

Histone deacetylase 4: A therapeutic target for cardiovascular diseases (Review)

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Abstract. Cardiovascular disease (CVD) is a major global health threat, as its incidence and mortality rates continue to rise, highlighting the urgent need for effective therapeutic strategies. Histone deacetylase 4 (HDAC4), a member of class IIa HDACs, has attracted increasing attention in recent years for its role in CVD. Studies have shown that HDAC4 can influence the development and progression of CVD such as cardiac hypertrophy, hypertension and atherosclerosis by regulating key pathophysiological processes including inflammation, fibrosis and apoptosis. The present review focuses on the functional roles of HDAC4 in CVD and examines the effects of pharmacological agents and physical exercise on its expression. Future research should further elucidate the molecular mechanisms underlying HDAC4's involvement in CVD to provide new theoretical foundations for clinical diagnosis and treatment.

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1. Introduction

Histone deacetylases (HDACs) are enzymes that regulate gene expression by deacetylating histones, thereby modulating their interaction with chromatin (1). HDACs play critical roles in controlling cell proliferation, differentiation and development (2). Among them, HDAC4 belongs to class IIa HDACs and is exclusively expressed in non-proliferating cells (3,4). Studies have shown that HDAC4 is highly expressed in the heart, brain, skeletal muscle and thymus (5,6).

CVD, a group of disorders affecting the heart or blood vessels, poses a significant threat to human health. Common types of CVD include heart failure (HF), myocardial infarction (MI) and coronary artery disease (CAD) (7). Multiple studies have demonstrated altered HDAC4 expression in CVD, suggesting its potential as a biomarker for patients with cardiovascular conditions (8-10). Moreover, previous findings indicate that HDAC4 contributes to the progression of CVD by regulating processes such as cardiac hypertrophy, inflammation, fibrosis and apoptosis (11-13).

In the present review, the biochemical properties of HDAC4 were analyzed and an in-depth discussion of its roles and mechanisms in CVD was provided. Additionally, factors that influence HDAC4 expression were summarized. Finally, a summary and outlook were added as a conclusion, aiming to provide new insights into the potential application of HDAC4 in the treatment of CVD.

2. Biochemical properties of HDAC4

HDAC4 is a Zn²⁺-dependent class IIa histone deacetylase with unique structural and biochemical characteristics (Fig. 1). It consists of an N-terminal region (residues 1-648) responsible for protein-protein interactions and a highly conserved C-terminal lysine deacetylase domain (residues 648-1084) (14,15). The N-terminal region contains a nuclear localization sequence

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(NLS) located between residues 247 and 285, which mediates the nuclear import of HDAC4 (16). Phosphorylation at Ser246, Ser467 and Ser632 provides binding sites for 14-3-3 chaperone proteins, which facilitate the nuclear export of HDAC4 by promoting its translocation to the cytoplasm (17). Compared with the N-terminus, the C-terminal region harbors the catalytic domain responsible for deacetylase activity and is considered the functional core of HDAC4. Additionally, a hydrophobic nuclear export sequence (NES) is located at residues 1051-1084 of the C-terminus (16). This NES mediates the nucleocytoplasmic shuttling of HDAC4 through interaction with chromosomal maintenance 1 (17). Interestingly, the Zn²⁺-binding residues (residues 667, 669, 675 and 751) and the catalytic active site are located within the C-terminal domain.

3. Function of HDAC4 in CVD

Regulating the inflammatory response. Inflammation is a response initiated by the immune system in reaction to infections or non-infectious tissue injury (18). Extensive research has confirmed that inflammation is a key contributor to the development of CVD (19-21). Emerging evidence indicates that HDAC4 plays a critical role in mediating inflammatory responses associated with CVD. *In vitro* experiments have shown that the inhibition of HDAC4 alleviates Ang II-induced inflammatory responses in rat aortic endothelial cells (RAECs) (22). Another study has reported that silencing HDAC4 reverses the TNF- α -induced expression of inflammatory markers vascular cell adhesion molecule-1 (VCAM-1) and phosphorylated nuclear factor kappa B (NF- κ B) in smooth muscle cells (SMCs) (23). Furthermore, HDAC4 knockout suppresses the effect of long non-coding RNA cancer susceptibility candidate 11 (lncRNA CASC11) in downregulating the expression of pro-inflammatory cytokines IL-6 and IL-1 β and promoting the expression of the anti-inflammatory cytokine IL-10 in human cardiac microvascular endothelial cells (CMECs) (24). Interestingly, a clinical study has shown that HDAC4 expression is reduced in patients with coronary heart disease (CHD), and it is negatively correlated with the levels of pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-6 (13) (Fig. 2A). This alteration may result from the influence of the inflammatory microenvironment on HDAC4 expression *in vivo*, or it may represent a compensatory response to the disease state in patients with CHD. Therefore, further studies are warranted to elucidate the context-dependent roles and underlying mechanisms of HDAC4 under different pathological conditions.

Regulation of myocardial fibrosis. Following myocardial injury, cardiac fibroblasts are activated and differentiate into myofibroblasts. These myofibroblasts exhibit proliferative and secretory properties that promote extracellular matrix remodeling and collagen deposition, ultimately leading to fibrotic scarring and HF (25). One study demonstrated that inhibition of HDAC4 expression downregulates the Ang II-induced expression of the cardiac pericyte fibrosis marker α -smooth muscle actin (α -SMA) (26). Another study showed that HDAC4 knockout suppresses myocardial fibrosis in mice with MI (27). By contrast, HDAC4 overexpression promotes myocardial fibrosis in MI mouse models (27,28). HDAC4-NT,

the N-terminal fragment of HDAC4, has also been investigated for its potential protective role. A study has shown that HDAC4-NT overexpression ameliorates cardiac hypertrophy and fibrosis caused by abhydrolase domain-containing 5 (ABHD5) deficiency. Mechanistically, this effect may be associated with the downregulation of genes such as natriuretic peptide B (Nppb), Myomaxin, nuclear receptor subfamily 4 group A member 1 (Nr4a1), glutamine-fructose-6-phosphate transaminase 2 (Gfpt2), and pyruvate dehydrogenase kinase 4 (Pdk4) (29). Similarly, another study confirmed that HDAC4-NT suppresses the expression of fibrosis-related genes collagen type III alpha 1 chain (Col3a1) and Col5a1 in transverse aortic constriction (TAC)-induced models (30) (Fig. 2B).

Regulation of apoptosis. Apoptosis, also known as programmed cell death, is an active process regulated by specific genes (31). It plays a crucial role in maintaining cellular homeostasis and in the prevention and treatment of CVD (32). Studies have shown that HDAC4 overexpression can induce apoptosis in cardiomyocytes (33,34). Mechanistically, this may be related to elevated expression of the pro-apoptotic protein, caspase-3 (33). Evidence indicates that HDAC4 is involved in the anti-apoptotic effects of the lncRNA CASC11 in human CMECs (24). Similarly, Wu *et al* (35) reported that silencing lncRNA taurine-upregulated gene 1 (TUG1) suppresses the expression of pro-apoptotic markers Bcl-2-associated X protein (Bax) and cleaved caspase-3 but enhances the expression of the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2); this effect is associated with increased HDAC4 expression. In addition, another study has revealed the regulatory role of HDAC4 in apoptosis; specifically, HDAC4 can inhibit cell death induced by the overexpression of microRNA (miR)-200b-3p (36) (Fig. 2C).

HDAC4 plays a regulatory role in inflammation, myocardial fibrosis and apoptosis in the context of CVD (Fig. 2). These findings highlight the significance of HDAC4 in the onset and progression of CVD. In the following sections, the specific mechanisms by which HDAC4 functions in various types of CVD, particularly its pathophysiological roles in common conditions such as cardiac hypertrophy and CHD, will be further explored. A thorough understanding of these mechanisms may offer new targets for the treatment of these diseases.

4. Roles and mechanisms of HDAC4 in different CVDs

Cardiac hypertrophy. Pathological cardiac hypertrophy is a key contributor to the development of HF (37). Numerous studies have confirmed that HDAC4 plays a critical role in the initiation and progression of cardiac hypertrophy (10,38). Specifically, overexpression of HDAC4 has been shown to upregulate the mRNA expression of the cardiac hypertrophy-associated gene atrial natriuretic factor (ANF) in mouse hearts (38).

In 2006, Backs *et al* (39) first proposed that Calcium/Calmodulin-dependent protein kinase II (CaMKII) regulates HDAC4 in the progression of cardiac hypertrophy. The Ca²⁺ release inhibitor dantrolene was found to reduce cardiomyocyte hypertrophy by inhibiting angiotensin II (AngII)-induced HDAC4 nuclear export (40). This finding was consistent with

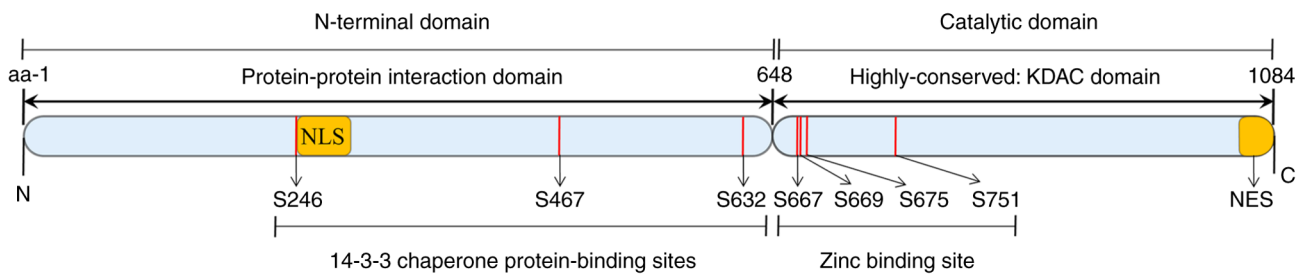


Figure 1. Schematic diagram of human histone deacetylase 4 functional domains. KDAC, Lysine deacetylase; NLS, Nuclear localization sequence; NES, Nuclear export sequence; aa, amino acid.

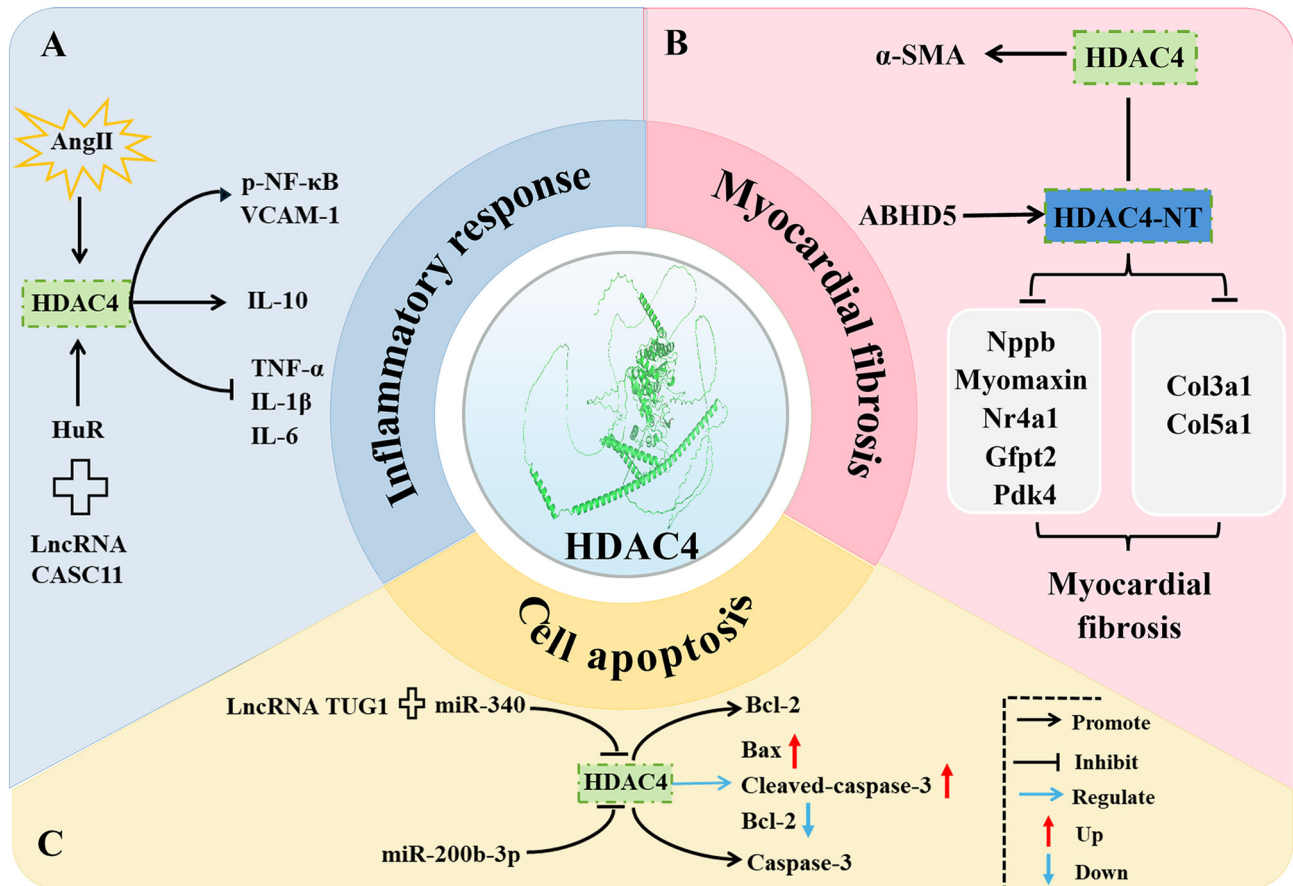


Figure 2. Function of HDAC4 in CVD. (A) Regulating the inflammatory response. (B) Regulation of myocardial fibrosis. (C) Regulation of apoptosis. AngII, angiotensinII; HDAC4, histone deacetylase 4; HuR, human antigen R; lncRNA CASC11, long non-coding RNA cancer susceptibility candidate 11; p-NF-κB, phosphorylated nuclear factor-kappa B; VCAM-1, vascular cell adhesion molecule-1; IL-10, interleukin-10; TNF-α, tumor necrosis factor-α; α-SMA, α-smooth muscle actin; ABHD5, abhydrolase domain containing 5; Nppb, natriuretic peptide B; Nr4a1, nuclear receptor subfamily 4 group A member 1; Gfpt2, glutamine-fructose-6-phosphate transaminase 2; Pdk4, pyruvate dehydrogenase kinase 4; Col3a1, collagen type III alpha 1 chain; lncRNA TUG1, long non-coding RNA taurine-upregulated gene 1; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein.

the observations reported by Zheng *et al* (41) in their study of AngII-treated atrial cardiomyocytes. A clinical study revealed that the expression of WW domain-containing E3 ubiquitin protein ligase 1 (WWP1) is elevated in the hearts of patients with HF, and similar results were observed in a mouse model of pathological cardiac hypertrophy induced by TAC. Furthermore, knockout of WWP1 inhibits TAC-induced upregulation of hypertrophic markers such as ANP, BNP and β-MHC. Mechanistically, the research group found that WWP1 can promote pathological cardiac hypertrophy in mice via the disheveled segment polarity protein

2 (DVL2)/CaMKII/HDAC4/myocyte enhancer factor 2C (MEF2C) axis (42). Interestingly, another study found that CaMKIIδA can regulate HDAC4 expression, leading to cardiomyocyte hypertrophy (43). TAC is a commonly used method to induce cardiac hypertrophy. One study demonstrated that casein kinase-2 interacting protein-1 (CKIP-1) inhibits TAC-induced cardiac hypertrophy by interacting with HDAC4 to repress MEF2C transcriptional activity. In addition, CKIP-1 promotes HDAC4 dephosphorylation via the recruitment of phosphatase-2A (PP2A), leading to the reduced expression of ANF, brain natriuretic peptide (BNP), and β-myosin heavy

chain (β -MHC) (9). An *in vivo* study reported that the 5-HT_{2A} receptor antagonist M100907 alleviates TAC-induced cardiac hypertrophy in mice by inhibiting the CaMKII/HDAC4 pathway (44). Moreover, HDAC4 has been associated with the anti-hypertrophic effects of lncRNAs. Liu *et al* (45) demonstrated that the overexpression of lncRNA-myosin heavy chain associated RNA transcript (MHRT) significantly suppresses the expression of hypertrophic markers atrial natriuretic peptide (ANP), BNP and β -MHC in *in vivo* and *in vitro* models. Intriguingly, MHRT overexpression in neonatal rat cardiomyocytes (NRCMs) leads to increased levels of specificity protein 1 (SP1) and HDAC4 proteins. Supplementation with mithramycin, an SP1 inhibitor, significantly reduces HDAC4 and SUMO1 expression. Subsequent experiments showed that MHRT overexpression reverses AngII-induced suppression of peroxisome proliferator-activated receptor γ coactivator 1 α (PGC1- α), peroxisome proliferator-activated receptor α (PPAR α) and sirtuin1 (SIRT1) SUMOylation. Silencing of SUMO1 abrogates the effect of MHRT, suggesting that lncRNA-MHRT inhibits cardiac hypertrophy by upregulating SP1/HDAC4 to promote SIRT1 SUMOylation and activate the PGC1- α /PPAR α axis (45). Given the broad involvement of HDAC4 in cardiac hypertrophy regulation, one study reported that knockdown of estrogen receptor β (ER β) abrogated the effect of estrogen [17- β -estradiol (E₂)] in reversing AngII-mediated suppression of HDAC4 and HDAC5 protein expression. Further investigation revealed that calcium signaling mediated AngII-induced HDAC4 phosphorylation, suggesting that the E₂/ER β axis may regulate HDAC4 expression through Ca²⁺ signaling, thereby influencing cardiac hypertrophy (46). Another study reported that the DPP-4 inhibitor teneligliptin reverses AngII-induced cardiomyocyte hypertrophy and the associated upregulation of ANF, NADPH oxidase 4 (Nox4), and phosphorylated HDAC4 in mice. However, co-administration of a glucagon-like peptide-1 (GLP-1) receptor antagonist attenuates the anti-hypertrophic effects of teneligliptin. *In vitro* experiments showed that GLP-1 receptor agonists reduce AngII-induced neonatal rat ventricular myocytes (NRVMs) hypertrophy by downregulating Nox4 expression and HDAC4 phosphorylation. Additionally, the inhibition of Nox4 reduces phosphorylated HDAC4 expression and alleviates AngII-induced hypertrophy, indicating that DPP-4 inhibitors may exert antihypertrophic effects via the GLP-1/Nox4/HDAC4 pathway (47). Mhatre *et al* (48) found that treatment of NRVMs with 25 ng/ml fibroblast growth factor 23 (FGF23) increases nuclear Ca²⁺ levels, as well as the expression of phosphorylated HDAC4 at S632 and cardiac hypertrophic markers ACTA-1 and RCAN-1. Further analysis confirmed that FGF23 mediates Ca²⁺ transfer via an inositol 1,4,5-triphosphate-dependent mechanism, promoting HDAC4 phosphorylation and leading to cardiomyocyte hypertrophy (48). Fan *et al* (49) observed that treatment of NRVMs with isoproterenol (ISO) leads to increased cell surface area, nuclear export of HDAC4, and upregulation of hypertrophic genes (for example, Nppa, Nppb and Myh7), as well as increased expression of phosphorylated CaMKII and HDAC4. The overexpression of galectin-1 (Gal-1) reverses these effects. Furthermore, the L-type calcium channel (LTCC) agonist Bay K8644 enhances p-CaMKII and p-HDAC4 expression, which is similarly inhibited by Gal-1 overexpression. These findings

suggested that targeting the Gal-1/LTCC/CaMKII/HDAC4 axis may provide a therapeutic strategy to ameliorate cardiac hypertrophy (49). A previous study revealed that HDAC4 mediates the inhibitory effects of Nox4 on phenylephrine (PE)-induced hypertrophy in NRVMs (50). In conclusion, studies have shown that HDAC4 expression is elevated in patients with cardiac hypertrophy. Overexpression of HDAC4 exacerbates hypertrophy by upregulating ANP, BNP and β -MHC, highlighting HDAC4 as a promising therapeutic target for the treatment of cardiac hypertrophy (Fig. 3).

CHD. CHD, a myocardial condition caused by atherosclerosis (AS) of the coronary arteries, remains the leading cause of mortality worldwide (51,52). Despite advancements in medical interventions, current treatment options for CHD are limited and often associated with complications. A recent study has proposed that HDAC4 expression levels may serve as a potential predictive biomarker for CHD (13). This hypothesis is supported by findings showing significantly reduced HDAC4 expression in the serum of patients diagnosed with CHD. Moreover, HDAC4 expression has been shown to correlate with several clinical indicators, including serum creatinine (Scr), low-density lipoprotein cholesterol (LDL-C), C-reactive protein (CRP), and blood glucose levels. In addition, correlation analysis revealed a negative association between HDAC4 and inflammatory markers such as TNF- α , IL-1 β and IL-6 (13). CMECs, which are among the most abundant cell types in the heart, play a crucial role in regulating coronary blood flow (53-55). A study has shown that lncRNA CASC11 can upregulate HDAC4 expression, thereby suppressing the secretion of IL-6 and IL-1 β and enhancing IL-10 expression in human CMECs under ox-LDL stimulation (24). Knockdown of HDAC4 reverses these effects, suggesting that HDAC4 plays a key regulatory role in the anti-inflammatory process mediated by CASC11. Furthermore, HDAC4 was found to mediate the effects of CASC11 in suppressing apoptosis and promoting angiogenesis (24). Bioinformatic analyses predicted that CASC11 interacts with the RNA-binding protein human antigen R (HuR), which binds to HDAC4, suggesting that CASC11 regulates HDAC4 expression through HuR-mediated stabilization. This mechanism likely contributes to the protective effects of CASC11 against ox-LDL-induced injury in CMECs (24). Collectively, these findings suggested that HDAC4 may serve as a promising biomarker for the prediction and potential therapeutic targeting of CHD (Fig. 4). However, further studies are warranted to elucidate the precise molecular mechanisms by which HDAC4 contributes to the pathogenesis of CHD.

Sick sinus syndrome (SSS). Preliminary studies have identified a correlation between the development of SSS and advancing age, with the condition primarily characterized by dysfunction of the sinoatrial node (SAN) (56,57). Currently, treatment options for SSS remain limited, highlighting the urgent need to explore novel therapeutic targets. In a recent study, Zhang *et al* (58) treated mouse atrial myocytes (HL-1 cells) with hydrogen peroxide (H₂O₂) to mimic oxidative stress conditions affecting SAN pace-making function. Their results demonstrated that H₂O₂ treatment leads to increased HDAC4 expression and its subsequent nuclear translocation, which in

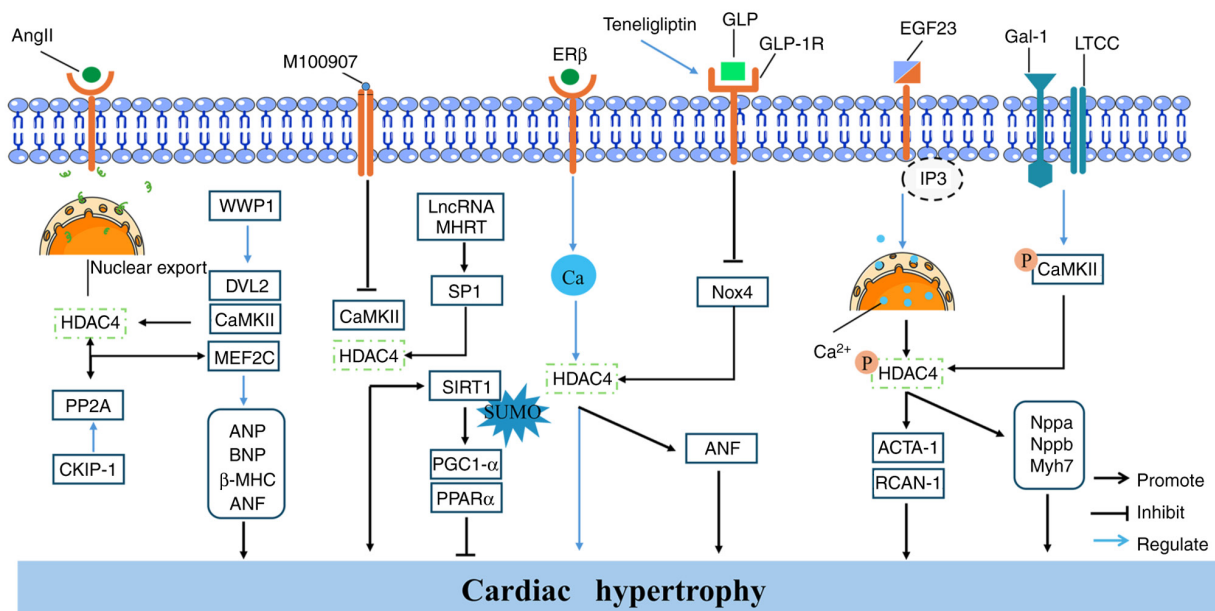


Figure 3. Role of HDAC4 in cardiac hypertrophy. Most studies have shown that AngII induces cardiac hypertrophy, and HDAC4 can promote the expression of ANP, BNP, β -MHC and ANF, thereby contributing to myocardial hypertrophy. It is well established that the CaMKII/HDAC4/MEF2C axis, as a classical signaling pathway, plays a crucial role in exacerbating cardiac hypertrophy. Additionally, HDAC4 mediates the effects of WWP1, CKIP-1, lncRNA MHRT and FGF23 in the progression of myocardial hypertrophy. HDAC4, histone deacetylase 4; AngII, angiotensinII; PP2A, phosphatase-2A; CKIP-1, casein kinase-2 interacting protein-1; WWP1, WW domain-containing E3 ubiquitin protein ligase 1; DVL2, disheveled segment polarity protein 2; CaMKII, calcium/calmodulin-dependent protein kinase II; MEF2C, myocyte enhancer factor 2C; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; β -MHC, β -myosin heavy chain; ANF, atrial natriuretic factor; MHRT, myosin heavy chain associated RNA transcript; SP1, specificity protein 1; SIRT1, sirtuin1; PGC1- α , proliferator-activated receptor γ coactivator 1 α ; PPAR α , peroxisome proliferator-activated receptor α ; ER β , estrogen receptor β ; GLP-1, glucagon-like peptide-1; Nox4, NADPH oxidase 4; FGF23, fibroblast growth factor 23; IP3, inositol 1,4,5-trisphosphate; Gal-1, galectin-1; LTCC, L-type calcium channel; Nppa, natriuretic peptide A; Myh7, myosin heavy chain 7.

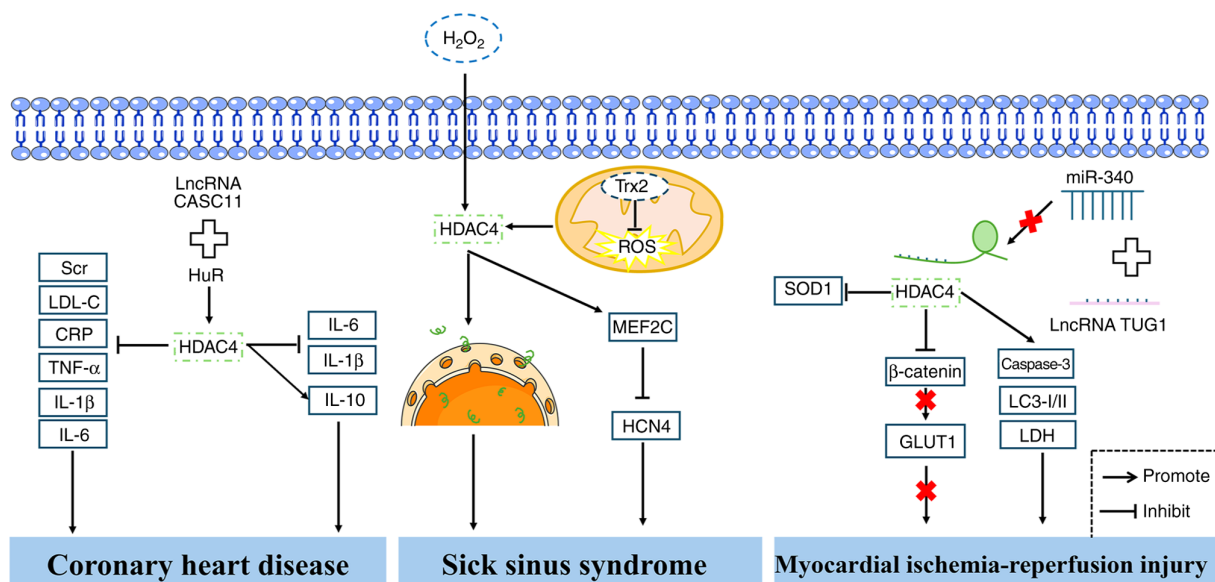


Figure 4. Role of HDAC4 in coronary heart disease, sick sinus syndrome and myocardial ischemia-reperfusion injury. HDAC4 can improve CHD by suppressing myocardial inflammatory responses. By contrast, HDAC4 may exacerbate disease progression in SSS and myocardial ischemia-reperfusion injury by aggravating oxidative stress, apoptosis, and lactate dehydrogenase leakage. HDAC4, histone deacetylase 4; Scr, serum creatinine; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; TNF- α , tumor necrosis factor- α ; IL-1 β , interleukin-1 β ; H₂O₂, hydrogen peroxide; HuR, human antigen R; lncRNA CASC11, long non-coding RNA cancer susceptibility candidate 11; Trx2, thioredoxin-2; ROS, reactive oxygen species; MEF2C, myocyte enhancer factor 2C; HCN4, hyperpolarization-activated cyclic nucleotide-gated potassium channel 4; SOD1, superoxide dismutase 1; GLUT1, glucose transporter type 1; lncRNA TUG1, long non-coding RNA taurine-upregulated gene 1; LC3-I/II, microtubule-associated protein 1A/1B-light chain 3; LDH, lactate dehydrogenase.

turn contribute to impaired SAN function (58). As the central organelle for maintaining energy metabolic homeostasis in sinoatrial node cells, mitochondria play a critical role in

regulating their electrophysiological excitability and rhythm stability (59,60). HDAC4 has been shown to play a crucial role in mediating the protective effects of thioredoxin-2

(Trx2) against sinus bradycardia by inhibiting mitochondrial reactive oxygen species (ROS) production within the SAN. Mechanistically, Trx2 deficiency can suppress the expression of hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 via the mitochondrial ROS-HDAC4-MEF2C signaling axis, resulting in SSS (61) (Fig. 4). These findings collectively suggested that HDAC4 may represent a key therapeutic target for the treatment of SSS.

Myocardial ischemia (MI)-reperfusion injury. MI-reperfusion injury refers to the damage inflicted on cardiomyocytes upon the restoration of blood flow following MI, and it has been shown to significantly affect patient prognosis (62). An *in vitro* and *in vivo* study demonstrated that the expression of the lncRNA TUG1 is elevated in the hearts of ischemia/reperfusion (I/R) mice and in cardiomyocytes subjected to hypoxia/reoxygenation (H/R). Bioinformatic analysis predicted a direct interaction between TUG1 and miR-340, which in turn targets HDAC4. Subsequent experiments confirmed that miR-340 overexpression reverses the upregulation of HDAC4 induced by TUG1. Moreover, TUG1 knockdown suppresses the H/R-induced expression of pro-apoptotic proteins Bax and cleaved caspase-3 while enhancing the expression of the anti-apoptotic protein Bcl-2 in cardiomyocytes. Conversely, HDAC4 overexpression promotes apoptosis under these conditions (35). Interestingly, silencing β -catenin reverses the upregulation of glucose transporter type 1 (GLUT1) induced by HDAC4 knockdown, suggesting that HDAC4 negatively regulates β -catenin, thereby promoting GLUT1 expression, as further supported by correlation analyses. *In vivo* experiments demonstrated that TUG1 knockdown improves cardiac function, reduces infarct size, and inhibits cardiomyocyte apoptosis in I/R mice. However, these protective effects were partially abrogated by the additional knockdown of miR-340 or GLUT1. These findings indicated that targeting the TUG1/miR-340/HDAC4/ β -catenin/GLUT1 regulatory axis may offer a novel therapeutic approach for MI-reperfusion injury (35). Mitochondrial quality control (including mitophagy, mitochondrial dynamics and mitochondrial biogenesis) has been recognized as a critical regulatory mechanism in the pathological progression of MI injury (63-66). A previous study found that HDAC4 overexpression increases H9c2 cell death, enhances mitochondrial membrane permeability transition pore activity, elevates lactate dehydrogenase release, and upregulates cleaved caspase-3 expression under H/R conditions (67). In line with these observations, Zhang *et al* (34) reported that HDAC4 overexpression in I/R mice exacerbates myocardial injury, as evidenced by increased infarct size, upregulation of autophagy-related proteins microtubule-associated protein 1A/1B-light chain 3 (LC3-I/II) and apoptosis marker caspase-3, and downregulation of the antioxidant protein superoxide dismutase 1 (SOD1), all of which contributed to worsened ventricular dysfunction. Notably, treatment with the HDAC inhibitor trichostatin A (TSA, 0.1 mg/kg) reversed these pathological changes, suggesting that HDAC4 overexpression aggravates I/R injury, whereas its inhibition may confer cardioprotective effects (34) (Fig. 4).

Hyperthyroid heart disease. According to statistics, ~2.5% of adults worldwide suffer from hyperthyroidism (68). Studies

have indicated that hyperthyroidism can lead to abnormal cardiac function (68,69). Nie *et al* (70) reported that intraperitoneal injection of thyroid hormone (L-thyroxine, T4) at a dose of 1 mg/kg/day in mice can induce a model of hyperthyroid heart disease (HHD) (70). However, inhibition of CaMKII activity was shown to improve arrhythmia, cardiac hypertrophy and fibrosis in HHD mice, accompanied with the downregulation of p-HDAC4 and MEF2a expression. In addition, an *in vitro* study demonstrated that treatment with LMK235, an HDAC4 inhibitor, effectively reverses the T4-induced increase in ANP expression (70). Another study revealed that treatment of NRCMs with T3 leads to elevated expression of hypertrophic genes, including ANP, BNP and α -actin, along with reduced expression of miR-1 and increased HDAC4 levels. Further experiments showed that overexpression of miR-1 can counteract the effects of T3. Notably, treatment of NRCMs with 85 nM HDAC4 inhibitor TSA significantly suppresses the expression of the hypertrophic gene α -MHC. These findings suggested that miR-1 may inhibit cardiac hypertrophy in HHD by negatively regulating HDAC4 expression (71). Given the increasing interest in the role of miRs in regulating HDAC4, additional research has demonstrated that miR-22 can alleviate cardiac hypertrophy by downregulating HDAC4 expression (72) (Fig. 5). In summary, the targeted inhibition of HDAC4 may represent a potential therapeutic strategy for ameliorating HHD.

MI. MI is a CVD with high lethality due to MI caused by insufficient coronary blood supply (73). However, current treatment options for MI remain limited, highlighting the urgent need to identify novel therapeutic targets (74). *In vivo* and *in vitro* studies have revealed that HDAC4 expression is elevated in MI (75,76). Overexpression of HDAC4 in MI mouse models has been shown to result in impaired cardiac function, enlarged cardiomyocytes, reduced vascular density, myocardial fibrosis, and increased expression of the hypertrophic marker ANP (28). Conversely, transplantation of cardiac stem cells (CSCs) transfected with siRNA targeting HDAC4 improves cardiac function in MI mice, suppresses myocardial hypertrophy and fibrosis, and promotes CSC-derived neovascularization and cardiomyocyte proliferation (27). A study has also shown that HDAC4 interferes with the inhibitory effect of G protein-coupled receptor kinase 4 on the autophagy-related genes LC3-II and Beclin-1 in the myocardium of MI mice (77). In another study, treatment with the HDAC4 inhibitor LMK235 was found to rescue the upregulation of SP1 and the fatty acid oxidation marker PPAR α induced by KN93, suggesting a novel therapeutic approach for MI (78). Additionally, Asensio-Lopez *et al* (75) reported that HDAC4 specifically interacts with yin-yang1 (Yy1) to suppress the expression of sST2, thereby inhibiting cardiomyocyte hypertrophy and the activation of phosphorylated inhibitor of nuclear factor κ B α (I κ B α)/NF- κ B signaling and ultimately ameliorating MI pathology (75). Current evidence indicates that HDAC4 is upregulated in patients with MI, suggesting its potential role as a key biomarker. Inhibition of HDAC4 expression has been shown to improve MI outcomes by suppressing myocardial hypertrophy, inflammation and fibrosis but promoting cardiomyocyte autophagy (Fig. 5). Hypoxia contributes to the development of MI (79). However,

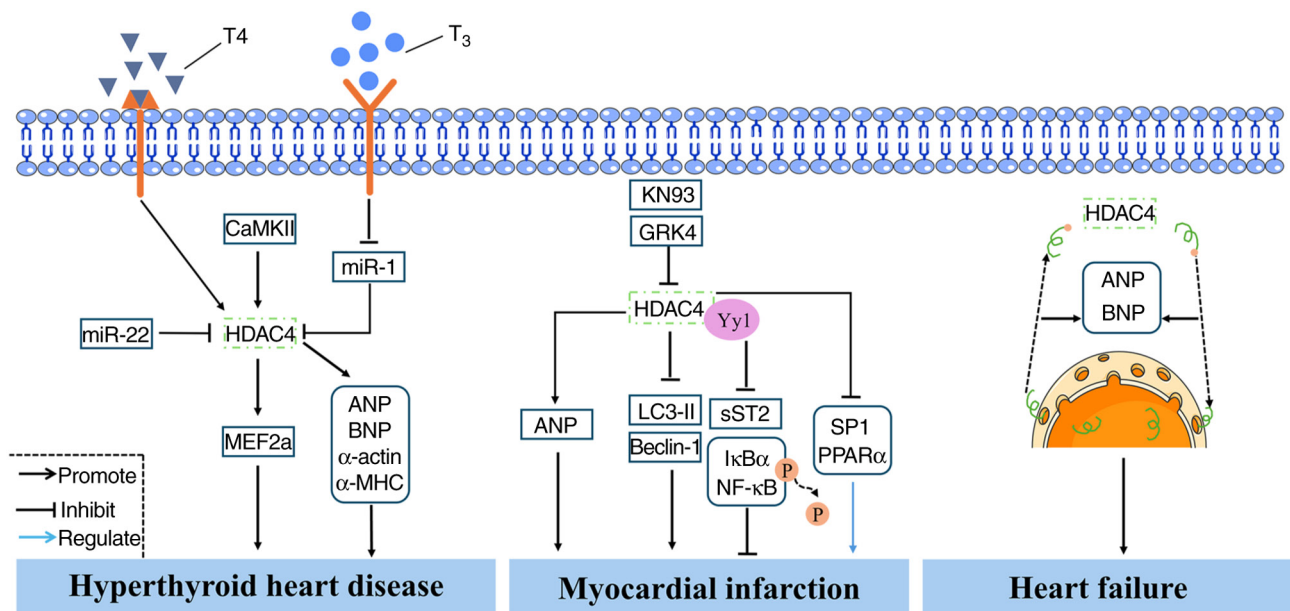


Figure 5. Role of HDAC4 in hyperthyroid heart disease, myocardial infarction and heart failure. HDAC4 exacerbates T3- or T4-induced HHD progression by inducing ANP, BNP, α -actin and α -MHC. Similarly, HDAC4 can also promote MI by upregulating ANP and suppressing myocardial autophagy. Additionally, studies have shown that HDAC4 nucleocytoplasmic shuttling plays a significant role in HF. HDAC4, histone deacetylase 4; T4, L-thyroxine; CaMKII, calcium/calmodulin-dependent protein kinase II; MEF2a, myocyte enhancer factor 2a; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; α -MHC, α -myosin heavy chain; GRK4, G protein-coupled receptor kinase 4; Yy1, Yin-yang1; ANP, atrial natriuretic peptide; LC3-II, microtubule-associated protein 1A/1B-light chain 3; I κ B α , inhibitor of nuclear factor κ B α ; NF- κ B, nuclear factor kappa B; SP1, specificity protein 1; PPAR α , peroxisome proliferator-activated receptor α .

a study has shown that hypoxia does not significantly alter HDAC4 expression in H9c2 cells. Instead, HDAC1 expression is increased under hypoxic conditions, indicating that relying solely on HDAC4 expression levels as a predictive biomarker for MI may have certain limitations (80).

HF. HF is widely recognized as the end stage of numerous CVDs and is associated with high morbidity and mortality rates (81). Therefore, the prevention and treatment of HF are of particular clinical importance. To date, numerous studies have demonstrated that HDAC4 plays a critical role in the pathogenesis of HF (29,82,83). Clinical evidence indicates that, compared with non-failing hearts, the nuclear expression of HDAC4 is reduced in the cardiomyocytes of patients with HF (5,84). Notably, HDAC4 nucleocytoplasmic shuttling has been found to be positively correlated with the expression of ANP and BNP (5). An animal study has reported that HDAC4 expression is elevated in the left ventricle of rat models of HF (83). Further research has shown that inhibition of HDAC4 expression improves cardiac function in HF mice and enhances myocardial glucose uptake (85) (Fig. 5). Collectively, these findings suggested that targeting HDAC4 may provide therapeutic benefits in the treatment of HF.

Hypertension. A recent study indicated that hypertension affects over one billion people worldwide (86). Although various approaches have been developed for the management of hypertension with advances in medical science, a definitive cure has yet to be achieved (87). A characteristic feature of hypertension is increased vascular stiffness (88). A study has shown that AngII treatment upregulates the expression of inflammatory cytokines (IL-6, VCAM-1 and inducible nitric

oxide synthase), autophagy markers (LC3-II, Beclin1 and Atg5), and HDAC4 in primary RAECs and *in vivo* in mice (22). Further investigation revealed that AngII-induced autophagy requires the involvement of endogenous forkhead box protein O3a (FoxO3a). Treatment of RAECs with autophagy inhibitors LY294002 or 3-MA suppresses the AngII-induced expression of inflammatory cytokines. Downregulation of HDAC4 inhibits AngII-induced vascular inflammation and reverses the AngII-mediated reduction in FoxO3a acetylation. These findings suggested that HDAC4 mediates the acetylation of FoxO3a and regulates AngII-induced excessive autophagy, thereby contributing to vascular inflammation (22). Similarly, Usui *et al* (89) also demonstrated that HDAC4 plays a key role in mediating vascular inflammation. In animal experiments, HDAC4 expression was found to be elevated in the mesenteric arteries of spontaneously hypertensive rats compared with Wistar Kyoto rats. *In vitro*, treatment of rat mesenteric artery SMCs with TNF- α upregulates the expression of inflammatory markers VCAM-1 and p-NF- κ B, as well as HDAC4. Notably, silencing HDAC4 with siRNA reverses the TNF- α -induced expression of these inflammatory markers in SMCs (23). Interestingly, HDAC4 protein levels were found to be decreased in the aorta of hypertensive rats but elevated in the mesenteric arteries, suggesting region-specific differences in HDAC4 expression. This highlights the limitation of evaluating disease progression based solely on HDAC4 levels in a single vascular bed (23). One study reported that MC1568, a class II HDAC inhibitor, suppresses the AngII-induced expression of p-HDAC4^{S632} and GATA-binding factor 6 (GATA6) in the kidneys and aortas of mice. An *in vitro* study further showed that HDAC4 promotes the expression of cell cycle regulatory genes E2F3 and cyclin E in vascular

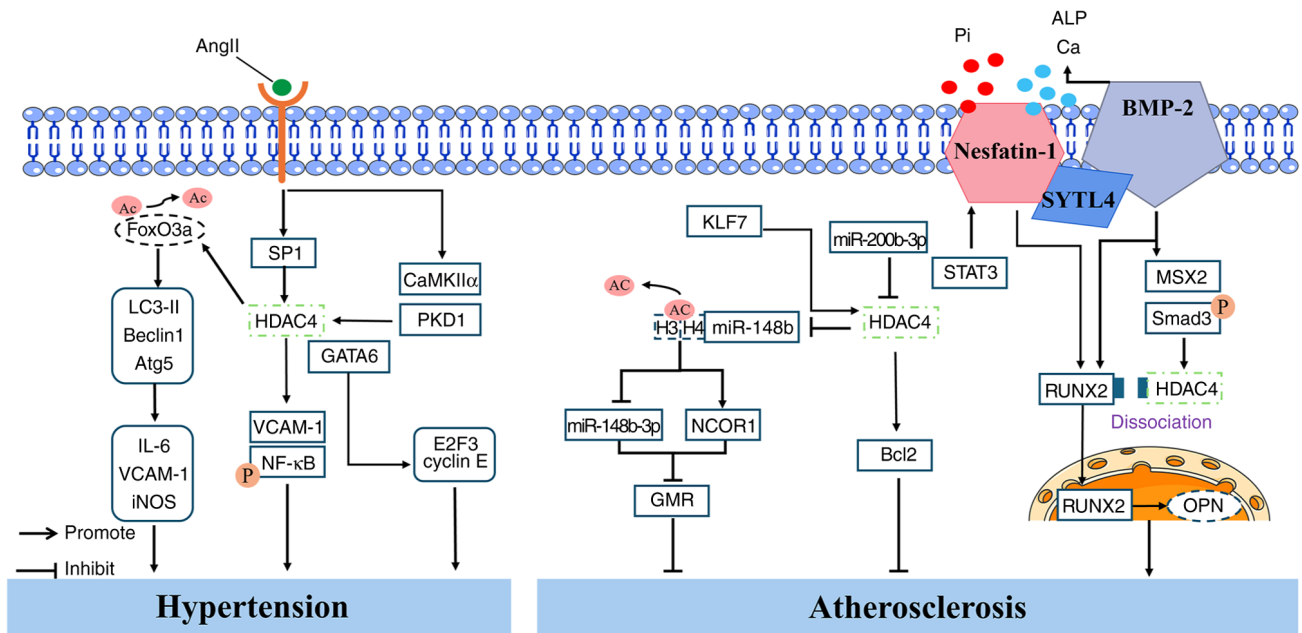


Figure 6. Role of HDAC4 in hypertension and atherosclerosis. HDAC4 promotes hypertension by enhancing the expression of inflammatory factors such as VCAM-1, IL-6 and p-NF- κ B. Additionally, HDAC4 can interact with GATA6 to upregulate the expression of cell cycle-related genes (E2F3 and cyclin E), thereby contributing to hypertension. By contrast, HDAC4 exerts inhibitory effects in AS. On one hand, HDAC4 suppresses AS by upregulating the expression of the anti-apoptotic protein Bcl2. On the other hand, HDAC4 also alleviates AS by inhibiting vascular calcification. AngII, Angiotensin II; HDAC4, histone deacetylase 4; FoxO3a, forkhead box protein O3a; LC3-II, microtubule-associated protein 1A/1B-light chain 3; IL-6, interleukin-6; VCAM-1, vascular cell adhesion molecule-1; iNOS, inducible nitric oxide synthase; SP1, specificity protein 1; NF- κ B, nuclear factor kappa B; CaMKII α , calcium/calmodulin-dependent protein kinase II α ; GATA6, GATA-binding factor 6; PKD1, pyruvate dehydrogenase kinase 1; ALP, alkaline phosphatase; BMP-2, bone morphogenetic protein 2; KLF7, Krüppel-like factor 7; NCOR1, nuclear receptor corepressor 1; GMR, glucose metabolic reprogramming; Bcl2, B-cell lymphoma 2.

smooth muscle cells (VSMCs). Notably, an endogenous association between HDAC4 and GATA6 was confirmed in VSMCs. An additional study demonstrated interactions among HDAC4, CaMKII α and PKD1 in 293T cells, which were disrupted by MC1568 treatment; thus, MC1568 attenuates VSMC hypertrophy and proliferation by down-regulating the CaMKII α /PKD1/HDAC4/GATA6 signaling pathway and alleviating hypertension (90). In summary, HDAC4 expression is elevated in multiple models of hypertension and contributes to disease progression by promoting vascular inflammation, VSMC hypertrophy and VSMC proliferation. These findings underscore the potential of targeting HDAC4 as a therapeutic strategy to delay the progression of hypertension (Fig. 6).

AS. AS is a chronic inflammatory disease characterized by the accumulation of atherosclerotic plaques within the arterial wall, resulting in reduced blood flow (91). Chen *et al* (92) demonstrated that HDAC4 mediates the role of Krüppel-like factor 7 (KLF7) in AS. Specifically, KLF7 binds to the HDAC4 promoter to activate HDAC4 transcription, which subsequently suppresses miR-148b-3p expression by reducing the acetylation of histones H3 and H4 at the miR-148b promoter. This suppression promotes the transcription of nuclear receptor corepressor 1 (NCOR1), thereby inhibiting GMR in macrophages and alleviating AS (92). AS is a major underlying cause of CAD. A clinical study revealed that miR-200b-3p is significantly upregulated in the epicardial adipose tissue of patients with CAD (36). Further *in vitro* experiments showed that the overexpression of miR-200b-3p downregulates HDAC4 expression

in HUVECs and reduces the expression of the anti-apoptotic protein Bcl-2. Notably, the overexpression of HDAC4 reverses miR-200b-3p-induced apoptosis, suggesting that HDAC4 plays a protective role against miR-200b-3p-mediated endothelial apoptosis in AS (36). Vascular calcification (VC) contributes to the progression of AS plaques. A recent study reported that HDAC4 is involved in VC (93). The researchers found that nesfatin-1 expression is elevated in patients with VS, in a vitamin D3-induced VC mouse model, and in sodium phosphate (Pi)-treated VSMCs. Moreover, nesfatin-1 expression was positively correlated with the severity of VC in patients (93). *In vivo* experiments showed that nesfatin-1 knockout reduces the expression of osteogenic markers RUNX2 and bone morphogenetic protein 2 (BMP-2) in the aortas of VC mice but enhances the expression of contractile proteins α -SMA and SM22 α . A further study revealed that BMP-2 promotes the expression of p-Smad3, HDAC4, RUNX2 and MSX2 in VSMCs; enhances the binding of RUNX2 to the OPN promoter; increases calcium content and alkaline phosphatase (ALP) activity; and inhibits the formation of the HDAC4/RUNX2 complex. These effects were reversed by nesfatin-1 knockout. Additionally, the proteasome inhibitor MG-132 was shown to prevent BMP-2 degradation induced by nesfatin-1 knockout. Bioinformatic analysis identified an interaction between SYTL4 and BMP-2, and knockdown of SYTL4 also inhibited BMP-2 ubiquitination and degradation triggered by nesfatin-1 knockout. This reduced calcium deposition and ALP activity under high-Pi conditions. Notably, the overexpression of STAT3 was found to upregulate the expression of nesfatin-1, BMP-2 and RUNX2, indicating that the

STAT3/nesfatin-1/BMP-2/HDAC4/RUNX2/OPN signaling axis contributes to VC progression (93) (Fig. 6). In summary, these findings highlight the potential of HDAC4 as a promising therapeutic target in the treatment of AS.

Other CVD. Diabetic cardiomyopathy (DC) refers to myocardial structural and functional impairments caused by diabetes, independent of other traditional confounding factors (94). DC has emerged as a significant threat to human health (95). Catalpol, one of the major active components of *Rehmannia glutinosa*, has been shown to exert cardioprotective effects. A study has found that knockdown of HDAC4 enhances the inhibitory effects of catalpol on the expression of pro-apoptotic proteins caspase-3 and Bax under high-glucose conditions, while promoting the expression of the anti-apoptotic protein Bcl-2. By contrast, upregulation of HDAC4 expression facilitates apoptosis (33). However, another study reported that cardiomyocyte-specific deletion of HDAC4 exacerbates cardiac dysfunction in diabetic mice (96). These contradictory findings suggested that the precise role of HDAC4 in DC remains controversial and warrants further investigation.

Dilated cardiomyopathy (DCM) is a cardiac disorder characterized by ventricular dilation and systolic dysfunction in the absence of abnormal loading conditions (97). A clinical study reported the elevated expression of p-HDAC4 in the hearts of patients with end-stage DCM (98). Similarly, increased p-HDAC4 levels have also been observed in the hearts of cTnT^{R141W} familial DCM mouse models (99). Notably, HDAC4 is involved in mediating the protective effects of Dickkopf 3, which suppresses the expression of hypertrophic marker ANF and myocardial fibrosis in DCM mice (99).

Aging is an important factor in the development of CVD (100). Studies have reported that senescence of vascular endothelial cells contributes to the development of AS, hypertension and other conditions (101,102). A recent study indicated that HDAC4 plays a critical role in mediating EC senescence. Silencing HDAC4 in proliferating ECs leads to the downregulation of MEF2A and p-eNOS^{Ser1177}, thereby promoting cellular senescence (103).

Acute coronary syndrome (ACS) is a clinical condition characterized by the sudden onset of acute ischemia or necrosis of the myocardium. ACS encompasses ST-segment elevation MI (STEMI), non-STEMI and unstable angina (104). A recent clinical study reported the decreased expression of HDAC4 in patients with ACS, with the lowest levels observed in those with STEMI. Furthermore, the study found that HDAC4 expression was negatively correlated with total cholesterol, LDL-C, CRP, cardiac troponin I, and a history of hyperlipidemia (105). These findings suggested that HDAC4 may serve as a predictive marker for adverse cardiovascular events.

The peptide ligand apelin and its receptor APJ play a critical role in regulating cardiovascular function. Homozygous APJ knockout mice exhibit partial embryonic lethality, and surviving embryos display cardiac and vascular defects. A further study has shown that the apelin-APJ pathway regulates cardiovascular function by modulating MEF2 activity through Gα13-mediated phosphorylation of HDAC4 and HDAC5. Targeted inhibition of HDAC4 phosphorylation and its cytoplasmic translocation may potentially address cardiovascular defects and embryonic lethality (106). A study involving

ventricular cardiomyocytes from mice, rabbits and humans revealed that HDAC4 is regulated not only by CaMKII but also by protein kinase A (PKA). Specifically, PKA was shown to regulate the nuclear accumulation of HDAC4 through phosphorylation at the S265/266 sites (107). This novel finding provides new insights for the development of therapeutic drugs or genetic interventions for CVD.

In summary, HDAC4 plays a crucial role in various CVDs. Studies have shown that HDAC4 is directly or indirectly involved in the onset and progression of CVD by modulating multiple biological processes, including cell proliferation, inflammatory responses and apoptosis. Moreover, an increasing number of studies suggested that the regulatory role of HDAC4 in CVD may be closely associated with mitochondrial function. As the central organelle responsible for maintaining energy homeostasis in cardiomyocytes, mitochondrial dysfunction is considered a major contributor to cell death and the progression of CVD (108-111). Recent evidence has shown that HDAC4 can modulate cardiomyocyte homeostasis by regulating the mitochondrial permeability transition pore. These findings suggest the existence of an as-yet undefined regulatory network between HDAC4 and mitochondrial function, and further elucidation of this interaction may deepen our understanding of CVD pathogenesis and provide a theoretical basis for targeted therapeutic strategies. However, despite numerous studies highlighting the potential role of HDAC4 in cardiovascular pathology, research on its specific molecular mechanisms and clinical applications remains in the exploratory stage. Therefore, further elucidation of the factors influencing HDAC4 expression is essential for the development of targeted therapeutic strategies.

5. Factors influencing the expression of HDAC4

Drugs and HDAC4. TSA is a commonly used hydroxamic acid-based HDAC inhibitor. A study has shown that 20 nmol/l TSA can promote the degradation of HDAC4 via the proteasome pathway, thereby inhibiting H/R-induced cardiomyocyte apoptosis and LDH release (112). Yang *et al* (22) reported that treatment of RAECs with 10 μM HDAC4 inhibitor tasquinimod can alleviate AngII-induced vascular inflammation. LMK235, another hydroxamic acid-based HDAC inhibitor, has been reported to exhibit high selectivity for HDAC4 (113). Chen *et al* (114) found that the intraperitoneal injection of 5 mg/kg LMK235 can abolish the protective effects of Huangqi Guizhi Wuwu decoction on microvascular and endothelial dysfunction in diabetic mice. However, another study has shown that LMK235 inhibits the expression of HDAC1, HDAC2, HDAC3, HDAC4, HDAC5 and HDAC7 induced by CaMKIIα overexpression. Thus, LMK235 may act as a broad-spectrum HDAC inhibitor, and its specificity for HDAC4 remains uncertain (115). MC-1568 is a commonly used inhibitor of HDAC4 and HDAC6. Research indicates that 1 μM MC-1568 can reduce the beating rate of cardiomyocytes in rabbit pulmonary veins, indicating its potential application in the regulation of arrhythmias (116).

An increasing body of research indicates that various drugs can modulate HDAC4 expression, thereby influencing the progression of CVD. A study has shown that

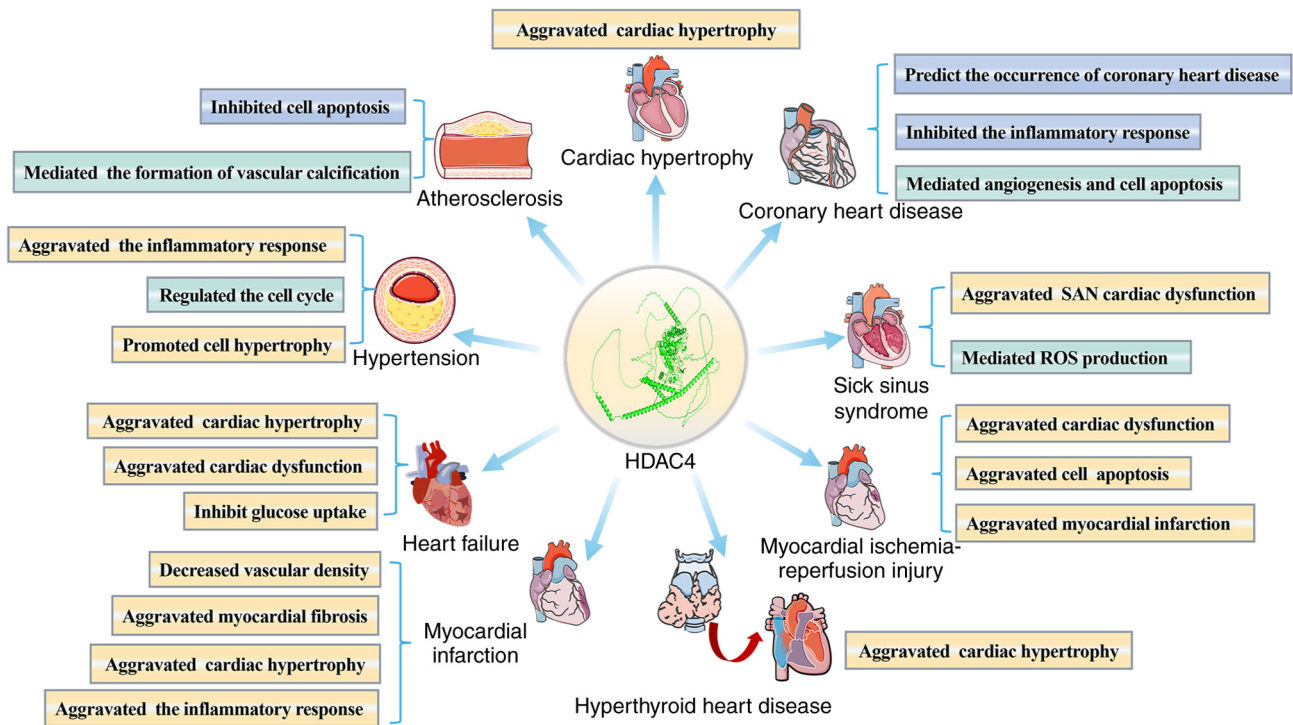


Figure 7. Potential mechanism of HDAC4 in cardiovascular diseases. HDAC4, histone deacetylase 4; SAN, sinoatrial node; ROS, reactive oxygen species.

1 μM lercanidipine or 0.1 μM tacrolimus can reverse the AngII-induced expression of cardiac hypertrophy markers ANP and BNP, possibly by inhibiting the CaMKII-HDAC4 signaling pathway (117). Similarly, Wang *et al* (118) found that 5 μM autocamide-2-related inhibitory peptide suppresses ISO-induced cardiac hypertrophy by inhibiting CaMKII and HDAC4 expression. Panax quinquefolium saponin was shown to downregulate CaMKII and HDAC4 expression in cardiomyocytes of rats subjected to hindlimb unloading, thereby improving cardiac function (119). Liu *et al* (120) reported that ISO induces hypertrophy in H9c2 cells and inhibits nuclear HDAC4 expression, whereas 5 $\mu\text{mol/l}$ isosteviol sodium (STVNa) reverses these effects. Moreover, the addition of the Trx1 inhibitor PX-12 attenuates the effects of STVNa (120). Leucine is considered an essential amino acid (121). The administration of 3% leucine to HFpEF female rats has been shown to inhibit the expression of HDAC4 in the heart, thereby improving diastolic dysfunction (8). Quercetin, which has been extensively studied for its cardiovascular benefits (122,123), was shown in an animal study to alleviate cardiac hypertrophy by downregulating HDAC4 and p-HDAC4^{Ser246} (123). Additionally, 20 nM insulin-like growth factor II (IGF-II) analogue Leu27IGF-II was found to increase the expression of CaMKII δ , p-HDAC4, p-HDAC5 and BNP in H9c2 cells. However, co-treatment with *Carthamus tinctorius* extract inhibits the expression of these proteins, suggesting that targeting HDAC4 holds therapeutic potential for cardiac hypertrophy (124). An earlier study identified that VSMCs contribute to increased vascular stiffness in hypertension (125). Choi *et al* (126) demonstrated that TMP269 inhibits class IIa HDACs (HDAC4, 5, 7, and 9) in VSMCs in a dose-dependent manner. Similarly, panobinostat (LBH589) was found to suppress class IIa HDAC activity. Notably,

10 μM TMP269 or LBH589 showed stronger inhibitory effects on HDAC4, HDAC5 and HDAC9 in VSMCs compared with TSA (126). Gallic acid, a dietary phenolic acid commonly found in edible plants (127,128), was also shown to inhibit class IIa HDAC activity in VSMCs. Interestingly, 100 μM sulforaphane inhibited the enzymatic activity of HDAC4, HDAC5 and HDAC7, whereas a low concentration (1 μM) increased their activity (126). A previous study reported that 50 μM nifedipine downregulates PE-induced p-HDAC4^{Ser632} expression and inhibits the nuclear export of HDAC4, thereby alleviating pathological cardiac hypertrophy (129). In addition, Guo *et al* (130) discovered that aconitine (AC), a key compound in *Aconitum* species, induces cardiotoxicity. Transcriptomic sequencing and molecular docking experiments demonstrated that AC promotes the interaction of HBB with ABHD5 and AMPK, thereby regulating the ABHD5/AMPK/HDAC4 axis and contributing to cardiotoxic effects (130).

Exercise and BDH1. Exercise, as a safe and effective multi-system intervention, has shown beneficial effects in the prevention and treatment of CVD (131). An animal study demonstrated that 2 weeks of exercise increased the expression of HDAC4-NT in the hearts of wild-type mice, whereas mice with cardiomyocyte-specific knockout of HDAC4 exhibited reduced exercise capacity (30). By contrast, suppression of HDAC4 expression was found to enhance exercise tolerance in mice with HF (85). Moreover, a recent study reported that high-intensity interval training improves cardiac function in HF by promoting skeletal muscle-derived meteorin-like, which activates the AMPK-HDAC4 signaling pathway (132). These findings suggested that exercise may regulate cardiac function via modulation of HDAC4, offering new insights into personalized interventions for CVD.

6. Conclusion and prospect

The present review examined the role and underlying mechanisms of HDAC4 in CVD, highlighting its regulatory potential in key pathophysiological processes such as inflammation, fibrosis, apoptosis and mitochondrial function. To date, an increasing body of evidence has demonstrated the involvement of HDAC4 in the progression of CVD, strongly suggesting that it may serve as a promising molecular target for early intervention or personalized therapy in the future (Fig. 7). In cardiac pathologies such as myocardial hypertrophy, CHD, SSS, MI-reperfusion injury, HHD, MI and HF, most studies have shown that HDAC4 inhibition can alleviate cardiac damage by negatively regulating cardiac function, suppressing myocardial inflammation and fibrosis, and reducing cardiomyocyte apoptosis. In hypertension, HDAC4 promotes vascular inflammation and hypertrophy of VSMCs. By contrast, HDAC4 appears to play a protective role in AS; for example, it can ameliorate AS by inhibiting miR-200b-3p-induced apoptosis. In DC, HDAC4 exhibits dual functions: On the one hand, its overexpression induces cardiomyocyte apoptosis. On the other hand, HDAC4 deletion exacerbates cardiac dysfunction in DC mice. These findings provide a theoretical foundation for the development of HDAC4-centered precision intervention strategies, which may facilitate a shift in CVD treatment from late-stage symptom management to early-stage molecular mechanism-based interventions.

However, there are still certain limitations in the reports on HDAC4 in CVD. First, the expression patterns and functional roles of HDAC4 in CVD induced by different pathological stimuli remain controversial. There is a lack of comprehensive analysis regarding its correlation with disease severity and clinical prognosis, which warrants further investigation. Notably, a previous study has revealed that HDAC4 inhibition can enhance exercise capacity in mice with HF (85). Second, current research on the safety, specificity and long-term efficacy of HDAC4-targeted interventions remains in its early stages, limiting the feasibility of clinical translation. Therefore, future studies should integrate multi-omics approaches such as transcriptomics, proteomics and metabolomics, combined with validation in large animal models and analyses of patient-derived samples, to comprehensively assess the mechanistic integrity and clinical translational potential of the HDAC4 signaling pathway. Lastly, the potential role of HDAC4 in diseases beyond the cardiovascular system warrants consideration. In pulmonary arterial hypertension (PAH), stromal-derived factor 1 has been shown to activate the CaMKII/HDAC4 signaling pathway, which stabilizes runt-related transcription factor 2, subsequently promoting osteopontin expression and contributing to pulmonary artery smooth muscle cell proliferation and vascular remodeling (133). Simultaneously, ongoing discussions surrounding the revised diagnostic threshold for mean pulmonary arterial pressure have underscored the urgent need for early molecular biomarkers in PAH (134). Thus, HDAC4 may serve as a promising regulatory target, offering new opportunities for mechanistic investigations and therapeutic interventions.

In summary, HDAC4 demonstrates potential as a biomarker for monitoring CVD. Despite existing controversies, ongoing research may confirm HDAC4 as a highly promising therapeutic target in cardiovascular medicine.

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Availability of data and materials

Not applicable.

Authors' contributions

XM was responsible for conceptualization, investigation, writing the original draft and illustration. RW was responsible for conceptualization, investigation, illustration, reviewing and editing the manuscript. AS was responsible for conceptualization, reviewing and editing the manuscript. XZ was responsible for illustration, reviewing and editing the manuscript. JZ was responsible for investigation, reviewing and editing the manuscript. SH was responsible for funding, supervision, reviewing and editing the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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