*Minireview* *Highlight article*

# Histone deacetylases in modulating cardiac disease and their clinical translational and therapeutic implications

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**Impact statement**

Histone deacetylases (HDACs) have recently been recognized as one of the most important regulated mechanism(s) in mediating cardiovascular development, myocardial injury, and hypertrophy. This detailed review of the functional role(s) and molecular mechanism(s) of histone deacetylase will provide the current view by which HDACs induce different biological signaling in the regulation of cardiac physiology and disease. More importantly, HDACs could be targeted to develop a new therapeutic strategy in treating cardiovascular disorders. Further studies of the specific roles and targets of HDACs will extend our knowledge of the biological impact and clinical implications of HDACs.

## Abstract

Cardiovascular diseases are the leading cause of mortality and morbidity worldwide. Histone deacetylases (HDACs) play an important role in the epigenetic regulation of genetic transcription in response to stress or pathological conditions. HDACs interact with a complex co-regulatory network of transcriptional regulators, deacetylate histones or non-histone proteins, and modulate gene expression in the heart. The selective HDAC inhibitors have been considered to be a critical target for the treatment of cardiac disease, especially for ameliorating cardiac dysfunction. In this review, we discuss our current knowledge of the cellular and molecular basis of HDACs in mediating cardiac development and hypertrophy and related pharmacologic interventions in heart disease.

**Keywords:** Histone deacetylase, epigenetics, acetylation, deacetylation, cardiovascular disease, hypertrophy

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## Introduction

Cardiovascular disease (CVD) is highly prevalent among the general population and considered to be the leading cause of mortality and morbidity in developed countries. Many forms of heart disease lead to a progressive loss of cardiomyocytes by apoptosis or necrosis, which may culminate in cardiac dysfunction and death (reviewed in literature[1–3]). Identifying molecular mechanisms related to epigenetic regulation might open new therapeutic strategies for CVD prevention.[4]

Preclinical and clinical data have indicated that exposure to environmental challenges could result in the modification of epigenetic marks. The epigenetic signature of myocytes and other cardiac components endures profound changes when the heart undergoes development, maturation, and disease.[5] The major epigenetic modifications include histone modifications, the modulation of mRNA stability, and translation through non-coding RNA. A comprehensive understanding of epigenetic regulation will lead to new therapeutic approaches for specifically targeting CVD.[6–11] For greater understanding of the relationship between epigenetic modifications and CVD risk, we respectfully refer the reader to seek excellent comprehensive reviews.[5,8,12–19] Major post-translational modifications of histones include acetylation, methylation, phosphorylation, ubiquitination, sumoylation, or ADP-ribosylation of distinct amino acids, which could lead to either activation or suppression of gene expression.[20–22] One of the most important epigenetic regulatory machineries, lysine acetylation, is reversible and is controlled by the opposing actions of acetyltransferase and deacetylase *in vivo* by histone acetyltransferases (HATs) and HDACs in an opposing

fashion to control the acetylation status of nucleosomal histones. More general information on the biological function of HDACs are included in various other reviews.[23–27] In this review, we focus on the latest developments in the understanding of the biological function of HDACs in the regulation of cardiomyocyte development and CVD.

## HDAC classifications and domain organization

Eighteen mammalian histone deacetylases can be subdivided into four distinct classes (classes I, IIa, IIb, III, and IV) based on phylogenetic analyses of protein sequence homology, homology to yeast Rpd3 with yeast HDACs, enzymatic activity, domain structure, and functional similarities (Figure 1).

Class I, which is homologous to Rpd3 in yeast, including HDACs 1, 2, 3, and 8, is ubiquitously expressed in human tissues. Class I HDACs are closely related to several other protein subunits, which includes Sin3 and N-CoR, to regulate histone deacetylation and transcriptional co-repression.[24,28] HDAC1 and HDAC2 usually form a variety of repressive complexes with different gene repressors to participate in regulatory functions, which is highly distinct from co-repressor complexes containing the Sin3-HDAC1/2 complex.[29]

Class II is homologous to yeast HDA1, and its N-terminal extension possesses conserved important domains for protein-protein interaction. The six members of this class are classified into two subclasses: IIa (HDAC 4, 5,7, and 9) and IIb (HDAC 6 and 10), which have restricted expression patterns unique to deacetylase activities acting as signal transducers that shuttle between the cytoplasm and the nucleus.[30–33] Class II HDACs show tissue-specific expression such as in skeletal muscle, heart,[34] and brain and shuttle between the nucleus and cytoplasm, indicating that their regulation could be more complex as compared to the predominantly nuclear class I HDACs.[35–37]

Class III or sirtuin, which is homologous to the silent information regulator 2 (Sir2) family of proteins, includes SIRT1-7.[26] SIRT1 and 7 both are found to control cardiac development and prevent stress- and/or aging-associated cardiac dysfunction.[38]

Finally, HDAC11, the sole member of class IV, is homologous with both class I and class II HDACs. However, because HDAC11's sequence has limited homology to class I and II HDACs, it has not yet been assigned to any of the other three classes.[39]

### HDAC mediates stem cell and cardiac commitments

During embryological cardiovascular system development, a set of the mesodermal germ layer origin cells differentiate into specific cell types and then merge to form the cardiac tube. Epigenetic and chromatin modifications play a critical function for embryonic and induced pluripotent stem cells (ESCs and iPSCs), mediating both differentiation and de-differentiation back to a pluripotent state. HATs and HDACs recruit specific transcription factors to control the evolution of cardiovascular development. Differentiation of embryonic stem cells into specific cardiac lineage commitments requires activation of multiple signaling pathways and a distinct subset of cardiac-specific transcription factors, which are closely modulated by distinct HDACs.[40,41] HDACs mediate stem cell and cardiac progenitor-derived cardiac commitments (Table 1).

### Class I HDAC

HDAC1 and HDAC2 are functionally redundant in cardiac morphogenesis, cardiac growth, and development and maintain cardiac phenotype and function. Global deletion of HDAC1 in mice leads to embryonic lethality.[42] Cardiomyocyte restricted knockout of this gene (under the alpha-MHC promoter) has no effect on the phenotype.[43] However, HDAC1 knockdown blunts differentiation and the spontaneous contraction of mouse ESC cells.[44] Embryoid body (EB) beating of HDAC1 knockdown ESCs treated with BMP2 or over-expression by Sox-17 showed an almost identical presentation to wild type cells.[45] During the early stage of cardiomyocyte differentiation in the murine P19CL6 embryonic carcinoma cells, WNT promoted cardiac transcription factor NKX2.5 expression and early cardiomyogenesis through the suppression of HDAC1.[46] Inhibition of HDAC activity elicited cardiac differentiation in association with an increased expression of cardiac-specific genes related to cell cycle arrest. Over-

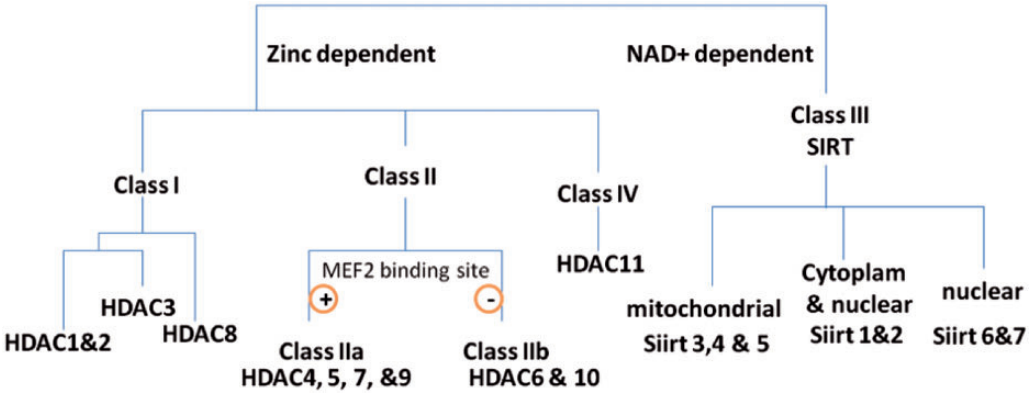


**Figure 1.** Eighteen mammalian histone deacetylase that are subdivided into four distinct classes based on phylogenetic analysis, enzymatic activity, domain structure and biological roles. HDAC: histone deacetylases. (A color version of this figure is available in the online journal.)

**Table 1.** HDACs mediates cardiac development and cardiogenesis.

| HDAC | Model | Biological functions and phenotypes in the heart | Refs |
|---|---|---|---|
| HDAC1 | Deficient mice | embryo lethality before E9.5 because of proliferation defects | 42,43 |
| | Deletion in myocardium | no apparent cardiac defects | 43 |
| | Knockdown mouse ESCs | suppresses cardiac differentiation and beating ability | 44,47 |
| | iPSC deficiency | impairs differentiation and electrophysiological properties of cardiomyocytes. | 44 |
| | P19CL16 cells | WNT signaling promotes the cardiac transcription factor NKX2.5 expression and early cardiomyogenesis via downregulation of HDAC1 | 46 |
| | Deletion in bone marrow mesenchymal cells | promotes the directed differentiation of bone marrow-derived mesenchymal stem cells into cardiomyocytes | 51,52 |
| HDAC2 | Knockout mice | perinatal lethality with severe cardiac defects that appear to reflect a non-myocyte-autonomous | 43 |
| | Knockout mice | Proliferation rates of cardiac myocytes in HDAC2 knockout mice were elevated | 55 |
| HDAC3 | Transgenic mice | postnatal cardiac myocyte proliferation, thickening of ventricular myocardium | 54 |
| HDAC3 | Deletion in cardiac progenitor cells | precocious cardiomyocyte differentiation, severe cardiac developmental defects, embryonic lethality | 56 |
| HDAC4 | P19 cell over-expression | suppresses cardiomyogenesis | 49 |
| SIRT1-7 | Stem cell and cardiac progenitor cells differentiation to cardomyocyte remains unclear. | | |

HDAC: histone deacetylases.

**Table 2.** The physiological role of HDACs in cardiac genesis, development and heart diseases.

| Subtype | Model | Phenotype and disease functions in the heart | Refs |
|---|---|---|---|
| HDAC1 | P19 cells | Suppression of HDAC1 activity stimulated cardiac differentiation | Liu et al.[46] |
| | Knockout mice | Embryo lethality before E9.5 because of proliferation defects | Montgomery et al.[43] |
| | | Embryonic stem cell differentiation | Dovey et al.[47] |
| | Cardiac-specific deletion | No apparent cardiac defects, HDAC2 functions redundantly with HDAC1 in the myocardium. | Montgomery et al.[43] |
| HDAC2 | Knockout mice | Resistant to cardiac hypertrophy when hearts exposed to hypertrophic stimuli. | Trivedi et al.[55] |
| | | Increase in proliferation at P1, Lethality after P1 | Montgomery et al.[43] |
| | Cardiac-specific deletion | No apparent cardiac defects, HDAC2 functions redundantly with HDAC1 in the myocardium. | Montgomery et al.[43] |
| | Transgenic mice | Cardiac hypertrophy | Trivedi et al.[55] |
| HDAC1 & HDAC2 | Cardiac-specific deletion | Neonatal lethality, accompanied by cardiac arrhythmias, dilated cardiomyopathy. | Montgomery et al.[43] |
| HDAC3 | Knockout mice | Lethality by E9.5 | Montgomery et al.[72] |
| | Cardiac-specific deletion | 3–4 months of lifespan, massive cardiac hypertrophy | |
| | Transgenic mice | Thickening of ventricular myocardium, reduction of both ventricular cavities in newborn | Trivedi et al.[54] |
| HDAC4 | Knockout mice | Die prenatally, premature ossification of developing bone | Vega et al.[83] |
| | Transgenic mice | Died prematurely | |
| | Transgenic mice | Died prematurely or lacked germline transmission | Ago et al.[86] |
| | C667/669S mutant mice | Significantly greater left ventricular, cardiac hypertrophy in response to reactive oxygen species stimuli | |
| HDAC5 | Knockout mice | Enlarged hearts in response to pressure overload | Chang et al.[57] |
| | | Contraction of cardiac muscle | Chang et al.[57] |
| HDAC7 | Knockout mice | Lethality at E11.5, severe hemorrhage from leaky and dilated blood vessels | Chang et al.[97] |
| HDAC9 | Knockout mice | Cardiac hypertrophy | Zhang et al.[74] |
| SIRT1 | Knockout mice | Lethality at birth, small size, heart valve defects | Cheng et al.[99] |
| | Over-expression in myocardium | High SIRT1 over-expression triggers cardiac hypertrophy and apoptosis. Low/moderate SIRT1 over-expression reduces cardiac hypertrophy and apoptosis | Alcendor et al.[100] |
| SIRT3 | Knockout mice | Cardiac hypertrophy and interstitial fibrosis at 8 weeks of age | Sundaresan et al.[105] |
| | Over-expression in myocardium | Resistant to stress-induced cardiac hypertrophy | |
| SIRT7 | Knockout mice | Shortened lifespan, extensive cardiac hypertrophy, fibrosis, and inflammatory cardiomyopathy | Vakhrusheva et al.[115] |

HDAC: histone deacetylases.

expression of HDAC1 inhibited cardiomyocyte commitments and downregulated the expression of transcriptional factors Gata4 and Nkx2.5. Activation of the WNT pathway attenuated HDAC1 expression, which was accompanied by the upregulation of Nkx2.5 expression. Both WNT3a and WNT3 are demonstrated to mitigate the expression of HDAC1, which is in contrast with the effect of SFRP2 and GSK3beta. In addition, co-transfection of beta-catenin and lymphoid enhancer-binding factor 1 (LEF1) resulted in a marked reduction of the expression of HDAC1.

Global knockout of HDAC2 led to perinatal lethality with severe cardiac defects, which displays a non-myocyte-autonomous function of HDAC2, because specific deletion of either HDAC1 or HDAC2 alone has not displayed a discernible effect on heart function. However, cardiomyocyte-specific knockout of both HDAC1 and HDAC2 led to the development of dilated cardiomyopathy and neonatal lethality, which is also accompanied by the upregulation of skeletal muscle-specific myofibrillar proteins and calcium channels.[43] Embryonic stem cells deficient in either HDAC1 or HDAC2 were still capable of developing EBs, allowing cells to undergo differentiation into the three primary germ layers. However, deficient EBs showed a strikingly abnormal development, spontaneous rhythmic contraction, and augmentation of cardiomyocytes.[47] During the ES cell differentiation into cardiomyocytes, acetylated GATA-4 had an increased DNA binding ability. Acetylation of GATA-4 as well as of histones is involved in the differentiation of ES cells into cardiac myocytes.[48–50] HDAC2 interacts with Hop and subsequently deacetylates Gata4 and downregulates cell cycle genes, thereby suppressing cardiomyocyte proliferation.

HDAC1 suppresses differentiation of bone mesenchymal stem cells (BMSCs) into cardiomyocytes. Thus, the expression of HDAC1 was found to be decreased in BMSCs during their differentiation into cardiomyocytes. HDAC1 is a negative regulator in cardiac cell differentiation derived from BMSCs. Compared with control BMSCs, the expression of cardiomyocyte-specific transcriptional levels was significantly upregulated in HDAC1 deficient stem cells. Deletion of HDAC1 promoted the directed differentiation of bone marrow-derived mesenchymal stem cells into cardiomyocytes.[51,52] Like 5-azacytidine (5-aza, a DNA methylation inhibitor), treatment with a histone deacetylase inhibitor, SAHA, stimulates BMSC differentiation into cardiomyocytes and transcription of cardiomyocyte-specific transcription factors such as GATA4, NKx2.5, and Mef2c.[53] Following the inhibition of HDAC1 or HDAC2 by small interfering RNAs, BMSCs exhibited a tendency towards cardiac linage commitment, which was accompanied by enhanced histone 3 and histone 4 acetylation at gene loci.[52]

HDAC3 over-expression in cardiomyocytes resulted in ventricular thickening, which especially occurs in the interventricular septum, and significantly reduced the ventricular cavity.[54] The increased thickness of myocardium in HDAC3 over-expression transgenic (HDAC3-Tg) mice results from enhanced hyperplasia in cardiomyocytes (postnatal cardiac myocyte proliferation) without cardiac hypertrophy. HDAC3 over-expression attenuates several critical cyclin-dependent kinase inhibitors, including Cdkn1a, Cdkn1b, Cdkn1c, Cdkn2b, and Cdkn2c. Unlike previously reported HDAC2-Tg mice,[55]HDAC3-Tg mice did not develop cardiac hypertrophy at 3 months of age. Furthermore, HDAC3 over-expression did not augment isoproterenol-induced cardiac hypertrophy when compared to wild-type littermates. Mouse cardiac progenitor cells lacking HDAC3 displayed precociously differentiated cardiomyocytes, severe cardiac defects, and upregulation of Tbx5 as well as embryonic lethality.[56] HDAC3 physically interacts with Tbx5 and regulates Tbx5 acetylation that results in the repression of Tbx5-dependent expression of cardiac lineage-specific genes, revealing that HDAC3 plays a key role to regulate early cardiogenesis.

### Class II HDAC

During the differentiation of P19 mouse embryonic carcinoma stem cells into cardiomyocytes, HDAC inhibitor trichostatin A induces the entry of mesodermal cells into cardiac muscle lineages through upregulation of Nkx2-5, MEF2C, GATA4, and cardiac alpha-actin.[49]Over-expression of HDAC4 suppresses cardiomyogenesis, as illustrated by the downregulation of cardiac specific genes. Class II HDAC activity can be suppressed by phosphorylation by calcium/calmodulin-dependent kinase (CaMK). Enhanced expression of an activated CaMKIV in P19 cells largely increased the transcriptional levels of Nkx2-5, GATA4, and MEF2C, stimulated cardiac muscle growth, and activated MEF2-regulated genes.[49] Additionally, HDAC activation also modulates the specification of mesoderm cells into cardiomyoblasts by the suppression of GATA4 and Nkx-2.5 cells in a stem cell model. The observations from Olson's laboratory indicated that the hearts of both HDAC5$^{-/-}$ and HDAC9$^{-/-}$ mice showed a normal development, but most HDAC5 and HDAC9 double knockout mice died as a result of heart defects, indicating a role for class II HDACs in the control of heart development and growth.[57] However, during the earliest stage of class II HDAC-induced regulation, cardiogenesis remains uncharacterized.

### SIRT (1–7)

The biological function of Sirts on stem cell and cardiac progenitor cell differentiation to cardiomyocytes remains unclear.

## HDAC in cardiac hypertrophy

Cardiac hypertrophy can occur in response to a variety of extrinsic and intrinsic physiological stimuli, while myocardial infarction, hypertension, myocyte death, remodeling, heart failure, and vascular disease can elicit maladaptive hypertrophy resulting in dilated dysfunction and congestive heart disease. At the cellular level, cardiomyocyte hypertrophy is characterized by an increase in cardiomyocyte size, enhanced protein synthesis, and heightened sarcomere organization. At the molecular level, the genetic programs progressing into cardiac hypertrophy are generally known to be diverse and complex. In response to

hypertrophic stimulation, cardiac transcription factors are profoundly associated with the production of cardiac hypertrophy or protective effects from cytotoxic stress.[58] Pathological hypertrophy is characterized by the re-induction of gene expression programs at the fetal stage, which results in the modulation of cardiac contractility and calcium handling and a down-regulation of their adult isoforms.[18,40,41] The studies from HDAC knockout mouse models have revealed the functional role of HDACs in development and hypertrophy.[59]

### Class I HDACs

*HDAC1 and HDAC2.* *HDAC1*-null mice die in utero before embryonic day 10.5 with proliferative defects and developmental retardation, possibly stemming from increased levels of cyclin-dependent kinase inhibitors $p21^{WAF1/CIP1}$ and $p27^{KIP1}$.[60] Mice lacking HDAC2 survived until the perinatal period, but manifested a broad spectrum of cardiac defects such as obliteration of the lumen of the right ventricle, apoptotic myocytes, and abundant hyperplasia.[43] HDAC1 and HDAC2 show redundant functions for modulating cardiac gene transcription and cardiomyocyte differentiation.[43] As cardiac-specific knockout of either HDAC1 or HDAC2 did not elicit a cardiac phenotype, such mutant mice survived to adulthood. However, cardiac-specific deletion of both genes led to neonatal lethality, in association with cardiac arrhythmias and dilated cardiomyopathy.

Similar to mice lacking cardiac HDAC1 and HDAC2, mice that over-expressed a dominant-negative form of REST, known as the neuron-restrictive silencer factor (NRSF), which is identified to recruit class I and class IIa HDACs, also developed dilated cardiomyopathy, ventricular arrhythmias, and sudden death.[61] Therefore, the combined losses of HDAC1 and HDAC2 may lead to inability of REST to repress the fetal genetic program associated with impaired calcium handling and contractility, thereby resulting in myocardial arrhythmia and heart failure. Furthermore, class I HDACs function as signal-dependent repressors of cardiac hypertrophy via inhibition of the gene encoding dual-specificity phosphatase 5 (DUSP5) DUSP5, a nuclear phosphatase that negatively regulates pro-hypertrophic signaling by ERK1/2.[62]

HDAC2 is regulated by serine phosphorylation, lysine ubiquitylation, tyrosine nitration, and cysteine nitrosylation. The hypertrophic stimuli selectively targets cardiac HDAC2 through the induction of heat shock protein 70 (Hsp70) that is physically associated with HSP70.[63] In addition, when cardiomyocytes were infected with an acetylation-mimicking mutant of HDAC2, the antihypertrophic effect of either nuclear tethering of HDAC5 with leptomycin B or HDAC5 over-expression was significantly attenuated.[64] Hypertrophic stimuli provokes casein kinase 2 translocation into the nucleus, which induces the consequent phosphorylation of HDAC2 at serine 394 (and other targets), ultimately leading to cardiomyocyte growth.[65]

Krüppel-like factor 4 (KLF4) is a novel anti-hypertrophic regulator. Over-expression of KLF4 inhibits three key features of cardiomyocyte hypertrophy. In contrast, cardiomyocyte-specific knockout of KLF4, a target of HDAC2, increases cardiomyocyte sensitivity to transverse aortic constriction and imposes high mortality rates.[66] In cardiomyocytes, KLF4 represses Nppa transcription, and thereby attenuates cardiac hypertrophy.[67] The phosphatidylinositol 3-kinase- (PI3K)-Akt-Gsk3$\beta$ signaling pathway is a pivotal controller of cardiomyocyte growth in cardiac development. HDAC2-null mice are resistant to hypertrophic stimuli due to the activation of glycogen synthase kinase 3 β (GSK3β), whereas HDAC2-Tg mice are sensitive to hypertrophic stimuli.[55] In contrast, HDAC2 transgenic mice over-expressing HDAC2 in the heart had augmented hypertrophy which is associated with inactivated GSK3beta. Furthermore, Inpp5f over-expression in mice blunted hypertrophy, whereas hypertrophy was intensified in Inpp5f knockout mice.[68] Exercise induces physiological hypertrophy and benefits the diabetic myocardium. Mammalian switch-independent 3A (mSin3A) and HDACs 1 and 2 modulate hypertrophic genes in association with REST and O-linked beta-N-acetylglucosamine transferase (OGT). Diabetes and exercise affect interactions in an opposite way between pro-hypertrophic transcription factors.[69] Cardiac hypertrophy is associated with an increase in human B-type natriuretic peptide (BNP) gene.[70] HDAC2 regulates BNP gene promoter activity in neonatal rat ventricular myocytes by the transcription factor YY1,[71] indicating that YY1 interaction with HDAC2 is related to BNP promoter transcriptional activation.

*HDAC3.* Unlike *HDAC2*-transgenic mice, over-expression of cardiac HDAC3 did not show spontaneous cardiac hypertrophy or increased sensitivity to hypertrophic stimuli.[54] Mice with myocardium-specific deletion of HDAC3 survive until 3 to 4 months of age with severe cardiac hypertrophy and fibrosis.[72]Cardiac-specific deletion of HDAC3 mice led to intensive myocardial hypertrophy and upregulation of genes related to the metabolic modulation of fatty acid uptake, fatty acid oxidation, and electron transport/oxidative phosphorylation in association with cardiac lipid accumulation and enhanced triglyceride content.

### Class II HDAC

The class IIa HDACs include HDAC4, HDAC5, HDAC7, and HDAC9, which are expressed in the heart (14–3-3). In addition, class II HDAC can directly bind to other pro-hypertrophic transcription factors including GATA4,[49,50]MADS-box family member serum response factor (SRF),[73] MEF2,[30,74,75] and NFAT[76] to repress their regulated genes. In response to stress, the heart hypertrophies in association with MEF2 activation and reprogramming. Class IIa HDACs, which repress the function of MEF2, serve as substrates for a stress-responsive kinase specific for conserved serines that modulate the interplay between MEF2 and HDAC. Signal-resistant HDAC mutants lacking these phosphorylation sites were found to be refractory to hypertrophy and inhibit hypertrophy.[74] The N-terminal regulatory domain of class II HDACs regulates the interplay between transcription factors, co-activators, and co-

repressors. The N-terminal regions of class II HDACs also have two conserved CaMK phosphorylation sites.[77–79] Phosphorylation of class II HDACs by CaMK and other kinases abrogate their tight interaction with MEF2 that result in the depression of transcriptional activity. HDAC5 phosphorylation mutants at serines 259 and 498 were found to be resistant to the PKC-induced signaling pathway and to attenuate the magnitude of cardiac hypertrophy.[80] Phosphorylation of HDAC5 by PKC or PKD causes this protein to specifically form a complex with 14–3-3 protein, which subsequently leads to the nuclear export of HDAC5.[81]

*HDAC4.* HDAC4 plays a global role in the regulation of gene transcription in different cell types, such as skeletal muscle, cardiomyocytes, chondrocytes, osteoblasts, and nerve cells.[82] HDAC4 knockout and transgenic mice studies demonstrate that HDAC4 mediates chondrocyte hypertrophy by interacting with Runx2 (Runt related transcription factor 2) during the development of the skeleton.[83] Hypertrophic stimuli induces HDAC4 oxidation, while thioredoxin 1, a small protein antioxidant, modulates it.[72,84,85] HDAC4 oxidation is induced by hypertrophic stimuli, thioredoxin1, a 12-kDa antioxidant.[86] Nicotinamide adenine dinucleotide phosphate oxidase 4 (Nox4) regulates HDAC4 cysteine oxidation in the control of myocardial hypertrophy in response to phenylephrine and pressure overload.[85] CaMKII induced-phosphorylation of HDAC4 enhances hypertrophic growth, which was blocked by a signal-resistant HDAC4 mutant.[87] Cyclic AMP-dependent protein kinase A (PKA) induces an N-terminal HDAC4 cleavage that could overcome the role of CaMKII in cardiomyocyte hypertrophy.[88] Several microRNAs regulate cardiomyocyte hypertrophy by binding 3'UTR of HDAC4. In miR-22-null mice, cardiac miR-22 was found to be essential for hypertrophic growth by directly targeting HDAC4.[89] Additionally, HDAC4 was also found to modulate myofilament contractile activity through mediating muscle LIM protein deacetylation.[90]

*HDAC5 and HDAC9.* HDAC5 knockout mice develop cardiac hypertrophy during the progression to ageing in response to pressure overload and calcineurin signaling.[57] In contrast, deletion of HDAC9 manifests a normal cardiac size and function at an early stage but become sensitized to hypertrophic signals and exhibit stress-dependent cardiomegaly with advanced age.[74] HDAC5 or HDAC9 knockout mice could survive to adulthood in the absence of apparent myocardial defects. However, mice in which both HDAC5 and HDAC9 are deleted show embryonic or early perinatal lethality with variable penetrance.[57] Mice lacking both HDAC5 and HDAC9 show a severe cardiac hypertrophy and display a propensity for thin-walled myocardium and lethal ventricular septal defects. Calmodulin and CaMKII both phosphorylate class IIa HDACs and are involved in cardiac hypertrophic signaling by forming a complex with 14–3-3 and inducing interaction with MEF2.[77,91] Calmodulin binding transcription activator 2 (CAMTA2), an indispensable transcription co-activator of hypertrophy, is activated by dissociation from HDAC5 and promotes transcription of genes responsible for cardiac hypertrophy. Cardiac development in response to neurohumoral signaling and pressure overload are defective in mice with a homozygous mutation in the CAMTA gene, and mice with HDAC5 deletions are sensitized.[92] In the adult ventricular myocyte model, the hypertrophic agonist endothelin-1 was found to result in HDAC5 phosphorylation and activated nuclear export of HDAC by triggering nuclear envelope $Ca^{2+}$ release via inositol 1–4,5-trisphosphate receptor activation.[93] HDAC5 interacts with transcription factor Yin Yang 1 (YY1) in cardiomyocytes and plays an anti-hypertrophic role in myocardial hypertrophy.[94] In addition, HDAC5 was phosphorylated by protein kinase A, which prevented its nuclear export and led to the inhibition of gene transcription and cardiac hypertrophy.[95]MEF2-interacting transcriptional repressor (MITR) is considered to be a predominant splice variant of HDAC9 expressed in the myocardium. MITR could efficiently attenuate the activity of MEF2 through the recruitment of other co-repressors. Disruption of these specific phosphorylation sites of mutants of MITR serve as signal-resistant repressors of cardiac hypertrophy.[96]

*HDAC 6, 7, 10.* Knockout of HDAC7 in mice produces vascular defects which culminate in embryonic lethality at E11.5 due to severe hemorrhage.[97] In these mice, the vascular structures, including the dorsal aorta and cardinal veins, were dilated and leaky, with sparse vascular smooth muscle. HDAC6 is dispensable for cardiovascular development, as HDAC6 knockout mice develop normally and grow to adulthood despite some immune response abnormalities. HDAC6 catalytic activity increases in the stressed heart but not in physiologic hypertrophy.[98] However, little is known about the role of HDAC10 in cardiac hypertrophy.

*SIRT (1–7).* SIRT1 and SIRT3 activation negatively regulates cardiac hypertrophy. SIRT1 deacetylates p53, preventing p53 from triggering cellular senescence and apoptosis in response to DNA damage and stress. Deletion of SIRT1 in mice results in mouse death perinatally, which is accompanied by significant neurological and cardiac malformations in atrial septal, ventricular septal, and heart valve defects.[99] SIRT1 was dramatically elevated in response to pressure overload and oxidative stress. The moderate expression of SIRT1 retards the progression towards aging of the heart, whereas a high dose of SIRT1 triggers the development of cardiomyopathy.[100]

SIRT1 protects cardiomyocytes from the apoptotic pathway and age-dependent degeneration as demonstrated by a dose dependent manner, in which SIRT1 displays a protective function at low doses but detrimental effects at high doses.[101] Peroxisome proliferator-activated receptor-alpha (PPAR alpha) is a master controller of the metabolic pathway and which regulates cardiac hypertrophy and metabolism. Over-expression of SIRT1 resulted in the deacetylation of the PPARalpha co-activator PGC-1alpha that induces cardiac protection.[102]

SIRT2 is a negative regulator of anoxia-reoxygenation tolerance. Specific inhibition of SIRT2 increased the production of a chaperone protein 14–3-3 ζ, which sequesters the Bcl2 antagonist of cell death (Bad) in the cytoplasm, thereby attenuating the pro-apoptotic buildup of Bad in mitochondrial membranes.[103]

SIRT3-deficient mice are born grossly normal but show the development of cardiac hypertrophy and interstitial fibrosis by 8 weeks of age.[104]SIRT3-deficient mice develop an even more severe cardiac hypertrophy when exposed to hypertrophic stimuli, while mice over-expressing SIRT3 in the myocardium are resistant to hypertrophy from similar stimuli. SIRT3-induced protective effects against stress-induced hypertrophy are likely mediated through the activation of the Foxo3a-dependent antioxidant and attenuation of the RAS, MAPK/ERK, and PI3K-Akt pathways.[105–107] SIRT3 deacetylates FOXO3 and protects mitochondria against oxidative stress through modulating mitochondrial mass, ATP production, and clearance of defective mitochondria.[108] SIRT3 deficiency exacerbates the aged hearts' susceptibility to ischemia-reperfusion injury.[109] SIRT3 deacetylates Ku70 and regulates the interaction of Ku70 with the proapoptotic Bax (Bcl2-associated X protein), thereby blocking the entry of Bax into the mitochondria to induce apoptotic signaling.[110] Another report demonstrated that reactive oxygen species (ROS)-mediated NF-kappa B activation was related to the downregulation of SIRT3, which develops protective effects in myocytes exposed to oxidative stress.[111]

SIRT4 and SIRT5-deficient mice were found to be born grossly until at least 18 months of age and did not illustrate obvious cardiac defects.[112,113]SIRT6-deficient mice show runting with lymphopenia, loss of subcutaneous fat, lordokyphosis, and severe metabolic disarrangements.[114]

SIRT7-knockout mice undergo shorter lifespans and develop cardiac dysfunction and inflammatory cardiomyopathy. SIRT7 mutant hearts are also characterized by extensive interstitial fibrosis. SIRT7 associated with p53 directly deacetylates p53 *in vitro*, which initiates hyperacetylation of p53 *in vivo*, increases apoptosis, and diminishes resistance to oxidative and genotoxic stress.[115]

## Clinical translation and therapeutic implications of HDAC inhibitors and SIRT activators

Altered expression of HDAC genes modulate the function of cardiomyocytes, endothelial cells, vascular smooth muscle cells, and macrophages in association with the transcription of key genes regulating important cellular events and cell survival in different conditions. Thus, HDACs recently were recognized as promising potential therapies for CVD treatment and other pathological disorders. Pathological features of heart failure are often observed in pathological conditions including increased stress associated with injury, genetic causes, infection, and aging, etc. In the present, class I/II HDAC inhibitors and SIRT activators are found to be involved in different pathways that control heart remodeling (Figure 2).

### Small molecules targeting HDACs

Small molecule HDAC inhibitors are usually designed as structural mimics of the endogenous acetyl–lysine ligand, which contain elements including a surface binding or cap group, a hydrocarbon linking motif, and a zinc-binding group (ZBG). The rationale for drug design has allowed the small molecule inhibitors to be selectively applied for either class I or class II HDACs.[116] HDACs inhibitors can be classified into several structural categories, including structurally distinct groups: hydroxamic acids (e.g. Trichostatin A [TSA], vorinostat, suberoylanilide hydroxamic acid [SAHA]; short chain fatty acids (e.g. phenylbutyrate, valproic acid); benzamides (e.g. MGCD0103, Entinostat [MG-275]; and cyclic peptides (e.g. depsipeptides).[117,118] Some classes of broad HDAC I and II inhibitors have recently been shown to be protective in animal models. HDAC inhibitors, including trichostatin A and sodium butyrate, showed a protective effect against the hypertrophic response in a dose-dependent manner[119] in response to a hypertrophic stimulus.[120] In infarcted rats, HDAC inhibitors such as valproic acid (VPA) and tributyrin suppressed myocardial remodeling following cardiac infarction.[121] TSA also preserved cardiac function and attenuated cardiac remodeling by stimulating endogenous repair.[122] Previously, we and others have found that TSA can significantly reduce myocardial infarct size in ischemia/reperfusion (I/R) injury in mice and rats.[123–126] For more general information in terms of therapeutic potential for HDAC inhibitors in the heart, we respectfully refer the reader to these comprehensive reviews.[34,127–132] Recent evidence supports that HDAC inhibition holds promise in developing a potentially new therapeutic strategy in the treatment of CVD. Treatment of several HDAC inhibitors were reported to mitigate myocardial hypertrophy and improve cardiac performance in pathological disease models.[133,134] Currently, treatment with VPA attenuates inflammation, cardiac hypertrophy, and fibrosis through acetylation of the mineralocorticoid receptor in rats.[135] The apicidin derivative, API-D, is capable of antagonizing myocardial hypertrophy and consequently the transition to cardiac dysfunction in mice subjected to thoracic aortic constriction.[136] The class II specific HDAC inhibitor MC1568 inhibits HDAC4 and HDAC5 activities without affecting HDAC3 activity in skeletal muscle and heart. Thereby, it may might have a therapeutic potential for the treatment of muscle and heart disease.[137] It also blocks HDAC4 enzymatic function and induces HDAC 4 proteasomal pathways of degradation.[138] In addition, HDAC expression increased significantly in heart failure and ischemic hearts, and HDAC inhibitors were found to effectively attenuate interstitial fibrosis and inflammation as well as ischemic injury.[139–143] In addition to the beneficial effects of small molecules to target HDACs, the genetic approach to target HDACs also demonstrates protective effects against pathological disorders. Experimental data have accumulated exciting observations in the review that FDA-approved HDAC inhibitors antagonize cardiac remodeling, myocardial ischemia/reperfusion, and related diseases.[144–148]

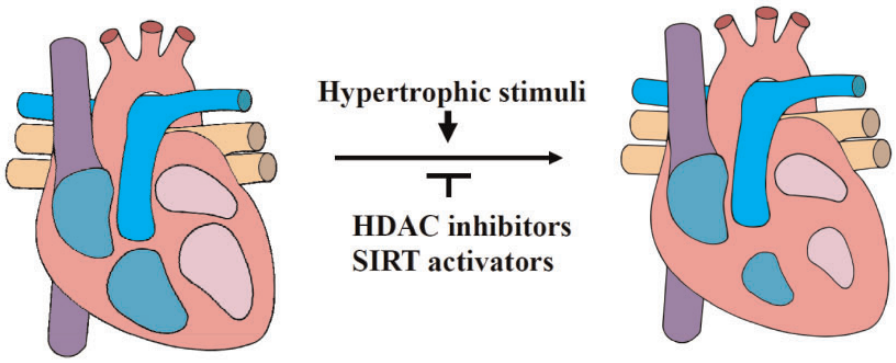


**Figure 2.** HDAC inhibitors and SIRT activators involved in signaling pathways in controlling heart remodeling. HDAC: histone deacetylases. (A color version of this figure is available in the online journal.)

### Pharmacologic targeting of SIRT

Unlike class I and II HDACs, activation of a member of a class III histone deacetylase (e.g., SIRT1 and SIRT3) abrogates pathological disorders associated with heart failure, protects myocytes from hypertrophic agonist-mediated cell death, and promotes endothelial angiogenic functions. Resveratrol, a polyphenol phytoalexin abundantly found in grape skin and in wine, protects cardiomyocytes from hydrogen peroxide-induced apoptosis by activating SIRT1, 3, 4, and 7.[149] SIRT1 and mitochondrial biogenesis are known to play a key role in controlling the production of ROS. Resveratrol-induced SIRT1 over-expression protected cardiomyocytes from oxidative injury, mitochondrial dysfunction, and cell deaths induced by ischemia-reperfusion.[150] Additionally, the beneficial effects are associated with the induction of mitochondrial genes, which include NDUFA1, NDUFA2, NDUFA13, and Mn-SOD.[151,152] They attenuated the extent of ischemia/reperfusion injury through an increase in peroxisome proliferator-activated receptor gamma co-activator-1 (PGC-1) alpha and enhanced mitochondrial biogenesis.[153] Treatment of cardiomyocytes with resveratrol prevents oxidative stress-derived lipid peroxidation byproduct 4-hydroxy-2-nonenal modification of the LKB1/AMPK signaling pathway that accelerates the progression towards heart failure. Resveratrol mitigates pro-apoptotic signaling in the senescent myocardium through deacetylation of SIRT1 in suppressing the Foxo1/Bim-associated pro-apoptotic signaling pathway.[154]Long-term treatment with resveratrol in mice activates SIRT1 and improves myocardial performance of senescent mice by attenuating Foxo1-associated pro-apoptotic signaling.[154] Resveratrol increases mitochondrial biogenesis and reduces Ang II-induced myocardial remodeling in rats.[155] Treatment of the patients with the SIRT1 activator resveratrol rescued the senescent phenotype.[156] Reductions in arterial SIRT1 are related to vascular endothelial dysfunction induced by aging. The SIRT1 activator SRT1720 reduces myocardial infarction in both aged and SIRT1(+/−) hearts,[157] ameliorating endothelial dysfunction in mice by activating COX-2 signaling and inhibiting oxidative stress and inflammation.[158] The treatment of mice with sildenafil, a phosphodiesterase-5 inhibitor, or adiponectin resulted in an increase in SIRT1 activity in the myocardium and demonstrated a protective effect, indicating a causal relationship between SIRT1 activation and cardioprotective effects.[159,160] In addition, Tadalafil-treated diabetic mice showed an improvement in myocardial function in association with increased SIRT1 activity and AMPK in the diabetic hearts.[161] Recently, statins that induced the upregulation of SIRT resulted in acetylation/deacetylation-dependent modification with about 100 detected proteins. These dynamic acetylations are likely to affect protein function and are important in regulating a statin-mediated pleiotropic effect. Therefore, targeting SIRT could be a promising approach to develop the therapeutic strategy to treat CVD.

## Conclusions

Our review indicates that HDACs are major regulators to control cardiac development and contribute to stem cell-derived cardiogenesis. Second, HDACs play a critical role in mediating myocardial hypertrophy, remodeling, and functional recovery after cardiac damage. Finally, HDACs are considered to be the most promising therapeutic targets for CVD treatment and other pathological disorders. Specific HDAC isoforms function differently in executing their biological roles (Table 2), which require the development of isoform specific HDAC inhibitors and activators for translational implications.

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