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Therapeutic Potential for HDAC Inhibitors in the Heart

Timothy A. McKinsey

Department of Medicine, Division of Cardiology, University of Colorado Denver, Aurora, Colorado 80045-0508; email: timothy.mckinsey@ucdenver.edu

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Abstract

Reversible protein acetylation provides a central mechanism for controlling gene expression and cellular signaling events. Two pharmacological inhibitors of protein deacetylation are currently approved for the treatment of human cancer, and numerous follow-on compounds are in clinical development for oncology and non-oncology indications. The inhibitors target members of a family of enzymes known as histone deacetylases (HDACs). Surprisingly, HDAC inhibitors have also been shown to be efficacious in preclinical models of heart failure. This review highlights roles of HDACs in the heart and the therapeutic potential of HDAC inhibitors for the treatment of heart failure.

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INTRODUCTION

The heart responds to pathological stresses, such as hypertension and myocardial infarction, by remodeling in a manner that is associated with myocyte hypertrophy, myocyte death, inflammation, and fibrosis, often resulting in impaired cardiac function and heart failure. More than 5 million adults in the United States suffer from heart failure, with an estimated annual cost to the American health care system of more than $37 billion. Despite improved standards of care, the five-year mortality rate following first admission for heart failure approaches 50%, highlighting the pressing need for new therapeutic approaches (1).

Treatment of heart failure often involves the use of drugs designed to inhibit signaling pathways triggered by cell surface receptors, such as the angiotensin and β-adrenergic receptors (2). However, given the many redundant signaling pathways that promote pathological cardiac remodeling, it has long been hypothesized that more effective therapeutic strategies would target downstream signaling mediators shared by several pathways.

In their quest to identify intracellular signaling mechanisms controlling heart failure, several labs have discovered important roles for histone deacetylases (HDACs) in the heart. HDACs catalyze the removal of acetyl groups from lysine residues in a variety of proteins. The best-characterized functions of HDACs are in the control of gene expression through their ability to deacetylate nucleosomal histones, resulting in alterations to chromatin structure that usually promote gene repression. However, a multitude of nonhistone substrates of HDACs have been identified, linking HDAC activity to diverse cellular processes in addition to gene regulation (3). For example, as discussed below, HDACs in the heart control events such as hypertrophy (4, 5), autophagy (6), fibrosis (7–9), contractility (10, 11), and energy metabolism (12).

Eighteen mammalian HDACs are encoded by distinct genes and are grouped into four classes (**Figure 1**). Class I, II and IV HDACs are zinc-dependent enzymes, whereas class III HDACs, also known as sirtuins, require nicotinamide adenine dinucleotide (NAD^+) for catalytic activity (13). This review focuses on the zinc-dependent HDACs because they are the targets of the small-molecule HDAC inhibitors that are efficacious in animal models of heart failure.

The first HDAC inhibitor reached the market in 2006 when the FDA approved vorinostat (SAHA), a hydroxamic acid pan-inhibitor of zinc-dependent HDACs, for the treatment of

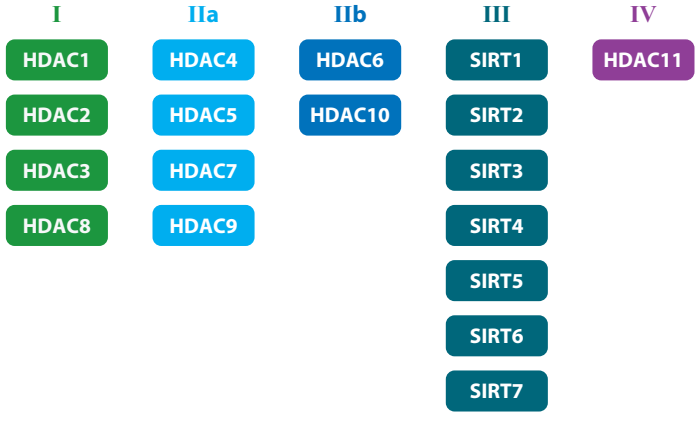

Figure 1

Histone deacetylase (HDAC) classes. HDACs are categorized into four distinct classes. Class II HDACs are further divided into two subclasses, IIa and IIb. Class III HDACs are also known as sirtuins (SIRT). Class I, II, and IV HDACs are zinc-dependent enzymes, whereas class III HDACs require nicotinamide adenine dinucleotide (NAD^+) for catalytic activity.

cutaneous T-cell lymphoma (CTCL) (14, 15). More recently, the cyclic peptide HDAC inhibitor, romidepsin, was also approved for treatment of CTCL. Significant efforts are also under way to develop HDAC inhibitors for non-oncology indications; perhaps most notable are programs focused on chronic inflammatory diseases (16). For example, in patients with systemic onset juvenile idiopathic arthritis, the broad-spectrum HDAC inhibitor, ITF2357, was shown to be safe and efficacious at relatively low concentrations (1.5 mg per kg per day) (17, 18). Importantly, anti-inflammatory doses of HDAC inhibitors are much lower than those required to kill tumor cells, suggesting that HDAC inhibitors could provide a safe means of treating chronic diseases. In addition to their beneficial effects in the clinic, HDAC inhibitors have served as valuable tools for assessing the roles of HDACs in various pathophysiological processes. This review focuses on promising preclinical data obtained with HDAC inhibitors in rodent models of heart failure, and challenges associated with translating these findings to the development of new drugs for heart disease.

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CONNECTING HDACS TO THE HEART

The initial drive to examine HDACs in the heart came with the discovery that class IIa HDACs interact with members of the myocyte enhancer factor-2 (MEF2) transcription factor family (19), which regulate cardiac hypertrophy. Cardiac hypertrophy in response to pathological stress is thought to be a compensatory mechanism that normalizes wall stress and enhances cardiac performance. However, long-term suppression of cardiac hypertrophy is associated with reduced morbidity and mortality in patients with hypertension, and thus chronic cardiac hypertrophy is now considered a maladaptive response (20, 21).

Overexpression of class IIa HDACs 4 (22), 5 (23–25), or 9 (25) coordinately suppresses MEF2-dependent transcription and agonist-dependent hypertrophy of cultured cardiac myocytes. In contrast, disruption of the gene encoding *HDAC9* in mice leads to activation of cardiac MEF2 activity (25), and mouse knockouts for *HDAC5* (26) or *HDAC9* (25) develop profound cardiac hypertrophy in response to pressure overload, and spontaneous, pathologic hypertrophy with advanced age. These results support a role for class IIa HDACs as endogenous inhibitors of cardiac hypertrophy.

Given the ability of class IIa HDACs to block cardiac hypertrophy, we hypothesized that HDAC inhibitors would promote pathological cardiac remodeling. However, experiments with cultured cardiac myocytes demonstrated a remarkable ability of HDAC inhibitors to suppress myocyte hypertrophy without inducing cell death (4). This seemingly paradoxical finding was subsequently explained by two discoveries. First, enzymatic assays revealed that class IIa HDACs are relatively insensitive to standard HDAC inhibitors, including those used in the initial studies of cardiac hypertrophy (27, 28). Second, it was determined that class IIa HDACs do not require catalytic activity to suppress hypertrophic signaling in cardiomyocytes (25).

HDAC INHIBITORS IN HEART FAILURE MODELS

The serendipitous discovery of the antihypertrophic action of HDAC inhibitors suggested a potential for these compounds in the treatment of human heart failure. Most of the compounds used in vivo have been general, pan-HDAC inhibitors. However, as described below, new classes of HDAC inhibitors have emerged that provide an opportunity to assess the safety and efficacy of isoform-selective HDAC inhibition in the heart.

HDAC Inhibitor Classes

The four main classes of HDAC inhibitors are hydroxamic acids, benzamides, short-chain fatty acids, and cyclic peptides (**Figure 2*a***). Relative potencies and selectivity profiles differ among and

within these classes (27). The hydroxamic acid class, which includes trichostatin A (TSA) and SAHA, is the most well known and is characterized by a tripartite structure composed of a zinc-binding "warhead" group that docks in the HDAC active site, a linker, and a surface recognition domain that interacts with residues near the entrance to the active site (29) (**Figure 2*a***). The strong zinc-chelating function of hydroxamic acids produces potent (low-nanomolar) pan-HDAC inhibitors. Benzamide HDAC inhibitors such as MS-275 are generally potent and highly selective for HDACs 1, 2, and 3 and exhibit slow, tight binding characteristics for the enzymes (30). In contrast, the short-chain fatty acids are weak (millimolar) HDAC inhibitors, with perhaps modest selectivity toward class I HDACs. Cyclic peptides tend to be selective for class I HDACs.

Compounds with aryl substitutions in place of the benzamide warhead are highly selective for HDAC1 and HDAC2 compared to other HDACs (31–34), whereas other benzamide scaffolds appear to be selective for HDAC3 (35). Selective hydroxamic acid inhibitors of HDAC8, a class I HDAC, have been found (36–38). Finally, the first known HDAC6/class IIb–selective inhibitor, tubacin, was described in 2003 (39). A recently discovered compound, Tubastatin A (40), exhibits greater selectivity for HDAC6 than tubacin does. The availability of isoform-selective HDAC inhibitors provides an opportunity to use chemical genetic strategies to dissect the roles of distinct HDAC isoforms in the pathogenesis of various diseases.

Compound Activity In Vivo

In vivo studies have demonstrated that HDAC inhibitors can effectively block and reverse pathological cardiac hypertrophy (**Figure 2**). Treatment with the hydroxamic acid, pan-HDAC inhibitor trichostatin A (TSA), or the short-chain fatty acid valproic acid blocks development of cardiac hypertrophy in transgenic mice with cardiac overexpression of homeodomain-only protein (Hop), an HDAC2-dependent serum response factor inhibitor (5). Similarly, pan-HDAC inhibitor treatment suppresses cardiac hypertrophy induced by continuous infusion of the β-adrenergic receptor agonist, isoproterenol (5), or of angiotensin II (8), as well as pressure overload imposed by transverse aortic constriction (8). TSA treatment was also shown to regress established cardiac hypertrophy in mice subjected to aortic constriction (8), and to reverse established atrial fibrosis in Hop-transgenic mice (41), suggesting a potential for HDAC inhibitors for the treatment of preexisting heart failure. Valproic acid has well-known use as an anticonvulsant and for mood stabilization; thus, based on its relative safety in humans, it could be tested in clinical trials for heart failure. However, it should be noted that valproic acid is a weak HDAC inhibitor and has many HDAC-independent pharmacological activities (42), including regulation of ion channels, glycogen synthase kinase-3β, and mitogen-activated protein kinases (43).

Figure 2

Structures and in vivo activities of HDAC inhibitors (HDACi) in murine and rat heart failure models. (*a*) Hydroxamic acid HDACi such as trichostatin A (TSA) have a tripartite structure consisting of a domain that recognizes the surface of HDAC enzymes, a linker region, and a hydroxamic acid group that chelates zinc in active sites of HDACs. Replacement of the hydroxamic acid with a benzamide group (*shaded gray*) creates compounds such as MS-275 that are highly selective for class I HDACs. Short-chain fatty acids such as butyrate and valproic acid are weak HDACi. An example of a cyclic peptide HDACi is shown. Romidepsin is approved for the treatment of cancer. (*b*) Models in which the compounds have demonstrated efficacy are shown. Scriptaid, SAHA, and TSA are pan-HDAC inhibitors (pan-HDACi), whereas apicidin-derivative (apicidin-D) and valproic acid have selectivity for class I HDACs. Other abbreviations: AngII, angiotensin II; DOCA, deoxycorticosterone acetate; Hop, homeodomain-only protein; ISO, isoproterenol; MI, myocardial infarction; SHR, spontaneously hypertensive rat; TAC, transverse aortic constriction; Tg, transgenic.

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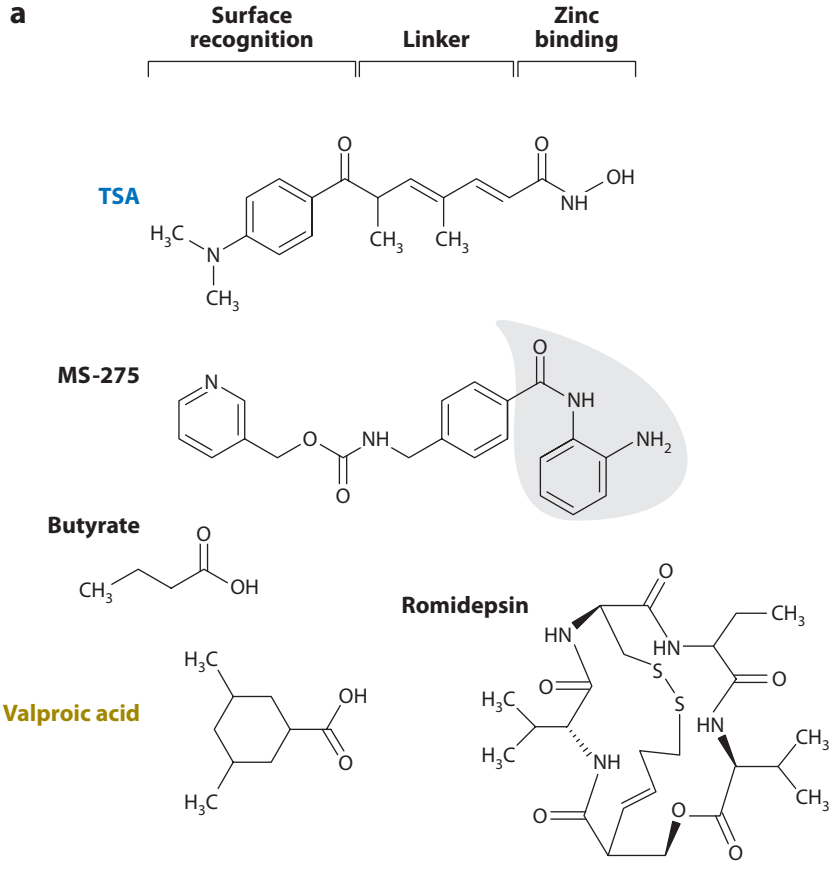

b **Efficacy of HDACi in preclinical models of heart failure**

Scriptaid (pan-HDACi)	SAHA (pan-HDACi)	Apicidin-D (class I HDACi)
Mouse TAC and MI	**Rat** DOCA	**Mouse** TAC

TSA (pan-HDACi)	Valproic acid (weak class I HDACi)
Mouse TAC, MI, AngII, ISO, Hop-Tg, Beclin-Tg	**Rat** TAC, MI, AngII, SHR **Mouse** TAC

Three weeks of treatment with TSA and another pan-HDAC inhibitor, scriptaid, blunted cardiac hypertrophy in a pressure-overload mouse model, reducing cardiomyocyte size and significantly improving ventricular performance (9). The reduction in cardiac hypertrophy and functional improvements were maintained in a nine-week study. TSA appeared to be well-tolerated, as chronic administration did not negatively impact survival. Pan-HDAC inhibitors have also been shown to reduce cell death and prevent maladaptive ventricular remodeling in models of cardiac ischemia (44–47).

Right ventricular (RV) heart failure is a common outcome of pulmonary hypertension. The role(s) of HDACs in RV remodeling remains poorly understood. Valproic acid was recently shown to block RV hypertrophy in response to pulmonary artery banding (PAB), as well as in pulmonary hypertension caused by monocrotaline-induced lung injury (48). In contrast, the pan-HDAC inhibitor, TSA, failed to block hypertrophy in response to PAB and actually appeared to worsen RV function (49). Additional investigation is needed to elucidate the roles of HDACs in RV remodeling, especially because maintenance of RV function in patients with pulmonary hypertension confers a survival advantage (50).

A critical next step is to determine which HDAC isoforms promote pathological remodeling of the heart. Studies in genetically engineered mice and cultured cardiomyocytes have suggested a role for HDAC2 in heart failure (49, 50), although these findings remain contentious (51, 52). More definitive answers will come from the use of small-molecule inhibitors of select HDAC isoforms. An apicidin derivative, which is predominantly selective for class I HDACs 1, 2, and 3, can suppress hypertrophy and improve cardiac performance in the presence of pressure overload (53). However, this compound appears to exhibit activity, albeit modest, against HDAC6 in vitro. These findings need to be extended by testing additional class I HDAC inhibitors and newer generations of HDAC1/2-, HDAC3-, HDAC6-, and HDAC8-selective compounds in animal models of heart failure (54).

MECHANISMS OF HDAC INHIBITOR ACTION IN THE HEART

The efficacy of HDAC inhibitors in heart failure models is likely due to the ability of the compounds to alter acetylation of histones and nonhistone proteins in multiple cells types (e.g., myocytes, fibroblasts and immune cells) and thereby alter diverse pathological mechanisms (e.g., myocyte hypertrophy, fibrosis and inflammation) that culminate in organ damage (**Figure 3**). As such, although HDAC inhibitors have one biochemical target (HDACs), they are likely to have multiple disease-modifying mechanisms of action. A systems biology approach may thus be required to fully understand the impact of HDAC inhibition on the heart.

Inhibition of Cardiac Hypertrophy

The mechanisms by which HDAC inhibitors suppress pathological cardiac hypertrophy are still being elucidated. Based on recent findings, it seems clear that a combination of chromatin and nonchromatin substrates for HDACs will play key roles. One transcriptional (i.e., chromatin-related) mechanism for efficacy of HDAC inhibitors in the heart involves the antihypertrophic transcription factor, krüppel-like factor 4 (KLF4). KLF4 overexpression blocks cardiac hypertrophy in culture (51, 52), and *KLF4* knockout mice develop exaggerated cardiac hypertrophy and fibrosis in response to pressure overload (52). Pan-HDAC inhibitors increase expression of KLF4 in cultured cardiomyocytes, and the resulting increase in KLF4 expression appears to be sufficient to block agonist-dependent hypertrophy of the cells (51).

In addition to promoting expression of protective genes, HDAC inhibitors also appear to block pathological gene expression, which is paradoxical because HDAC activity is typically associated

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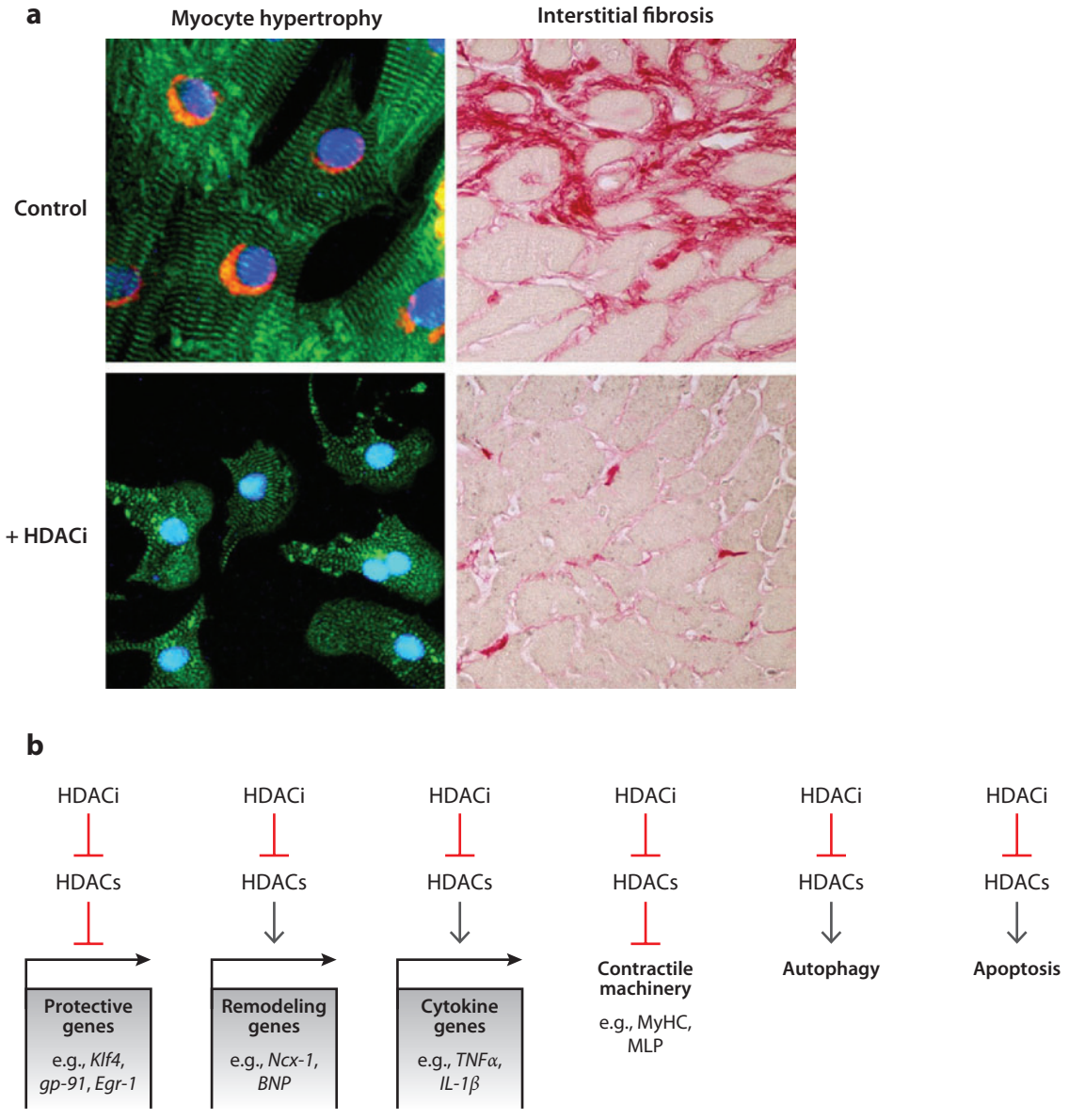

Figure 3

Inhibition of cardiac hypertrophy and interstitial fibrosis by HDAC inhibitors. (*a*) Inhibition of cardiac hypertrophy and fibrosis. The initial demonstration that HDAC inhibitors block cardiac hypertrophy was made with cultured neonatal rat ventricular myocytes. HDAC inhibitor (HDACi) treatment blocks agonist-mediated enhancement of sarcomere organization (*green*) and expression of hypertrophic markers such as atrial natriuretic factor (*orange*); nuclei are blue. In vivo, HDAC inhibitors block pathological cardiac interstitial fibrosis, as evidenced by the picrosirius red-stained collagen in mouse heart. (*b*) HDAC inhibitors appear to confer benefit to the heart via multiple mechanisms, including derepression of protective genes and inhibition of induction of remodeling and proinflammatory genes. HDAC inhibitors also have nontranscriptional effects in the heart, such as enhancing acetylation of sarcomeric proteins and blunting pathways for autophagy and apoptosis. Abbreviations: Klf4, krüppel-like factor 4; gp-91, NADPH-oxidase subunit; Egr-1, early growth response factor-1; Ncx-1, sodium-calcium exchanger-1; BNP, brain natriuretic peptide; TNFα, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; MyHC, myosin heavy chain; MLP, muscle LIM protein.

with gene repression. Two studies revealed mechanisms by which HDAC inhibitors repress genes in the heart. Expression of the gene encoding B-type natriuretic peptide (BNP) is enhanced in ventricular myocytes during pathological cardiac hypertrophy, and circulating BNP levels are used clinically as a surrogate measure of heart failure. Employing cultured neonatal rat cardiac myocytes, Gardner and colleagues demonstrated that upregulation of BNP expression in response to endothelin signaling is dependent on association of HDAC2 with the Yin Yang 1 (YY1) transcription factor on the *BNP* gene promoter (53). YY1 is acetylated in cardiac myocytes, and deacetylation of this transcription factor by HDAC2 enhances its ability to stimulate BNP gene transcription. TSA treatment disrupts YY1:HDAC2 complexes and suppresses endothelin-induced BNP expression.

Menick and colleagues used cultured adult feline cardiac myocytes to demonstrate that HDAC1 activity stimulates sodium-calcium exchanger (NCX1) expression during cardiac hypertrophy by deacetylating the Nkx2.5 transcription factor (54). Deacetylated Nkx2.5 associates with the p300 histone acetyltransferase, binds the *NCX1* promoter, and activates transcription. Treatment with the HDAC1 inhibitor TSA led to Nkx2.5 acetylation, disruption of the association of Nkx2.5 with p300, and a concurrent decrease in *NCX1* transcription. These studies of BNP and NCX1 gene regulation exemplify mechanisms whereby HDAC inhibitors can repress cardiac gene expression by altering the acetylation state of nonhistone proteins.

Inhibition of Cardiac Autophagy and Apoptosis

Autophagy is a mechanism for degrading proteins and organelles via lysosomes. In the heart, increased afterload triggers autophagic activity, which appears to contribute to the pathogenesis of heart failure (55). Hill and colleagues demonstrated that excessive cardiac autophagy in a murine model of pressure overload is effectively blocked by TSA (6). TSA also inhibited autophagy in a more severe model involving cardiac-specific overexpression of a key component of the autophagy pathway, beclin. Importantly, TSA was capable of reversing preexisting cardiac hypertrophy and improving cardiac function in beclin-transgenic mice subjected to pressure overload. RNA interference studies with cultured cardiac myocytes supported a role for class I HDACs 1 and 2 in agonist-dependent cardiac autophagy. Together, the data suggest that efficacy of HDAC inhibitors in heart failure models is due, in part, to suppression of class I HDAC-dependent pathological autophagy.

In a Langendorff hanging heart model of ischemia-reperfusion injury, TSA was shown to reduce infarct size and improve cardiac function in a manner dependent on the p50 subunit of the NF-κB transcription factor (46). TSA treatment promoted p50 acetylation and enhanced NF-κB DNA binding activity. NF-κB is known to stimulate expression of antiapoptotic genes, so HDAC inhibitors can provide cardioprotection by suppressing programmed cell death. In other studies of cardiac injury, TSA-mediated cardioprotection was associated with increased acetylation and catalytic activity of p38 MAP kinase (47), enhanced activity of NADPH-oxidase (56), and downregulation of hypoxia-inducible factor-1α (44). Because HDAC inhibitors promote apoptosis in tumor cells, there was initial concern that HDAC inhibition would exacerbate cell killing in the heart and promote heart failure. However, results from multiple labs using several different models demonstrate that HDAC inhibitors block rather than stimulate cardiomyocyte death.

Inhibition of Cardiac Fibrosis and Inflammation

Much of the beneficial effects of HDAC inhibitors in models of heart failure are likely due to inhibition of pathological fibrosis, although surprisingly little is known about the antifibrotic mechanisms of HDAC inhibitors in the heart (57). It seems likely that HDAC inhibitors block cardiac fibrosis by multiple mechanisms, including inhibition of cardiac fibroblast proliferation

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or migration, induction of genes that suppress extracellular matrix production from fibroblasts, suppression of proinflammatory cues for fibrosis, and blockade of the endothelial-to-mesenchymal transition (Endo-MT).

Endo-MT initiates a process of pathological dedifferentiation of vascular endothelial cells into matrix-producing mesenchymal cells. During this process, excessive numbers of cardiac fibroblasts are produced in adult hearts in response to pressure overload (58) and myocardial infarction (59). Cardiac Endo-MT is stimulated by Transforming Growth Factor-Beta (TGF-β) and suppressed by Bone Morphogenic Protein-7 (BMP-7) (58), which blocks fibrosis (60). Endothelin-1, a potent vasoconstrictor with promitogenic properties, stimulates cardiac fibrosis by promoting Endo-MT (61). At least part of the antioncogenic action of HDAC inhibitors is due to blockade of a related process, epithelial-to-mesenchymal transition (EMT) (62). As such, future studies should address whether HDAC inhibition alters Endo-MT in the heart.

HDAC inhibitors are also likely to have direct effects on cardiac fibroblasts. TSA blocks TGF-β-mediated induction of collagen synthesis in cultured rat ventricular fibroblasts (9). HDAC inhibitors do not affect TGF-β-mediated phosphorylation or nuclear translocation of SMAD transcription factors, which control collagen gene expression, but do appear to suppress other signaling mediators (e.g., ERK, AKT and PI3K) that influence collagen synthesis (63, 64). HDAC inhibitors are also capable of blocking differentiation of fibroblasts into profibrotic, contractile myofibroblasts by inhibiting expression of α-smooth muscle actin (65).

Pro-inflammatory cytokines activate cardiac fibroblasts to produce extracellular matrix (66). At least part of the antifibrotic action of HDAC inhibitors may be due to their anti-inflammatory action. In spontaneously hypertensive rats (SHR), treatment with valproic acid for 20 weeks led to reduced LV expression of the proinflammatory cytokines IL-1β and TNFα, inhibition of cardiac fibrosis, and improved cardiac function (67). In a related study, Iyer and colleagues examined effects of SAHA on plasma cytokine levels in a rat deoxycorticosterone acetate (DOCA)-salt model of hypertensive cardiomyopathy (7). After four weeks of treatment, SAHA significantly reduced circulating levels of multiple proinflammatory cytokines, including IL-1β, IL-6 and TNFα, and these decreases correlated with reduced cardiac hypertrophy and suppression of interstitial fibrosis in the LV. HDAC inhibition lowered systemic blood pressure in both SHR and DOCA-rats, suggesting possible effects of HDACs on vascular remodeling.

It is not known how HDAC inhibitors exert their anti-inflammatory effects in the context of heart failure. In models of organ rejection, HDAC inhibitors have shown remarkable efficacy, reducing proinflammatory cytokine expression and increasing survival in a mouse bone marrow transplant model of graft-versus-host disease (68, 69). The protective effects of HDAC inhibitors in these models appear to be due to induction of regulatory T cells (Tregs), which possess potent anti-inflammatory properties (70). HDAC inhibitors stimulate Treg production by promoting acetylation of the FoxP3 transcription factor, a master regulator of Treg differentiation (69). A recent report showed that Treg number and function are significantly reduced in patients with chronic heart failure, and the degree of Treg impairment correlates with severity of the heart failure phenotype (71) Consistent with these clinical findings, adoptive transfer of Tregs significantly reduces angiotensin II-mediated cardiac remodeling in a mouse model (72). Studies that address whether beneficial effects of HDAC inhibitors in heart failure models correlate with enhanced production and activity of Tregs should be enlightening.

Improved Cardiac Contractility

Work by Gupta and colleagues revealed that HDAC3 localizes to cardiac sarcomeres, implicating this deacetylase in the control of cardiac contractility (11). The thick filament of the mammalian

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sarcomere consists of two myosin isoforms, fast-contracting alpha-myosin heavy chain (α-MyHC) and slow-contracting beta-myosin heavy chain (β-MyHC). Stress signals enhance the expression of β-MyHC and reduce the expression of adult α-MyHC; the consequences include diminished myofibrillar ATPase activity and impaired contractility (73). Both α- and β-MyHC are acetylated and deacetylation of these proteins by HDAC3 reduces their affinity for actin, resulting in decreased actin sliding velocity of the myosin heads (11).

Class IIa HDAC4 also localizes to cardiac sarcomeres, where it appears to decrease myofilament calcium sensitivity by promoting deacetylation of muscle LIM protein (MLP) (10). It remains unclear whether MLP is a direct substrate of HDAC4. Indeed, for many years it was believed that class IIa HDACs lacked intrinsic catalytic activity, because recombinant forms fail to deacetylate canonical HDAC substrates. The catalytic activity of class IIa HDACs has been attributed to associated class I HDACs instead (74). However, a synthetic substrate that is efficiently deacetylated by class IIa HDACs has been identified (28). The endogenous substrates of class IIa HDACs in the heart have not been identified. Further investigation is needed to address the role of HDAC4 in the control of cardiac contractility, as well as the general role of class IIa HDAC catalytic activity in the heart.

Blood Pressure

Some of the in vivo efficacy observed with HDAC inhibitors in animal models of heart failure could be due to effects of the compounds on blood pressure. SAHA and valproic acid were shown to lower mean arterial pressure in deoxycorticosterone acetate (DOCA)-treated and spontaneously hypertensive rats, respectively (75, 76). In contrast, TSA had no effect on development of systemic hypertension in mice chronically infused with angiotensin II (77). Future studies will need to carefully address possible effects of HDAC inhibitors on vascular remodeling and blood pressure control in the context of heart and renal failure.

HDAC ACTIVITY IN THE HEART—TARGET VALIDATION?

Attempts to validate roles for proteins in disease processes have traditionally focused on assessments of protein expression and activity. Several studies have addressed whether HDAC activity is altered in the heart in response to stress stimuli.

Global HDAC activity is increased in hypertrophic SHR rat hearts (67), in hearts of transgenic mice with cardiac hypertrophy due to overexpression of Hop (5), and in a model of cardiac ischemia-reperfusion injury (44). Kee and coworkers used sequential immunoprecipitation-HDAC activity assays to provide evidence that HDAC2, but not HDAC1, is activated in the heart in response to hypertrophic stimuli, including pressure overload due to aortic constriction (78). HDAC2 was transiently activated following aortic constriction, and this activation preceded hypertrophic growth of the heart. Another study reported rapid induction of HDAC3 catalytic activity in neonatal rat ventricular myocytes (NRVMs) treated with lipopolysaccharide (LPS) (79). Conversely, HDAC catalytic activity was reduced in NRVMs exposed to hypoxic conditions (80). Recently, we have found that cardiac HDAC6 expression and catalytic activity are elevated in models of chronic hypertension (81). The role of this HDAC isoform in the heart remains unknown.

It should be emphasized that increased expression and catalytic activity of HDACs are not requisites to establish that the enzymes are valid drug targets. For example, a class I HDAC might be aberrantly recruited to the promoter region of a protective gene in response to cardiac stress signals, and derepression of this gene with an HDAC inhibitor would thus provide benefit to the

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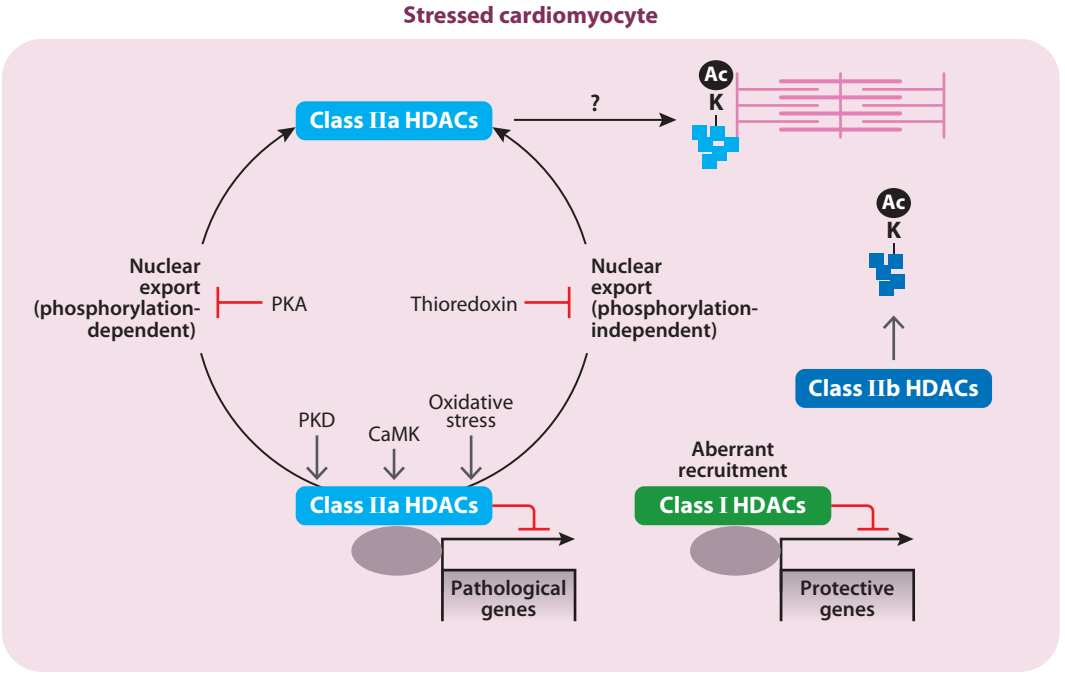

Figure 4

Effects of cardiac stress signals on HDACs. Class IIa HDACs normally repress pathological cardiac gene expression. In response to stress signals, class IIa HDACs undergo nuclear export, resulting in derepression of downstream target genes. Protein kinase D (PKD) and calcium/calmodulin-dependent kinase (CaMK) directly phosphorylate class IIa HDACs to trigger their nuclear export; protein kinase A (PKA) can antagonize phosphorylation-dependent nuclear export of HDACs. Oxidative stress can promote phosphorylation-independent nuclear export of class IIa HDACs, and this is antagonized by thioredoxin. Class I HDACs are thought to be aberrantly recruited to protective genes in stressed myocardium. Class IIb HDAC6 resides in the cytoplasm and deacetylates substrates such as tubulin. The role of class IIb HDACs in cardiac remodeling is unknown. HDAC inhibitors will have dramatically different effects on cardiac cells depending on the localization of HDACs. For example, in stressed cardiac myocytes, HDAC inhibitors will derepress protective genes through inhibition of class I HDACs.

heart (**Figure 4**). This concept is exemplified by the antioncogenic actions of HDAC inhibitors, which are largely mediated by derepression of proapoptotic and antiproliferative genes (e.g., cyclin-dependent kinase inhibitor, p21) (15). Class IIa HDACs are subject to signal-dependent nuclear export in response to cardiac stress stimuli. The mechanisms for class IIa HDAC nuclear export in the heart involve protein kinase D- or Ca^{2+}/calmodulin-dependent kinase-dependent phosphorylation of the enzymes (22, 24, 82–84), and oxidation of cysteine residues in the catalytic domains of the HDACs (85, 86). Phosphorylation-dependent nuclear export of class IIa HDACs can be blocked by protein kinase A (87–89), and the oxidative stress pathway for relocalizing the HDACs is sensitive to thioredoxin (85). An inhibitor of class IIa HDAC enzymatic activity would thus be expected to have profoundly different effects on nuclear or cytoplasmic processes depending on the activation state of these signaling pathways.

CLINICAL TRANSLATION AND CONCLUSIONS

The preclinical results described above provide a rationale for the evaluation of HDAC inhibitors in patients with heart failure. However, given the novelty of this approach, additional research is

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needed and caution is warranted. Proof-of-concept (POC) trials with small numbers of patients would be particularly instructive. Myocyte hypertrophy and interstitial fibrosis are sensitive to HDAC inhibition and are hallmarks of heart failure with preserved ejection fraction (HFpEF), making this condition an attractive indication for HDAC inhibitor therapy. There are no FDA-approved drugs for HFpEF, and current treatments for systolic heart failure provide little benefit to patients with this condition (90, 91). Echocardiographic measures of diastolic function, such as the ratio of peak early and atrial inflow velocities (E/A ratio), could be used as endpoints in a phase IIa POC trial of HDAC inhibitors. To further validate this approach, preclinical evaluation of HDAC inhibitors should be extended to models of HFpEF, such as Dahl salt-sensitive rats (92).

Given the efficacy of HDAC inhibitors in models of cardiac ischemia, postmyocardial infarction (MI) remodeling is another indication for which HDAC inhibitors should be considered. A small POC trial might be patterned after the recent clinical evaluation of the interleukin-1 receptor antagonist, anakinra, in patients with acute ST-segment elevation myocardial infarction (STEMI) (93). In that trial, cardiac magnetic resonance imaging and echocardiography were employed ~3 months post-MI to assess effects of anakinra on indices of LV end-systolic and end-diastolic volumes.

In terms of potential toxicity and side effects, pan-HDAC inhibitors are generally regarded as effective and well tolerated for the treatment of cancer (15). In addition to nausea and fatigue, HDAC inhibitors can produce transient thrombocytopenia and, in some instances, myelosuppression (94–97). Cancer therapy is frequently based on maximum tolerated doses of compounds. However, for heart failure, efficacious doses of HDAC inhibitors will likely be significantly lower than those required for cancer therapy, and thus may be well tolerated. Precedent for this was established in another non-oncology indication, systemic onset juvenile idiopathic arthritis, where the pan-HDAC inhibitor, ITF2357, was shown to be safe and efficacious at relatively low concentrations (98). Dose-response studies in preclinical models are needed to establish the therapeutic indices for assessment of efficacy in response to pan-HDAC inhibitors in the setting of heart failure. These studies should also include HDAC inhibitors in combination with current heart failure standards of care to assess potential synergy.

One can hypothesize that isoform-selective HDAC inhibitors will be safer than pan-HDAC inhibitors, although clinical experience with isoform-selective HDAC inhibitors is limited (99). A key next step in this regard is to determine which HDAC isoform(s) is pathological in the heart, and if selective inhibition of this HDAC can effectively treat heart failure. Genetic approaches for determining the roles of certain HDACs in the heart have been complicated by functional redundancy and early lethality associated with global gene deletion (100, 101). Studies of emerging classes of HDAC1/2-, HDAC3-, HDAC6- and HDAC8-selective compounds should facilitate efforts to define the roles of these HDAC isoforms in heart failure.

Much remains to be learned about the mechanisms governing the beneficial effects of HDAC inhibitors in the heart. HDAC inhibitors block processes such as cardiac hypertrophy, inflammation and fibrosis, but the mechanistic underpinnings of these effects are poorly understood. The efficacy of HDAC inhibitors in the heart is likely due to effects on many biochemical pathways (transcriptional and nontranscriptional) in multiple cell types (myocytes, fibroblasts, endothelial cells and others). Understanding the roles of HDACs in heart failure will require the combined use of in vivo systems and cell-based models that employ primary cells, and will undoubtedly be aided by the use of isoform-selective HDAC inhibitors. These studies, together with expanded efficacy and safety testing of HDAC inhibitors in heart failure models, have the potential to lay the foundation for discovery of innovative drugs to treat millions of patients worldwide.

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FUTURE ISSUES

1. Which HDAC isoforms are involved in the pathogenesis of heart failure?
2. How do HDACs contribute to the pathogenesis of heart failure? Which biochemical pathways and in which cell types do HDACs have roles in heart failure?
3. Will isoform-selective HDAC inhibition provide a safe and effective means of preventing and reversing heart failure?
4. Do HDAC inhibitors synergize with current standard-of-care therapies for heart failure?

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