts [64]. These findings suggest that HDACs are involved in the process of skin fibrosis and that HDAC4 is an essential epigenetic regulator of myofibroblastic differentiation.

An increase in the expression of HDAC1 and HDAC2 and a decrease in histone acetylation were observed in tubulointerstitial injury induced by UUO (unilateral ureteral obstruction) [65]. Treatment with TSA attenuatedmacrophage infiltration and fibrotic changes in this model. The induction of CSF-1 (colonystimulating factor-1), a chemokine known to be involved in macrophage infiltration in tubulointerstitial injury, was reduced in the injured kidney of mice treated with TSA. TSA, valproate and the knockdown of either HDAC1 or HDAC2 also significantly reduced CSF-1 expression induced by TNF-α in renal tubular

cells. These results suggest that tubular HDAC1 and HDAC2 may contribute to the production of CSF-1, macrophage infiltration and profibrotic responses in response to injury and implicates a potential use of HDAC inhibition in reducing inflammation and fibrosis in tubulointerstitial injury. Our studies have also shown that HDAC1 and HDAC2 are involved in regulating proliferation of renal interstitial fibroblasts [66]. Silencing either HDAC1 or HDAC2 with siRNA significantly inhibited cell proliferation, decreased the expression of cyclin D1 and increased the expression of p57, a negative cell-cycle regulator [66]. Furthermore, inhibition of HDAC activity with TSA blocked the proliferation and activation of renal interstitial fibroblasts in a rat model of UUO and in a rat renal interstitial fibroblast line (NRK-49F) *in vitro* [30]. In *in vitro* studies employing cultured NRK-49F cells, TSA treatment inhibited fibroblast proliferation as indicated by decreasing cell numbers and suppressing cyclin D1 expression. TSA also blocked fibroblast activation as shown by diminishing expression of α-SMA and fibronectin. These suggest that pharmacological HDAC inhibition may exert antifibrotic activity by inactivation of renal interstitial fibroblasts.

HSCs (hepatic stellate cells) are the major cellular sources of ECMin chronic liver diseases leading to fibrosis. In a humanHSC line, sodium valproate, a class I HDACI, exerts antifibrogenic activity by blocking the TGF-β1 autocrine loop and inhibiting TGF-β1-induced collagen type 1 α1 expression [67]. Another HDACI, TSA, affects the development of the actin cytoskeleton and inhibits collagen types I and III and α-SMA in HSCs, thereby abrogating the process ofHSC transdifferentiation [68,69]. These findings indicate that the antifibrogenic effect of HDACIs in the liver results from inhibiting transdifferentiation of stellate cells into myofibroblasts and the subsequent production of ECM.

In human fibroblasts from patients with idiopathic pulmonary fibrosis, Spiruchostatin A, a class I HDACI, inhibits TGF-β1-induced expression of α-SMA, collagen I and collagen III, and soluble collagen release [70]. In addition, HDAC inhibition prevents cardiac hypertrophy induced by AngII (angiotensin II) infusion and aortic banding and reverses atrial arrhythmia inducibility and fibrosis in cardiac hypertrophy independent of AngII [71,72]. HDACIs inhibit α-SMA expression and collagen synthesis and diminish DNA binding of AP-1 (activating protein-1), a key transcription factor in profibrogenic signalling in pancreatic stellate cells [73]. Collectively, these studies suggest a potential antifibrotic effect of HDACIs in a variety of organs.

There are several possible mechanisms accounting for antifibrotic effects of HDACIs. In a number of tissues, activation of STAT3 increases expression of multiple profibrotic genes and is required for activation of renal interstitial fibroblasts and the progression of renal fibrosis [74]. Administration of TSA could suppress transcriptional activation of STAT3, leading to inactivation of renal fibroblasts [30]. In addition, TSA treatment inhibits the activity of STAT- dependent signal transduction pathways in NIH 3T3 cells and sarcoma cells [75,76]. Lee et al. [77] have shown that HDACI-induced hyperacetylation of histones H3 and H4 was associated with the down-regulation of fibronectin transcription. Yoshikawa et al. [78] examined the effect of TSA on the EMT (epithelial-to-mesenchymal transition) in cultured tubular epithelial cells and found that TSA can prevent TGF-β1-induced EMT. Mechanistic studies revealed that TSA induced the expression of two inhibitory factors of

TGF-β1 signals: Id2 (inhibitors of DNA binding/differentiation 2) and BMP-7 (bone morphogenetic protein-7). A ChIP (chromatin immunoprecipitation) assay confirmed that histone acetylation was involved in the downregulation of E-cadherin and the up-regulation of Id2 and BMP-7 [78]. Overall, although the mechanisms of HDACI-exerted antifibrotic effects remain incompletely understood, transcriptional activation of repressors and acetylation of non-histone proteins may, in part, explain their antifibrotic effects [77].

HDACs AND IMMUNOMODULATION

Increasing evidence has implicated protein acetylation in innate and adaptive immune pathways [79]. Classical HDACs have been identified to play a key role in regulating TLR (Toll-like receptor) and IFN signalling pathways in innate immunity, as well as antigen presentation, helper T-cell polarization, lymphocyte development and function [79]. It has been demonstrated that HDACIs down-regulate the expression of numerous host defence genes, including pattern recognition receptors, kinases, transcription regulators, cytokines, chemokines, growth factors and co-stimulatory molecules, as assessed by genome-wide microarray analyses [80]. HDACIs have also been shown to induce the expression of Mi-2β and enhance the DNA-binding activity of the Mi-2/NuRD (nucleosome remodelling deacetylase) complex that acts as a transcriptional repressor of macrophage cytokine production. Furthermore, HDACIs can increase the susceptibility to bacterial and fungal infections, but confer protection against toxic and septic shock [80]. Recent studies have also shown that a tubastatin A analogue, a selective HDAC6 inhibitor, augments the immunosuppressive effect of Foxp3$^+$ (forkhead box P3$^+$) T_{reg}-cells (regulatory T-cells) and inhibits the mitotic division of effector T-cells [23]. Therefore these findings suggest that HDACIs are able to regulate the expression of innate immune genes and host defences against microbial pathogens, and that HDACIs are mostly immunosuppressive. The immunosuppressive properties of HDACIs are associated with skewed dendritic cell differentiation and impaired cytokine secretion by dendritic cells [81-83]. The observed defects in dendritic cell function on exposure to HDACIs seem to reflect the obstruction of signalling through NF-κB, IRF-3 and IRF-8 [81].

On the basis of the immunosuppressive effects, HDACIs may be potent agents for decreasing autoimmunity and transplant rejection. Edens et al. [84] have shown that treatment with TSA induces antigen-specific energy in both cloned and naïve CD4$^+$ T-cells, suggesting their potential to induce immune tolerance in organ transplantation. Tao and Hancock [85] have reported that HDAC inhibition promoted the generation of T_{reg}-cells and enhanced their functions. In addition, administration of FR276457, a hydroxamic derivative, can inhibit T-cell proliferation and prolong allograft survival, thereby exhibiting marked immunosuppressive effects in a rat heterotopic cardiac transplant model [86] and in a canine renal transplant model [87].

Foxp3$^+$ T_{reg}-cells play a key part in limiting autoimmunity and maintaining peripheral tolerance, and mutations of Foxp3 lead to lethal autoimmunity in humans and mice [88-92]. Therapeutic manipulation of Foxp3 acetylation using HDACIs can promote the development and suppressive functions of Foxp3$^+$ T_{reg}-cells, with beneficial consequences in models of transplant rejection, colitis and arthritis [93-97]. In murine models of T-celldependent

disease, treatment with TSA or SAHA decreased the severity of T_H2 (T-helper 2)-associated lung airway hypersensitivity responses [98], renal disease in MRL/lpr mice [99], colitis [100], RA (rheumatoid arthritis) [101,102], graft-versus-host disease post-bone marrow transplantation [103] and the 'cytokine storm' induced by the CD3 monoclonal antibody therapy used in a bone-marrow-transplant-conditioning regimen [104].

HDACs AND INFLAMMATION

Alterations in the balance of histone acetylation and deacetylation could affect many aspects of cellular function, including cell growth, differentiation, cell death, cell–cell and cell–matrix interactions, and the inflammatory response [105]. The inflammatory response is triggered by some stimulus-regulated transcription factors and involves a large number of differential expression genes [106,107]. Recent studies have demonstrated that HDAC3 is required for the expression of numerous inflammatory genes, including IFN-β-dependent genes [e.g. Nos2 and Ptgs2 (prostaglandin-endoperoxide synthase 2)] and IFN-β-independent genes, such as IL (interleukin)-6, in macrophages in response to LPS (lipopolysaccharide) [108]. HDAC4 has also been shown to regulate vascular inflammatory responses and promote hypertension. Inhibition of HDAC4 by siRNA blocked TNF-induced monocyte adhesion, VCAM-1 (vascular cell adhesion molecule-1) expression and transcriptional activity of NF-κB in cultured rat mesenteric arterial smooth muscle cells [109]. Therefore inhibition of HDAC activity might exert antiinflammatory effects.

In addition, HDACIs appear to be potent anti-inflammatory agents. TSA suppresses IL-6 production by accelerating IL-6 mRNA decay in RA fibroblast-like synoviocyte and macrophages [110]. Sodium valproate represses IL-12 and TNF-α production, and promotes IL-10 expression in macrophages exposed to LPS [111]. In an endotoxaemia model, SAHA exhibits dosedependent inhibition of the circulating level of pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and IFN-γ induced by LPS [112]. In the collagen-induced arthritis mouse model, MS-275 has been shown to decrease serum IL-6 and IL-1β levels [102]. SAHA and TSA also inhibit the production of the inflammatory cytokines IL-12, IFN-γ, IL-6 and IL-10 in isolated splenocytes of MRL-lpr/lpr mice, a murine model of SLE (systemic lupus erythematosus) [99]. Moreover, HDACIs can ameliorate inflammatory bowel diseases. For example, butyrate can effectively treat Crohn's disease [113] and ulcerative colitis [114]. It has been reported that colitis was associated with increased local expression of HDAC9. Inhibition of HDAC9 prevented colitis and reduced established colitis in mice [95]. Recent findings in humans [115] have also indicated that a novel HDAC inhibitor, ITF2357, exerts its anti-inflammatory capacity. Therefore HDACIs may be a new and promising drug class for the treatment of inflammatory diseases such as SLE, arthritis, endotoxaemia and inflammatory bowel disease.

HDACs AND METABOLIC DISORDERS

The aetiology of diabetes is complex and multifactorial with contributions from many genes and unknown environmental factors. There is evidence showing a genetic association between diabetes and HDACs. GWAS (genome-wide association studies) have found a significant linkage between the chromosomal region 6q21, where HDAC2 is located, and

both Type 1 diabetes mellitus and Type 2 diabetes mellitus [116-118]. Another locus identified in GWAS of Type 2 diabetes mellitus lies on chromosome 19q13; the HDAC Sirt2 maps to this region [116,117].

In patient with diabetes, β-cell dysfunction is associated with a variable degree of insulin resistance [119]. Studies have demonstrated that regulation of the expression of insulin from β-cells is under the control of acetylation [116,119,120]. At high glucose levels, Pdx1 (pancreatic and duodenal homeobox factor 1), which is involved in glucose-stimulated insulin gene expression, interacts with the HAT p300, leading to increased acetylation of histone H4 in the insulin promoter. These events appear to be necessary for preproinsulin transcription induced by glucose [119,121-125]. Conversely, at low glucose levels, where insulin production is shut off, the acetylation of histone H4 at the insulin promoter is abolished, correlatingwith the recruitment ofHDAC1 andHDAC2 to the insulin promoter by Pdx1 [119,121,126]. Mosley and Ozcan [119] have reported that exposure of mouse insulinoma 6 cells to high concentrations of glucose results in the hyperacetylation of histone H4 at the insulin gene promoter, which correlateswith the increased level of insulin gene transcription. In addition, hyperacetylation of histone H4 in response to high concentrations of glucose also occurs at the GLUT (glucose transporter)-2 gene promoter. Recent studies demonstrated that class IIa HDAC4, HDAC5 and HDAC9 regulated the production of insulin in β-cells and somatostatin in δ-cells [127]. Treatment with MC1568, a selective class IIa HDACI, promoted the expression of Pax4, a crucial factor required for proper β- and δ-cell differentiation, and amplifies endocrine β- and δ-cells in pancreatic explants [127]. Inhibition of HDACs has also been shown to have important functions in preventing β-cell inflammatory damage, improving insulin resistance, promoting β-cell development, proliferation, differentiation and function, and positively having an impact on late diabetic microvascular complications [121]. Both pharmacological and genetic inhibition of HDAC3 has been shown to protect β-cells against cytokine-induced apoptosis and restores glucose-stimulated insulin secretion [128]. In addition, oral administration of ITF2357, a class I and II HDACI, improved islet function, reduced iNOS (inducible NOS) levels and apoptosis [129]. IL-1β is a key mediator of insulin resistance and β-cell failure mediated effects on isolated β-cells [130]. A novel HDACI, THS-78-5, has been shown to protect against the IL-1β-mediated loss in β-cell viability and to attenuate IL- 1β-induced iNOS expression and subsequent NO release [130], partly by inhibition of IL-1β-induced transactivation of NF-κB. HDACIs also hold promise as possible treatments for late diabetic complications, such as diabetic nephropathy [77,131] and retinal ischaemia [132]. ThereforeHDACIs may prove to be novel agents for the treatment of diabetes mellitus.

In addition to the regulation of glucose, HDACs are also involved in the regulation of lipid metabolism. It has been reported that HDAC3 suppresses cytosolic PEPCK (phosphoenolpyruvate carboxykinase) transcription by inhibiting the transcriptional activators PPAR (peroxisome-proliferator-activated receptor)-γ and CREB (cAMP-response-element-binding protein) [133]. This mechanism is responsible for inhibition of glyceroneogenesis in adipocytes, which contributes to lipodystrophy in aP2-p65 transgenic mice [133]. Recent findings have also indicated that HDACIs are involved in certain crucial metabolic pathways. TSA treatment results in a clear repression of genes involved in the

cholesterol biosynthetic pathway, thus downregulating cholesterol biosynthesis, which is associated with the down-regulation of SREBP-2 (sterol-regulatory-element-binding protein-2) [18]. TSA also repress the expression of genes involved in other associated metabolic pathways, including fatty acid biosynthesis and glycolysis [18]. HDACIs may be useful as potential therapeutic entities for the control of cholesterol levels in humans.

CONCLUSIONS

Current studies have shown that HDACs are critical enzymes involved not only in the development of cancer, but also other diseases such as interstitial fibrosis, autoimmune, inflammatory diseases, and metabolic disorders. HDACIs have been tested for their therapeutic effects in treating these diseases in clinical trials and/or animal models. However, the underlying mechanism(s) by which HDACIs play a role in inhibiting cancer and other disease initiation and progression remains incompletely understood. A better understanding of the role of HDACs in these diseases will lead to the development of new drugs and specific treatment strategies. The use of HDACIs as novel therapeutic agents has shown great promise for these compounds as effective therapies in a variety of diseases, suggesting the need for further research to develop therapeutic agents for clinical trials.

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References

1. Khan O, La Thangue NB. HDAC inhibitors in cancer biology: emerging mechanisms and clinical applications. Immunol Cell Biol. 2012; 90:85–94. [PubMed: 22124371]
2. Inche AG, La Thangue NB. Chromatin control and cancer-drug discovery: realizing the promise. Drug Discovery Today. 2006; 11:97–109. [PubMed: 16533707]
3. Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discovery. 2006; 5:769–784. [PubMed: 16955068]
4. Nightingale KP, O'Neill LP, Turner BM. Histone modifications: signalling receptors and potential elements of a heritable epigenetic code. Curr Opin Genet Dev. 2006; 16:125–136. [PubMed: 16503131]
5. Roth SY, Denu JM, Allis CD. Histone acetyltransferases. Annu Rev Biochem. 2001; 70:81–120. [PubMed: 11395403]
6. Thiagalingam S, Cheng KH, Lee HJ, Mineva N, Thiagalingam A, Ponte JF. Histone deacetylases: unique players in shaping the epigenetic histone code. Ann N Y Acad Sci. 2003; 983:84–100. [PubMed: 12724214]
7. Fu W, Wu K, Duan J. Sequence and expression analysis of histone deacetylases in rice. Biochem Biophys Res Commun. 2007; 356:843–850. [PubMed: 17399684]
8. Verdin E, Dequiedt F, Kasler HG. Class II histone deacetylases: versatile regulators. Trends Genet. 2003; 19:286–293. [PubMed: 12711221]
9. Blander G, Guarente L. The Sir2 family of protein deacetylases. Annu Rev Biochem. 2004; 73:417–435. [PubMed: 15189148]
10. Trapp J, Jung M. The role of NAD^+ dependent histone deacetylases (sirtuins) in ageing. Curr Drug Targets. 2006; 7:1553–1560. [PubMed: 17100594]

11. Gao L, Cueto MA, Asselbergs F, Atadja P. Cloning and functional characterization of HDAC11, a novel member of the human histone deacetylase family. J Biol Chem. 2002; 277:25748–25755. [PubMed: 11948178]
12. Weichert W, Roske A, Gekeler V, Beckers T, Ebert MP, Pross M, Dietel M, Denkert C, Rocken C. Association of patterns of class I histone deacetylase expression with patient prognosis in gastric cancer: a retrospective analysis. Lancet Oncol. 2008; 9:139–148. [PubMed: 18207460]
13. Park SY, Jun JA, Jeong KJ, Heo HJ, Sohn JS, Lee HY, Park CG, Kang J. Histone deacetylases 1, 6 and 8 are critical for invasion in breast cancer. Oncol Rep. 2011; 25:1677–1681. [PubMed: 21455583]
14. Osada H, Tatematsu Y, Saito H, Yatabe Y, Mitsudomi T, Takahashi T. Reduced expression of class II histone deacetylase genes is associated with poor prognosis in lung cancer patients. Int J Cancer. 2004; 112:26–32. [PubMed: 15305372]
15. Aldana-Masangkay GI, Rodriguez-Gonzalez A, Lin T, Ikeda AK, Hsieh YT, Kim YM, Lomenick B, Okemoto K, Landaw EM, Wang D, et al. Tubacin suppresses proliferation and induces apoptosis of acute lymphoblastic leukemia cells. Leuk Lymphoma. 2011; 52:1544–1555. [PubMed: 21699378]
16. Mariadason JM, Corner GA, Augenlicht LH. Genetic reprogramming in pathways of colonic cell maturation induced by short chain fatty acids: comparison with trichostatin A, sulindac, and curcumin and implications for chemoprevention of colon cancer. Cancer Res. 2000; 60:4561–4572. [PubMed: 10969808]
17. Glaser KB, Staver MJ, Waring JF, Stender J, Ulrich RG, Davidsen SK. Gene expression profiling of multiple histone deacetylase (HDAC) inhibitors: defining a common gene set produced by HDAC inhibition in T24 and MDA carcinoma cell lines. Mol Cancer Ther. 2003; 2:151–163. [PubMed: 12589032]
18. Chittur SV, Sangster-Guity N, McCormick PJ. Histone deacetylase inhibitors: a new mode for inhibition of cholesterol metabolism. BMC Genomics. 2008; 9:507. [PubMed: 18959802]
19. Seuter S, Heikkinen S, Carlberg C. Chromatin acetylation at transcription start sites and vitamin D receptor binding regions relates to effects of 1alpha,25-dihydroxyvitamin D3 and histone deacetylase inhibitors on gene expression. Nucleic Acids Res. 2012; 41:110–124. [PubMed: 23093607]
20. Tsapis M, Lieb M, Manzo F, Shankaranarayanan P, Herbrecht R, Lutz P, Gronemeyer H. HDAC inhibitors induce apoptosis in glucocorticoid-resistant acute lymphatic leukemia cells despite a switch from the extrinsic to the intrinsic death pathway. Int J Biochem Cell Biol. 2007; 39:1500–1509. [PubMed: 17499001]
21. Baumann P, Junghanns C, Mandl-Weber S, Strobl S, Oduncu F, Schmidmaier R. The pan-histone deacetylase inhibitor CR2408 disrupts cell cycle progression, diminishes proliferation and causes apoptosis in multiple myeloma cells. Br J Haematol. 2012; 156:633–642. [PubMed: 22211565]
22. Mizutani H, Hiraku Y, Tada-Oikawa S, Murata M, Ikemura K, Iwamoto T, Kagawa Y, Okuda M, Kawanishi S. Romidepsin (FK228), a potent histone deacetylase inhibitor, induces apoptosis through the generation of hydrogen peroxide. Cancer Sci. 2010; 101:2214–2219. [PubMed: 20624163]
23. Kalin JH, Butler KV, Akimova T, Hancock WW, Kozikowski AP. Second-generation histone deacetylase 6 inhibitors enhance the immunosuppressive effects of Foxp3+ T-regulatory cells. J Med Chem. 2012; 55:639–651. [PubMed: 22165909]
24. Botrugno OA, Robert T, Vanoli F, Foiani M, Minucci S. Molecular pathways: old drugs define new pathways: non-histone acetylation at the crossroads of the DNA damage response and autophagy. Clin Cancer Res. 2012; 18:2436–2442. [PubMed: 22512979]
25. Lin KT, Wang YW, Chen CT, Ho CM, Su WH, Jou YS. HDAC inhibitors augmented cell migration and metastasis through induction of PKCs leading to identification of low toxicity modalities for combination cancer therapy. Clin Cancer Res. 2012; 18:4691–4701. [PubMed: 22811583]
26. Shan Z, Feng-Nian R, Jie G, Ting Z. Effects of valproic acid on proliferation, apoptosis, angiogenesis and metastasis of ovarian cancer *in vitro* and *in vivo*. Asian Pac J Cancer Prev. 2012; 13:3977–3982. [PubMed: 23098503]

27. Furumai R, Ito A, Ogawa K, Maeda S, Saito A, Nishino N, Horinouchi S, Yoshida M. Histone deacetylase inhibitors block nuclear factor-κB-dependent transcription by interfering with RNA polymerase II recruitment. Cancer Sci. 2011; 102:1081–1087. [PubMed: 21299717]
28. Lindstrom TM, Mohan AR, Johnson MR, Bennett PR. Histone deacetylase inhibitors exert time-dependent effects on nuclear factor-κB but consistently suppress the expression of proinflammatory genes in human myometrial cells. Mol Pharmacol. 2008; 74:109–121. [PubMed: 18375836]
29. Bajbouj K, Mawrin C, Hartig R, Schulze-Luehrmann J, Wilisch-Neumann A, Roessner A, Schneider-Stock R. p53-dependent antiproliferative and pro-apoptotic effects of trichostatin A (TSA) in glioblastoma cells. J Neuro-oncol. 2012; 107:503–516.
30. Pang M, Kothapally J, Mao H, Tolbert E, Ponnusamy M, Chin YE, Zhuang S. Inhibition of histone deacetylase activity attenuates renal fibroblast activation and interstitial fibrosis in obstructive nephropathy. Am J Physiol Renal Physiol. 2009; 297:F996–F1005. [PubMed: 19640900]
31. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000; 100:57–70. [PubMed: 10647931]
32. Kinzler KW, Vogelstein B. Cancer-susceptibility genes. Gatekeepers and caretakers. Nature. 1997; 386:761–763. [PubMed: 9126728]
33. Ray BK, Dhar S, Henry CJ, Rich A, Ray A. Epigenetic regulation by Z-DNA silencer function controls cancer-associated ADAM-12 expression in breast cancer: cross talk between MECP2 and NFI transcription factor family. Cancer Res. 2012; 73:736–744. [PubMed: 23135915]
34. Tommasi S, Zheng A, Weninger A, Bates SE, Li XA, Wu X, Hollstein M, Besaratinia A. Mammalian cells acquire epigenetic hallmarks of human cancer during immortalization. Nucleic Acids Res. 2012; 41:182–195. [PubMed: 23143272]
35. Fraga MF, Ballestar E, Villar-Garea A, Boix-Chornet M, Espada J, Schotta G, Bonaldi T, Haydon C, Ropero S, Petrie K, et al. Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer. Nat Genet. 2005; 37:391–400. [PubMed: 15765097]
36. Melnick AM, Westendorf JJ, Polinger A, Carlile GW, Arai S, Ball HJ, Lutterbach B, Hiebert SW, Licht JD. The ETO protein disrupted in t(8;21)-associated acute myeloid leukemia is a corepressor for the promyelocytic leukemia zinc finger protein. Mol Cell Biol. 2000; 20:2075–2086. [PubMed: 10688654]
37. Zapotocky M, Mejstrikova E, Smetana K, Stary J, Trka J, Starkova J. Valproic acid triggers differentiation and apoptosis in AML1/ETO-positive leukemic cells specifically. Cancer Lett. 2012; 319:144–153. [PubMed: 22261333]
38. Schlottmann S, Erkizan HV, Barber-Rotenberg JS, Knights C, Cheema A, Uren A, Avantaggiati ML, Toretsky JA. Acetylation increases EWS-FLI1 DNA binding and transcriptional activity. Front Oncol. 2012; 2:107. [PubMed: 22973553]
39. Xie HJ, Noh JH, Kim JK, Jung KH, Eun JW, Bae HJ, Kim MG, Chang YG, Lee JY, Park H, Nam SW. HDAC1 inactivation induces mitotic defect and caspase-independent autophagic cell death in liver cancer. PLoS ONE. 2012; 7:e34265. [PubMed: 22496786]
40. Jung KH, Noh JH, Kim JK, Eun JW, Bae HJ, Xie HJ, Chang YG, Kim MG, Park H, Lee JY, Nam SW. HDAC2 overexpression confers oncogenic potential to human lung cancer cells by deregulating expression of apoptosis and cell cycle proteins. J Cell Biochem. 2012; 113:2167–2177. [PubMed: 22492270]
41. Gupta M, Han JJ, Stenson M, Wellik L, Witzig TE. Regulation of STAT3 by histone deacetylase-3 in diffuse large B-cell lymphoma: implications for therapy. Leukemia. 2012; 26:1356–1364. [PubMed: 22116549]
42. Kanno K, Kanno S, Nitta H, Uesugi N, Sugai T, Masuda T, Wakabayashi G, Maesawa C. Overexpression of histone deacetylase 6 contributes to accelerated migration and invasion activity of hepatocellular carcinoma cells. Oncol Rep. 2012; 28:867–873. [PubMed: 22766642]
43. Hayashi A, Horiuchi A, Kikuchi N, Hayashi T, Fuseya C, Suzuki A, Konishi I, Shiozawa T. Type-specific roles of histone deacetylase (HDAC) overexpression in ovarian carcinoma: HDAC1 enhances cell proliferation and HDAC3 stimulates cell migration with downregulation of E-cadherin. Int J Cancer. 2010; 127:1332–1346. [PubMed: 20049841]
44. Leggatt GR, Gabrielli B. Histone deacetylase inhibitors in the generation of the anti-tumour immune response. Immunol Cell Biol. 2012; 90:33–38. [PubMed: 22064708]

45. Pecuchet N, Cluzeau T, Thibault C, Mounier N, Vignot S. Histone deacetylase inhibitors: highlight on epigenetic regulation. Bull Cancer. 2010; 97:917–935. [PubMed: 20483706]
46. Suzuki K, Oneyama C, Kimura H, Tajima S, Okada M. Down-regulation of the tumor suppressor C-terminal Src kinase (Csk)-binding protein (Cbp)/PAG1 is mediated by epigenetic histone modifications via the mitogen-activated protein kinase (MAPK)/phosphatidylinositol 3-kinase (PI3K) pathway. J Biol Chem. 2011; 286:15698–15706. [PubMed: 21388951]
47. Banik D, Khan AN, Walseng E, Segal BH, Abrams SI. Interferon regulatory factor-8 is important for histone deacetylase inhibitor-mediated antitumor activity. PLoS ONE. 2012; 7:e45422. [PubMed: 23028998]
48. Kurundkar D, Srivastava RK, Chaudhary SC, Ballestas ME, Kopelovich L, Elmets CA, Athar M. Vorinostat, an HDAC inhibitor attenuates epidermoid squamous cell carcinoma growth by dampening mTOR signaling pathway in a human xenograft murine model. Toxicol Appl Pharmacol. 2012; 266:233–244. [PubMed: 23147569]
49. Richon VM, Sandhoff TW, Rifkind RA, Marks PA. Histone deacetylase inhibitor selectively induces p21WAF1 expression and gene-associated histone acetylation. Proc Natl Acad Sci U S A. 2000; 97:10014–10019. [PubMed: 10954755]
50. Vrana JA, Decker RH, Johnson CR, Wang Z, Jarvis WD, Richon VM, Ehinger M, Fisher PB, Grant S. Induction of apoptosis in U937 human leukemia cells by suberoylanilide hydroxamic acid (SAHA) proceeds through pathways that are regulated by Bcl-2/Bcl-XL, c-Jun, and p21CIP1, but independent of p53. Oncogene. 1999; 18:7016–7025. [PubMed: 10597302]
51. Al-Yacoub N, Fecker LF, Mobs M, Plotz M, Braun FK, Sterry W, Eberle J. Apoptosis induction by SAHA in cutaneous T-cell lymphoma cells is related to downregulation of c-FLIP and enhanced TRAIL signaling. J Invest Dermatol. 2012; 132:2263–2274. [PubMed: 22551975]
52. Park JH, Ahn MY, Kim TH, Yoon S, Kang KW, Lee J, Moon HR, Jung JH, Chung HY, Kim HS. A new synthetic HDAC inhibitor, MHY218, induces apoptosis or autophagy-related cell death in tamoxifen-resistant MCF-7 breast cancer cells. Invest New Drugs. 2012; 30:1887–1898. [PubMed: 21983700]
53. Kang FW, Que L, Wu M, Wang ZL, Sun J. Effects of trichostatin A on HIF-1*a* and VEGF expression in human tongue squamous cell carcinoma cells *in vitro*. Oncol Rep. 2012; 28:193–199. [PubMed: 22552321]
54. Sasakawa Y, Naoe Y, Noto T, Inoue T, Sasakawa T, Matsuo M, Manda T, Mutoh S. Antitumor efficacy of FK228, a novel histone deacetylase inhibitor, depends on the effect on expression of angiogenesis factors. Biochem Pharmacol. 2003; 66:897–906. [PubMed: 12963476]
55. Qian DZ, Wang X, Kachhap SK, Kato Y, Wei Y, Zhang L, Atadja P, Pili R. The histone deacetylase inhibitor NVP-LAQ824 inhibits angiogenesis and has a greater antitumor effect in combination with the vascular endothelial growth factor receptor tyrosine kinase inhibitor PTK787/ZK222584. Cancer Res. 2004; 64:6626–6634. [PubMed: 15374977]
56. Advani A, Huang Q, Thai K, Advani SL, White KE, Kelly DJ, Yuen DA, Connelly KA, Marsden PA, Gilbert RE. Long-term administration of the histone deacetylase inhibitor vorinostat attenuates renal injury in experimental diabetes through an endothelial nitric oxide synthase-dependent mechanism. Am J Pathol. 2011; 178:2205–2214. [PubMed: 21514434]
57. Sidana A, Wang M, Shabbeer S, Chowdhury WH, Netto G, Lupold SE, Carducci M, Rodriguez R. Mechanism of growth inhibition of prostate cancer xenografts by valproic acid. J Biomed Biotechnol. 2012; 2012:180363. [PubMed: 23093837]
58. Noro R, Miyanaga A, Minegishi Y, Okano T, Seike M, Soeno C, Kataoka K, Matsuda K, Yoshimura A, Gemma A. Histone deacetylase inhibitor enhances sensitivity of non-small-cell lung cancer cells to 5-FU/S-1 via down-regulation of thymidylate synthase expression and up-regulation of $p21^{waf1/cip1}$ expression. Cancer Sci. 2010; 101:1424–1430. [PubMed: 20384633]
59. Fakih MG, Fetterly G, Egorin MJ, Muindi JR, Espinoza-Delgado I, Zwiebel JA, Litwin A, Holleran JL, Wang K, Diasio RB. A phase I, pharmacokinetic, and pharmacodynamic study of two schedules of vorinostat in combination with 5-fluorouracil and leucovorin in patients with refractory solid tumors. Clin Cancer Res. 2010; 16:3786–3794. [PubMed: 20463088]
60. Iwahashi S, Ishibashi H, Utsunomiya T, Morine Y, Ochir TL, Hanaoka J, Mori H, Ikemoto T, Imura S, Shimada M. Effect of histone deacetylase inhibitor in combination with 5-fluorouracil on

pancreas cancer and cholangiocarcinoma cell lines. J Med Invest. 2011; 58:106–109. [PubMed: 21372494]

61. Konsoula Z, Cao H, Velena A, Jung M. Adamantanyl-histone deacetylase inhibitor H6CAHA exhibits favorable pharmacokinetics and augments prostate cancer radiation sensitivity. Int J Radiat Oncol Biol Phys. 2011; 79:1541–1548. [PubMed: 21277099]
62. Saelen MG, Ree AH, Kristian A, Fleten KG, Furre T, Hektoen HH, Flatmark K. Radiosensitization by the histone deacetylase inhibitor vorinostat under hypoxia and with capecitabine in experimental colorectal carcinoma. Radiat Oncol. 2012; 7:165. [PubMed: 23017053]
63. Shoji M, Ninomiya I, Makino I, Kinoshita J, Nakamura K, Oyama K, Nakagawara H, Fujita H, Tajima H, Takamura H, et al. Valproic acid, a histone deacetylase inhibitor, enhances radiosensitivity in esophageal squamous cell carcinoma. Int J Oncol. 2012; 40:2140–2146. [PubMed: 22469995]
64. Glenisson W, Castronovo V, Waltregny D. Histone deacetylase 4 is required for TGFβ1-induced myofibroblastic differentiation. Biochim Biophys Acta. 2007; 1773:1572–1582. [PubMed: 17610967]
65. Marumo T, Hishikawa K, Yoshikawa M, Hirahashi J, Kawachi S, Fujita T. Histone deacetylase modulates the proinflammatory and -fibrotic changes in tubulointerstitial injury. Am J Physiol Renal Physiol. 2010; 298:F133–F141. [PubMed: 19906951]
66. Pang M, Ma L, Liu N, Ponnusamy M, Zhao TC, Yan H, Zhuang S. Histone deacetylase 1/2 mediates proliferation of renal interstitial fibroblasts and expression of cell cycle proteins. J Cell Biochem. 2011; 112:2138–2148. [PubMed: 21465537]
67. Watanabe T, Tajima H, Hironori H, Nakagawara H, Ohnishi I, Takamura H, Ninomiya I, Kitagawa H, Fushida S, Tani T, et al. Sodium valproate blocks the transforming growth factor (TGF)-β1 autocrine loop and attenuates the TGF-β1-induced collagen synthesis in a human hepatic stellate cell line. Int J Mol Med. 2011; 28:919–925. [PubMed: 21822535]
68. Niki T, Rombouts K, De Bleser P, De Smet K, Rogiers V, Schuppan D, Yoshida M, Gabbiani G, Geerts A. A histone deacetylase inhibitor, trichostatin A, suppresses myofibroblastic differentiation of rat hepatic stellate cells in primary culture. Hepatology. 1999; 29:858–867. [PubMed: 10051490]
69. Rombouts K, Knittel T, Machesky L, Braet F, Wielant A, Hellemans K, De Bleser P, Gelman I, Ramadori G, Geerts A. Actin filament formation, reorganization and migration are impaired in hepatic stellate cells under influence of trichostatin A, a histone deacetylase inhibitor. J Hepatol. 2002; 37:788–796. [PubMed: 12445420]
70. Davies ER, Haitchi HM, Thatcher TH, Sime PJ, Kottmann RM, Ganesan A, Packham G, O'Reilly KM, Davies DE. Spiruchostatin A inhibits proliferation and differentiation of fibroblasts from patients with pulmonary fibrosis. Am J Respir Cell Mol Biol. 2012; 46:687–694. [PubMed: 22246864]
71. Liu F, Levin MD, Petrenko NB, Lu MM, Wang T, Yuan LJ, Stout AL, Epstein JA, Patel VV. Histone-deacetylase inhibition reverses atrial arrhythmia inducibility and fibrosis in cardiac hypertrophy independent of angiotensin. J Mol Cell Cardiol. 2008; 45:715–723. [PubMed: 18926829]
72. Kee HJ, Sohn IS, Nam KI, Park JE, Qian YR, Yin Z, Ahn Y, Jeong MH, Bang YJ, Kim N, et al. Inhibition of histone deacetylation blocks cardiac hypertrophy induced by angiotensin II infusion and aortic banding. Circulation. 2006; 113:51–59. [PubMed: 16380549]
73. Bulow R, Fitzner B, Sparmann G, Emmrich J, Liebe S, Jaster R. Antifibrogenic effects of histone deacetylase inhibitors on pancreatic stellate cells. Biochem Pharmacol. 2007; 74:1747–1757. [PubMed: 17889833]
74. Pang M, Ma L, Gong R, Tolbert E, Mao H, Ponnusamy M, Chin YE, Yan H, Dworkin LD, Zhuang S. A novel STAT3 inhibitor, S3I-201, attenuates renal interstitial fibroblast activation and interstitial fibrosis in obstructive nephropathy. Kidney Int. 2010; 78:257–268. [PubMed: 20520592]
75. Catania A, Iavarone C, Carlomagno SM, Chiariello M. Selective transcription and cellular proliferation induced by PDGF require histone deacetylase activity. Biochem Biophys Res Commun. 2006; 343:544–554. [PubMed: 16554031]

76. Klampfer L, Huang J, Swaby LA, Augenlicht L. Requirement of histone deacetylase activity for signaling by STAT1. J Biol Chem. 2004; 279:30358–30368. [PubMed: 15123634]
77. Lee HB, Noh H, Seo JY, Yu MR, Ha H. Histone deacetylase inhibitors: a novel class of therapeutic agents in diabetic nephropathy. Kidney Int Suppl. 2007:S61–S66. [PubMed: 17653213]
78. Yoshikawa M, Hishikawa K, Marumo T, Fujita T. Inhibition of histone deacetylase activity suppresses epithelial-to-mesenchymal transition induced by TGF-β1 in human renal epithelial cells. J Am Soc Nephrol. 2007; 18:58–65. [PubMed: 17135397]
79. Shakespear MR, Halili MA, Irvine KM, Fairlie DP, Sweet MJ. Histone deacetylases as regulators of inflammation and immunity. Trends Immunol. 2011; 32:335–343. [PubMed: 21570914]
80. Roger T, Lugrin J, Le Roy D, Goy G, Mombelli M, Koessler T, Ding XC, Chanson AL, Reymond MK, Miconnet I, et al. Histone deacetylase inhibitors impair innate immune responses to Toll-like receptor agonists and to infection. Blood. 2011; 117:1205–1217. [PubMed: 20956800]
81. Nencioni A, Beck J, Werth D, Grunebach F, Patrone F, Ballestrero A, Brossart P. Histone deacetylase inhibitors affect dendritic cell differentiation and immunogenicity. Clin Cancer Res. 2007; 13:3933–3941. [PubMed: 17606727]
82. Banchereau J, Briere F, Caux C, Davoust J, Lebecque S, Liu YJ, Pulendran B, Palucka K. Immunobiology of dendritic cells. Annu Rev Immunol. 2000; 18:767–811. [PubMed: 10837075]
83. Reis e Sousa C. Activation of dendritic cells: translating innate into adaptive immunity. Curr Opin Immunol. 2004; 16:21–25. [PubMed: 14734106]
84. Edens RE, Dagtas S, Gilbert KM. Histone deacetylase inhibitors induce antigen specific anergy in lymphocytes: a comparative study. Int Immunopharmacol. 2006; 6:1673–1681. [PubMed: 16979121]
85. Tao R, Hancock WW. Regulating regulatory T cells to achieve transplant tolerance. Hepatobiliary Pancreat Dis Int. 2007; 6:348–357. [PubMed: 17690028]
86. Kinugasa F, Yamada T, Noto T, Matsuoka H, Mori H, Sudo Y, Mutoh S. Effect of a new immunosuppressant histon deacetylase (HDAC) inhibitor FR276457 in a rat cardiac transplant model. Biol Pharm Bull. 2008; 31:1723–1726. [PubMed: 18758066]
87. Kinugasa F, Nagatomi I, Nakanishi T, Noto T, Mori H, Matsuoka H, Sudo Y, Mutoh S. Effect of the immunosuppressant histone deacetylase inhibitor FR276457 in a canine renal transplant model. Transpl Immunol. 2009; 21:198–202. [PubMed: 19409992]
88. Brunkow ME, Jeffery EW, Hjerrild KA, Paeper B, Clark LB, Yasayko SA, Wilkinson JE, Galas D, Ziegler SF, Ramsdell F. Disruption of a new forkhead/winged-helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse. Nat Genet. 2001; 27:68–73. [PubMed: 11138001]
89. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, Kelly TE, Saulsbury FT, Chance PF, Ochs HD. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet. 2001; 27:20–21. [PubMed: 11137993]
90. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science. 2003; 299:1057–1061. [PubMed: 12522256]
91. Fontenot JD, Gavin MA, Rudensky AY. Foxp3 programs the development and function of $CD4^+$ $CD25^+$ regulatory T cells. Nat Immunol. 2003; 4:330–336. [PubMed: 12612578]
92. Khattri R, Cox T, Yasayko SA, Ramsdell F. An essential role for Scurfin in $CD4^+$ $CD25^+$ T regulatory cells. Nat Immunol. 2003; 4:337–342. [PubMed: 12612581]
93. Wang L, de Zoeten EF, Greene MI, Hancock WW. Immunomodulatory effects of deacetylase inhibitors: therapeutic targeting of $FOXP3^+$ regulatory T cells. Nat Rev Drug Discovery. 2009; 8:969–981. [PubMed: 19855427]
94. Tao R, de Zoeten EF, Ozkaynak E, Chen C, Wang L, Porrett PM, Li B, Turka LA, Olson EN, Greene MI, et al. Deacetylase inhibition promotes the generation and function of regulatory T cells. Nat Med. 2007; 13:1299–1307. [PubMed: 17922010]
95. de Zoeten EF, Wang L, Sai H, Dillmann WH, Hancock WW. Inhibition of HDAC9 increases T regulatory cell function and prevents colitis in mice. Gastroenterology. 2010; 138:583–594. [PubMed: 19879272]

96. Reilly CM, Thomas M, Gogal R Jr, Olgun S, Santo A, Sodhi R, Samy ET, Peng SL, Gilkeson GS, Mishra N. The histone deacetylase inhibitor trichostatin A upregulates regulatory T cells and modulates autoimmunity in NZB/W F1 mice. J Autoimmun. 2008; 31:123–130. [PubMed: 18650065]

97. Saouaf SJ, Li B, Zhang G, Shen Y, Furuuchi N, Hancock WW, Greene MI. Deacetylase inhibition increases regulatory T cell function and decreases incidence and severity of collagen-induced arthritis. Exp Mol Pathol. 2009; 87:99–104. [PubMed: 19577564]

98. Choi JH, Oh SW, Kang MS, Kwon HJ, Oh GT, Kim DY. Trichostatin A attenuates airway inflammation in mouse asthma model. Clin Exp Allergy. 2005; 35:89–96. [PubMed: 15649272]

99. Mishra N, Reilly CM, Brown DR, Ruiz P, Gilkeson GS. Histone deacetylase inhibitors modulate renal disease in the MRL-lpr/lpr mouse. J Clin Invest. 2003; 111:539–552. [PubMed: 12588892]

100. Glauben R, Batra A, Fedke I, Zeitz M, Lehr HA, Leoni F, Mascagni P, Fantuzzi G, Dinarello CA, Siegmund B. Histone hyperacetylation is associated with amelioration of experimental colitis in mice. J Immunol. 2006; 176:5015–5022. [PubMed: 16585598]

101. Nishida K, Komiyama T, Miyazawa S, Shen ZN, Furumatsu T, Doi H, Yoshida A, Yamana J, Yamamura M, Ninomiya Y, et al. Histone deacetylase inhibitor suppression of autoantibody-mediated arthritis in mice via regulation of p16INK4a and $p21^{WAF1/Cip1}$ expression. Arthritis Rheum. 2004; 50:3365–3376. [PubMed: 15476220]

102. Lin HS, Hu CY, Chan HY, Liew YY, Huang HP, Lepescheux L, Bastianelli E, Baron R, Rawadi G, Clement-Lacroix P. Anti-rheumatic activities of histone deacetylase (HDAC) inhibitors *in vivo* in collagen-induced arthritis in rodents. Br J Pharmacol. 2007; 150:862–872. [PubMed: 17325656]

103. Reddy P, Maeda Y, Hotary K, Liu C, Reznikov LL, Dinarello CA, Ferrara JL. Histone deacetylase inhibitor suberoylanilide hydroxamic acid reduces acute graft-versus-host disease and preserves graft-versus-leukemia effect. Proc Natl Acad Sci U S A. 2004; 101:3921–3926. [PubMed: 15001702]

104. Li N, Zhao D, Kirschbaum M, Zhang C, Lin CL, Todorov I, Kandeel F, Forman S, Zeng D. HDAC inhibitor reduces cytokine storm and facilitates induction of chimerism that reverses lupus in anti-CD3 conditioning regimen. Proc Natl Acad Sci U S A. 2008; 105:4796–4801. [PubMed: 18347343]

105. Huang L. Targeting histone deacetylases for the treatment of cancer and inflammatory diseases. J Cell Physiol. 2006; 209:611–616. [PubMed: 17001696]

106. Medzhitov R, Horng T. Transcriptional control of the inflammatory response. Nat Rev Immunol. 2009; 9:692–703. [PubMed: 19859064]

107. Smale ST. Selective transcription in response to an inflammatory stimulus. Cell. 2010; 140:833–844. [PubMed: 20303874]

108. Chen X, Barozzi I, Termanini A, Prosperini E, Recchiuti A, Dalli J, Mietton F, Matteoli G, Hiebert S, Natoli G. Requirement for the histone deacetylase Hdac3 for the inflammatory gene expression program in macrophages. Proc Natl Acad Sci U S A. 2012; 109:E2865–E2874. [PubMed: 22802645]

109. Usui T, Okada M, Mizuno W, Oda M, Ide N, Morita T, Hara Y, Yamawaki H. HDAC4 mediates development of hypertension via vascular inflammation in spontaneous hypertensive rats. Am J Physiol Heart Circ Physiol. 2012; 302:H1894–H1904. [PubMed: 22389387]

110. Grabiec AM, Korchynskyi O, Tak PP, Reedquist KA. Histone deacetylase inhibitors suppress rheumatoid arthritis fibroblast-like synoviocyte and macrophage IL-6 production by accelerating mRNA decay. Ann Rheum Dis. 2012; 71:424–431. [PubMed: 21953341]

111. Wu C, Li A, Leng Y, Li Y, Kang J. Histone deacetylase inhibition by sodium valproate regulates polarization of macrophage subsets. DNA Cell Biol. 2012; 31:592–599. [PubMed: 22054065]

112. Leoni F, Zaliani A, Bertolini G, Porro G, Pagani P, Pozzi P, Dona G, Fossati G, Sozzani S, Azam T, et al. The antitumor histone deacetylase inhibitor suberoylanilide hydroxamic acid exhibits antiinflammatory properties via suppression of cytokines. Proc Natl Acad Sci U S A. 2002; 99:2995–3000. [PubMed: 11867742]

113. Segain JP, Raingeard de la Bletiere D, Bourreille A, Leray V, Gervois N, Rosales C, Ferrier L, Bonnet C, Blottiere HM, Galmiche JP. Butyrate inhibits inflammatory responses through NFκB inhibition: implications for Crohn's disease. Gut. 2000; 47:397–403. [PubMed: 10940278]
114. Luhrs H, Gerke T, Muller JG, Melcher R, Schauber J, Boxberge F, Scheppach W, Menzel T. Butyrate inhibits NF-κB activation in lamina propria macrophages of patients with ulcerative colitis. Scand J Gastroenterol. 2002; 37:458–466. [PubMed: 11989838]
115. Furlan A, Monzani V, Reznikov LL, Leoni F, Fossati G, Modena D, Mascagni P, Dinarello CA. Pharmacokinetics, safety and inducible cytokine responses during a phase 1 trial of the oral histone deacetylase inhibitor ITF2357 (givinostat). Mol Med. 2011; 17:353–362. [PubMed: 21365126]
116. Gray SG, Ekstrom TJ. The human histone deacetylase family. Exp Cell Res. 2001; 262:75–83. [PubMed: 11139331]
117. Nerup J, Pociot F. A genomewide scan for type 1-diabetes susceptibility in Scandinavian families: identification of new loci with evidence of interactions. Am J Hum Genet. 2001; 69:1301–1313. [PubMed: 11598829]
118. van Tilburg JH, Sandkuijl LA, Strengman E, van Someren H, Rigters-Aris CA, Pearson PL, van Haeften TW, Wijmenga C. A genome-wide scan in type 2 diabetes mellitus provides independent replication of a susceptibility locus on 18p11 and suggests the existence of novel loci on 2q12 and 19q13. J Clin Endocrinol Metab. 2003; 88:2223–2230. [PubMed: 12727978]
119. Mosley AL, Ozcan S. Glucose regulates insulin gene transcription by hyperacetylation of histone h4. J Biol Chem. 2003; 278:19660–19666. [PubMed: 12665509]
120. Chakrabarti SK, Francis J, Ziesmann SM, Garmey JC, Mirmira RG. Covalent histone modifications underlie the developmental regulation of insulin gene transcription in pancreatic β cells. J Biol Chem. 2003; 278:23617–23623. [PubMed: 12711597]
121. Christensen DP, Dahllof M, Lundh M, Rasmussen DN, Nielsen MD, Billestrup N, Grunnet LG, Mandrup-Poulsen T. Histone deacetylase (HDAC) inhibition as a novel treatment for diabetes mellitus. Mol Med. 2011; 17:378–390. [PubMed: 21274504]
122. Mosley AL, Corbett JA, Ozcan S. Glucose regulation of insulin gene expression requires the recruitment of p300 by the β-cell-specific transcription factor Pdx-1. Mol Endocrinol. 2004; 18:2279–2290. [PubMed: 15166251]
123. Evans-Molina C, Garmey JC, Ketchum R, Brayman KL, Deng S, Mirmira RG. Glucose regulation of insulin gene transcription and pre-mRNA processing in human islets. Diabetes. 2007; 56:827–835. [PubMed: 17327454]
124. Qiu Y, Guo M, Huang S, Stein R. Insulin gene transcription is mediated by interactions between the p300 coactivator and PDX-1, BETA2, and E47. Mol Cell Biol. 2002; 22:412–420. [PubMed: 11756538]
125. Qiu Y, Sharma A, Stein R. p300 mediates transcriptional stimulation by the basic helix-loop-helix activators of the insulin gene. Mol Cell Biol. 1998; 18:2957–2964. [PubMed: 9566915]
126. Mosley AL, Ozcan S. The pancreatic duodenal homeobox-1 protein (Pdx-1) interacts with histone deacetylases Hdac-1 and Hdac-2 on low levels of glucose. J Biol Chem. 2004; 279:54241–54247. [PubMed: 15496408]
127. Lenoir O, Flosseau K, Ma FX, Blondeau B, Mai A, Bassel-Duby R, Ravassard P, Olson EN, Haumaitre C, Scharfmann R. Specific control of pancreatic endocrine β- and δ-cell mass by class IIa histone deacetylases HDAC4, HDAC5, and HDAC9. Diabetes. 2011; 60:2861–2871. [PubMed: 21953612]
128. Chou DH, Holson EB, Wagner FF, Tang AJ, Maglathlin RL, Lewis TA, Schreiber SL, Wagner BK. Inhibition of histone deacetylase 3 protects β cells from cytokine-induced apoptosis. Chem Biol. 2012; 19:669–673. [PubMed: 22726680]
129. Lewis EC, Blaabjerg L, Storling J, Ronn SG, Mascagni P, Dinarello CA, Mandrup-Poulsen T. The oral histone deacetylase inhibitor ITF2357 reduces cytokines and protects islet β cells *in vivo* and *in vitro*. Mol Med. 2011; 17:369–377. [PubMed: 21193899]
130. Susick L, Senanayake T, Veluthakal R, Woster PM, Kowluru A. A novel histone deacetylase inhibitor prevents IL-1β induced metabolic dysfunction in pancreatic β-cells. J Cell Mol Med. 2009; 13:1877–1885. [PubMed: 20141611]

131. Villeneuve LM, Natarajan R. The role of epigenetics in the pathology of diabetic complications. Am J Physiol Renal Physiol. 2010; 299:F14–F25. [PubMed: 20462972]

132. Crosson CE, Mani SK, Husain S, Alsarraf O, Menick DR. Inhibition of histone deacetylase protects the retina from ischemic injury. Invest Ophthalmol Visual Sci. 2010; 51:3639–3645. [PubMed: 20164449]

133. Zhang J, Henagan TM, Gao Z, Ye J. Inhibition of glyceroneogenesis by histone deacetylase 3 contributes to lipodystrophy in mice with adipose tissue inflammation. Endocrinology. 2011; 152:1829–1838. [PubMed: 21406501]

Abbreviations

AngII	angiotensin II
BMP-7	bone morphogenetic protein-7
Cbp	C-terminal Src kinase-binding protein
CSF-1	colony-stimulating factor-1
ECM	extracellular matrix
EMT	epithelial-to-mesenchymal transition
Foxp3	forkhead box P3
5-FU	5-fluorouracil
GWAS	genome-wide association studies
HAT	histone acetyltransferase
HDAC	histone deacetylase
HDACI	HDAC inhibitor
HER2	human epidermal growth factor receptor 2
HIF1α	hypoxia-inducible factor-1α
HSC	hepatic stellate cell
Id2	inhibitors of DNA binding/differentiation 2
IFN	interferon
IL	interleukin
c-FLIP	cellular Fas-associated death domain-like IL-1β-converting enzyme-inhibitory protein
IRF	interferon regulatory factor
LPS	lipopolysaccharide
NF-κB	nuclear factor κB
NOS	nitric oxide synthase
iNOS	inducible NOS
NuRD	nucleosome remodelling deacetylase

PAG1	phosphoprotein associated with glycosphingolipid-enriched microdomains 1
Pdx1	pancreatic and duodenal homeobox factor 1
PEPCK	phosphoenolpyruvate carboxykinase
pRb	retinoblastoma protein
RA	rheumatoid arthritis
SAHA	suberoylanilide hydroxamic acid
siRNA	small interfering RNA
SLE	systemic lupus erythematosus
SREBP-2	sterol-regulatory-element-binding protein-2
STAT3	signal transducer and activator of transcription 3
TGF-β1	transforming growth factor β1
TNF	tumour necrosis factor
TRAIL	TNF-related apoptosis-inducing ligand
T_{reg}-cell	regulatory T-cell
TS	thymidylate synthase
TSA	trichostatin A
UUO	unilateral ureteral obstruction
α-SMA	α-smooth muscle actin
VPA	valproic acid

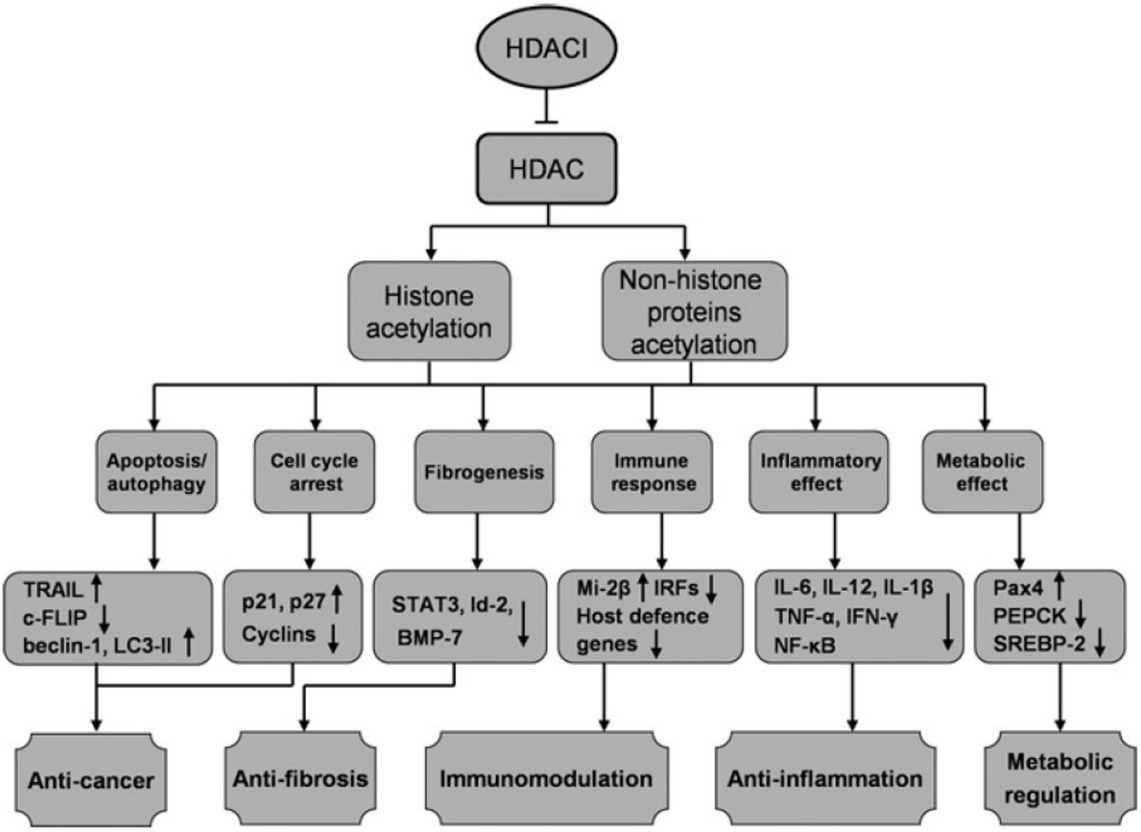

Figure 1. HDACI targets and downstream effects

Inhibition of HDACs by HDACIs induces acetylation of histone proteins, as well as non-histone proteins, which leads to the alteration in various physiological and pathological processes, including apoptosis/autophagy, cell cycle, fibrogenesis, immune response, inflammation and metabolism. Therefore HDACIs may be potent therapeutic agents for anticancer, antifibrosis, anti-inflammatory and immunomodulation, and regulating metabolic disorders.

Table 1

Applications of HDACIs in various disease models

Disease model	HDACI	HDAC specificity	Mechanism(s)	Effects
Cancer	TSA, SAHA and MS-275	Class I and/or class II HDACs	Up-regulates tumour suppressing genes (p53, p21, pRb, tob1, Hep27, Cbp/PAG1 and IRF-8); down-regulates oncogenes (Src, HIF1α and HER2). [17,45-47]	
	MHY218	Class I/II HDACs	Induces apoptosis or autophagic cell death [52]	Inhibits tumor growth and impairs its proliferation
	SAHA	Class I/II HDACs	Inhibits mTOR signalling pathway; reduces Akt and ERK signalling pathways. [48]	
	Valproic acid	Class I HDACs	Induces tumour cell-cycle arrest, cell differentiation, and inhibition of growth of tumour vasculature [57]	
Interstitial fibrosis	Spiruchostatin A	Class I HDACs	Inhibits the proliferation and differentiation of fibroblasts in idiopathic pulmonary fibrosis [70]	Inhibits TGF-β1-induced increased expression of α-SMA, collagen I and collagen III, and soluble collagen release in idiopathic pulmonary fibrosis [70]
	TSA	Class I/II HDACs	Reduces expression of CSF-1 [65], and inhibits STAT3 activation and tubular cell apoptosis [30] in UUO	Attenuates macrophage infiltration, the proliferation of renal fibroblasts, the expression of α-SMA and fibronectin induced by UUO [30,65]
	SK-7041	Class I HDACs	Down-regulates expression of EGR-1, but the exact mechanism remain unclear [72]	Alleviates cardiac hypertrophy induced by chronic infusion of AngII or by aortic banding [72]
Immune dysfunction diseases	TSA	Class I/II HDACs	Down-regulates the expression of numerous host defence genes; impairs innate immune responses; induces expression of Mi-2β and enhances the DNA-binding activity of Mi-2/NuRD complex [80]	Enhances the susceptibility to bacterial and fungal infections but protects against toxic and septic shock [80]
	Tubastatin A analogues	HDAC 6	Enhances the ability of T_{reg}-cells to inhibit the mitotic division of effector T-cells [23]	Enhances the immunosuppressive effects of $Foxp3^+$ T_{reg}-cells [23]
	FR276457	Class I/II HDACs	Inhibits the proliferation of T-cell line and suppresses mononuclear cell infiltration and vasculitis [86,87]	Prevents allograft rejection and prolongs allograft survival in a rat cardiac transplant model [86] and in a canine renal transplant model [87]
Inflammatory diseases	TSA	Class I/II HDACs	Accelerates IL-6 mRNA decay in RA fibroblast-like synoviocytes and macrophages [110]	Disrupts IL-6 production in RA synovial cells [110]
	Sodium valproate	Class I HDACs	Represses the production of IL-12 and TNF-α by LPS-induced macrophage activation, but promotes IL-10 expression [111]	Skews the phenotype of LPS-stimulated mouse macrophage cell line RAW264.7 and primary mouse bone marrow macrophages from M1 to M2 [111]
	SAHA	Class I/II HDACs	Inhibits the circulating level of pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and IFN-γ induced by LPS [112]	Reduces the production of pro-inflammatory cytokines *in vivo* and *in vitro* [112]

Disease model	HDACI	HDAC specificity	Mechanism(s)	Effects
Metabolic disorders	MC1568	Class II HDACs	Enhances expression of Pax4, a key factor required for proper β-and δ-cell differentiation, and amplifies endocrine β-and δ-cells [127]	Enhances β-and δ-cell development [127]
	ITF2357	Class I/II HDACs	Increases islet cell viability, enhances insulin secretion, inhibits MIP-1α and MIP-2 release, reduces iNOS production and apoptosis, and inhibits the production of nitrite, TNF-α and IFN-γ [129]	Favours β-cell survival during inflammatory conditions [129]
	TSA	Class I/II HDACs	Down-regulates gene expression involved in the cholesterol biosynthetic pathway and fatty acid biosynthesis, and glycolysis-associated pathways [18]	Regulates cholesterol metabolism [18]

EGR-1, early growth response gene 1; ERK, extracellular-signal-regulated kinase; mTOR, mammalian target of rapamycin.