# Role and research progress of histone modification in cardiovascular diseases (Review)

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**Abstract.** As society evolves and lifestyles change, there has been a notable rise in the incidence of cardiovascular diseases due to a parallel rise in associated risk factors. In recent years, considerable research has been conducted on the impact of histone modifications in relation to these conditions. Processes such as acetylation, methylation and phosphorylation of histones, mediated by specific enzymes, are essential in the regulation of gene expression, which in turn influences cellular functions and the progression of diseases. Research shows that alterations in specific histone modifications are closely linked to the onset and advancement of cardiovascular conditions. For instance, significant variations in histone deacetylases and H3K27 methylation have been observed in cases of heart failure and myocardial ischemia-reperfusion injury. In the present review, it was aimed to summarize recent findings in this area, providing a foundation for further exploration of the mechanisms by which histone modifications contribute to cardiovascular diseases.

**Contents**



## 1. Introduction

Cardiovascular diseases encompass a range of conditions that impact the heart and blood vessels, including coronary artery disease, hypertension and cardiomyopathy. These diseases have emerged as significant contributors to global mortality, representing a serious risk to health and life. The development of cardiovascular disease can be complex and multifaceted. It involves a number of factors, including genetics, the environment, lifestyle and age. Research strongly suggests that epigenetic changes serve a significant role in the development and progression of cardiovascular disorders, acting as a regulatory mechanism that can alter gene function/expression/activity without changing the content of DNA sequences. Epigenetics is widely considered the primary regulatory mechanism by which cells respond to environmental changes, as it allows for alterations in gene expression without changing the underlying DNA sequence, making it a flexible way for cells to adapt to different conditions (1). Mechanisms associated with epigenetics including DNA methylation, histone modification and non-coding RNA activity notably influence the function and expression level of cardiovascular disease-related genes, thereby participating in the occurrence and development of these diseases. Related studies have confirmed that histone modification serves an important role in the occurrence and development of cardiovascular diseases. Given the significant role of histone modification in the regulation of the expression of cardiovascular disease-related genes, it is essential to investigate the mechanisms underlying histone modification and to elucidate its critical influence on the progression of cardiovascular diseases. An improved understanding of the regulatory mechanisms in the development of cardiovascular disease may help to identify new therapeutic targets and provide beneficial effects for patients. On this basis, the mechanism of histone modification in cardiovascular disease will be reviewed to provide new ideas for clinical research of cardiovascular disease.

## 2. Structure and function of histones

Histones are fundamental proteins found in both eukaryotic and prokaryotic organisms and serve as the primary protein constituents of chromatin (2). There are six known histones, namely, H1, H2A, H2B, H3, H4 and archaea histones. Histone octamers are composed of four types of histone proteins: H2A, H2B, H3 and H4, with each type contributing two molecules. A total of ~200 base pairs of DNA wrap around these histone

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octamers, forming a structural unit known as a nucleosome. Nucleosomes constitute the fundamental building blocks of chromatin, formed by DNA wrapped around a set of eight proteins called histones, known as histone octamer (3). Within a nucleosome core, histone proteins consist of a globular domain that forms the core structure, while their amino-terminal tails extend outwards and are subject to various modifications such as methylation, acetylation, ubiquitination, crotonylation and lactylation. The specific modification mechanism is demonstrated in Fig. 1.

Histone modifications can alter the compactness of chromatin by altering the affinity between histones and DNA double strands, essentially controlling whether chromatin is in a loosened (accessible) or condensed (less accessible) state. Aberrant histone modifications lead to imbalanced expression of cardiovascular disease-related genes, resulting in changes in cellular phenotype and cardiac function. The study of cardiovascular diseases has largely centered on acetylation, methylation and ubiquitination. Consequently, the present review comprehensively discussed the functional roles of these processes and their reversible and dynamic regulatory mechanisms. Histone methylation usually occurs on lysine or arginine residues, and its activity is regulated by histone methyltransferases and demethylases (4). Histone acetylation is mediated by histone acetyltransferases (HATs). This loosens the chromatin structure, making DNA more accessible to transcription factors and thus promoting transcriptional activation. The opposite progression implies that histone deacetylase (HDAC) removes the acetyl group, thereby condensing nucleosomes and leading to transcriptional repression (5). Ubiquitin is a key covalent modification mechanism, which covalently links ubiquitin peptide chains containing 76 amino acids to lysine residues of histones through the continuous action of the E1 activating enzyme, E2 binding enzyme and E3 ligase (6). Mono-ubiquitination is a type of protein modification where a single ubiquitin molecule is attached to a protein, it is most commonly observed on histones H2A and H2B, where there are two well-defined modification sites (7,8). In histone acetylation, chromatin is directly loosened by neutralizing the positive charge on histones, thereby reducing their affinity for DNA. In methylation such as (H3K4me3 or H3K27me3) and ubiquitination, the overall charge of histones is not changed, instead, chromatin architecture is regulated by recruiting effector proteins such as chromatin remodeling enzymes or transcriptional repressors (9). During the ubiquitination process such as H2BK120 ubiquitination, nucleosome remodeling during processes such as DNA repair or transcription elongation is facilitated primarily through recruiting deubiquitinating enzymes and chromatin remodeling complexes including SWI/SNF (10).

Crotonylation, a post-translational modification mediated by crotonyl-transferase, involves the enzymatic transfer of crotonyl groups from crotonyl-coenzyme A to lysine residues on target proteins (11). In somatic cells, genomic mapping studies have revealed that histone crotonylation marks are primarily localized within 200-300 base pairs flanking transcription start sites, exhibiting symmetrical distribution around the transcriptional initiation core region (12). These findings establish histone crotonylation as an epigenetic signature marking promoter-specific transcriptional activation and active transcription hubs. Histone lactylation, another modification, operates through the covalent conjugation of lactyl moieties to lysine residues, enabling context-dependent regulation of transcriptional programs associated with metabolic adaptation (13). Previous studies focusing on histone modifications in cardiovascular diseases have found that histone modifications may affect a wide range of cardiovascular diseases, including atherosclerosis (As), heart failure, myocardial infarction (MI), cardiomegaly and myocardial ischemia-reperfusion injury (MIRI) (14,15). The specific histone modifications in these cardiovascular diseases and their associated molecular mechanisms are illustrated in Fig. 2.

## 3. Histone modifications in cardiovascular disease

*Histone modifications and As*. As is a disease characterized by lipid metabolism disorders and endothelial dysfunction. It is linked to histone modifications that regulate inflammatory pathways, with Nox5, a newly identified NADPH oxidase, serving a key role by generating superoxide, leading to oxidative stress and promoting As development. During inflammation, the proteins belonging to the histone acetylation system (p300 and HAT1) become elevated, leading to increased acetylation of the Nox5 gene promoter region. This suggests that histone acetylation is involved in As development (16). Consequently, regulating Nox5 expression through epigenetic pathways may be a new approach to treating As, instead of directly removing reactive oxygen species (ROS). Silent Information Regulator 1 (SIRT1), a member of the HDAC family of HDACs, slows the progression of As by inhibiting macrophage *LOX-1* gene expression and decreasing the phagocytosis of oxidized low-density lipoprotein by macrophages, thereby leading to a reduction in subendothelial lipid deposition (17). Krüppel-like factor 2 (KLF2), a transcription factor, serves a crucial role in maintaining the anti-inflammatory and anti-atherosclerotic properties of endothelial cells. However, its activity is negatively regulated by HDAC5, which binds directly to KLF2 and prevents its proper functioning by downregulating KLF2-dependent endothelial nitric oxide synthase expression. It ultimately leads to impaired endothelial cell function and increased risk of As development (18). Sabinyl-anilino-hydroxamic acid (SAHA, also known as Vorinostat or MK0683) is a well-characterized HDAC inhibitor (19). As a pan-inhibitor targeting multiple HDAC isoforms, SAHA theoretically enhances histone acetylation levels through broad suppression of HDAC activity, including HDAC5, thereby theoretically promoting transcriptional activation of KLF2 to exert anti-atherosclerotic effects. However, the precise mechanisms underlying SAHA-mediated upregulation of KLF2 require further elucidation. A previous study has demonstrated that SAHA is a novel KLF2 activator that prevents endothelial inflammation *in vitro* and the development of As *in vivo* (20). Based on *in vitro* and *in vivo* experimental data, SAHA reduces monocyte adhesion primarily by inhibiting tumor necrosis factor α (TNFα)-stimulated upregulation of vascular cell adhesion molecule 1 (VCAM1). Given that VCAM1 is a target molecule of KLF2 (21), the aforementioned study further investigated whether the downregulation of VCAM1 by SAHA depended on the KLF2 pathway. Overexpression of KLF2 was found to

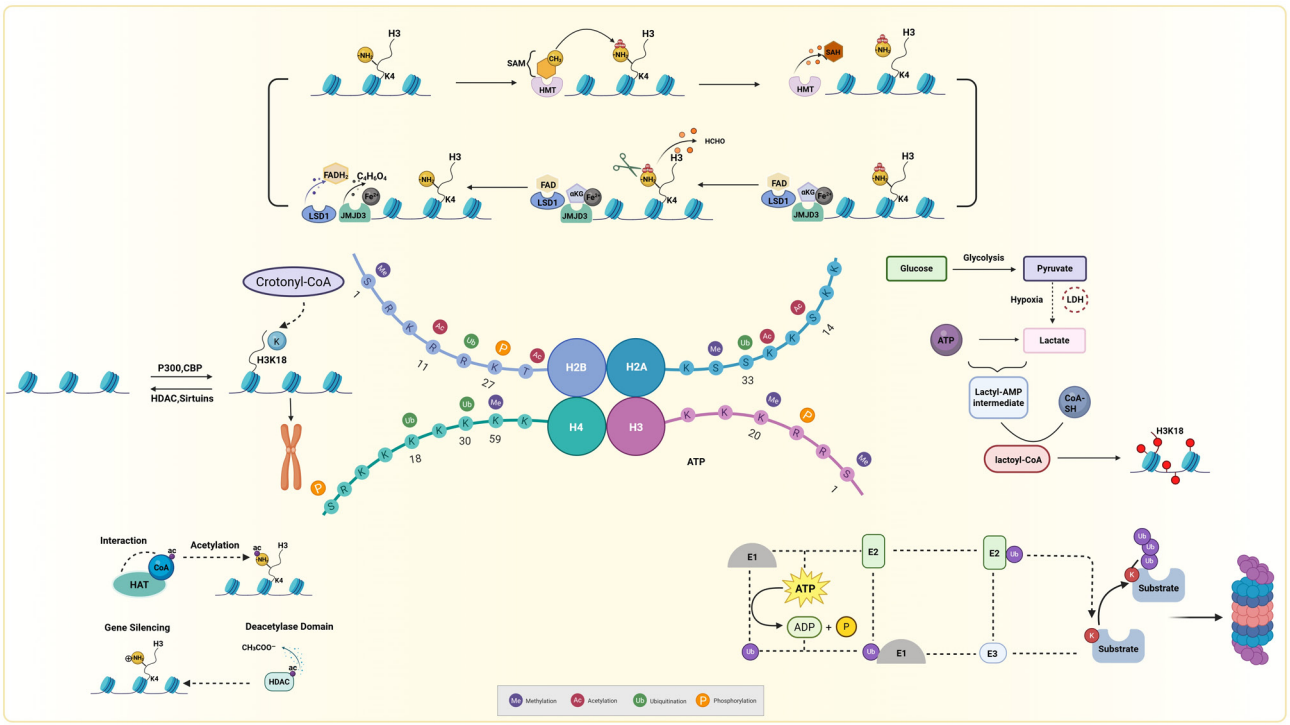


Figure 1. Mechanisms of histone modification. HAT, histone acetyltransferase; HDAC, histone deacetylase; CBP, creb binding protein; P300, e1a binding protein p300; SAM, s-adenosyl methionine; HMT, histone methyltransferase; FAD, flavin adenine dinucleotide; $FADH_2$, reduced flavin adenine dinucleotide; LSD1, lysine-specific demethylase 1; JMJD3, jumonji domain-containing protein 3; SAH, s-adenosyl-l-homocysteine; ATP, adenosine triphosphate; ADP, adenosine diphosphate. This figure was created with BioRender.com (https://www.biorender.com/).

inhibit the induction of the TNFα-mediated proinflammatory molecule VCAM1 in endothelial cells (22), suggesting that the anti-atherosclerotic effect of SAHA may be partially realized through a KLF2-dependent anti-inflammatory mechanism. In addition, the upregulation of KLF2 by SAHA may further exert its anti-atherosclerotic effect by promoting the expression of a series of genes with antithrombotic, anti-inflammatory and antiproliferative functions (23-25). Thus, SAHA may be suitable for targeting the early inflammatory process of As. Wang *et al* (26) demonstrated that HDAC3 upregulation inactivates NF-κB/p65 signaling by enhancing microRNA (miR)-19b-mediated peroxisome proliferator-activated receptor gamma (PPARγ) expression. HDAC3 is highlighted as a possible therapeutic target for treating As in this mechanism, as it inhibits inflammatory responses and slows the progression of As.

Endothelial-to-mesenchymal transition (EndMT) was also regarded as a novel therapeutic target for cardiovascular diseases (27). A previous study found that the HDAC3 inhibitor RGFP966 inhibited EndMT in the aortic root of $ApoE^{-/-}$ mice, reducing the development of As in the aortic root of $ApoE^{-/-}$ mice (28).

SUV39H1, a key enzymatic regulator of histone methylation, catalyzes trimethylation of histone H3 at lysine 9 (H3K9me3), thereby inducing transcriptional silencing of downstream genes through chromatin compaction (29). Experimental evidence indicates that pharmacological suppression of SUV39H1 elevates p21 expression by attenuating H3K9me3 enrichment at the p21 promoter (30), highlighting its therapeutic potential in modulating vascular smooth muscle cell (VSMC) hyperproliferation.

Further investigations reveal context-dependent regulatory roles of SUV39H1. While it demonstrates a robust repressive effect on cell cycle inhibitors, such as p21 and p27Kip1, its regulatory influence on proliferation-associated genes, such as Id3, is comparatively reduced. This differential activity may contribute to pathological VSMC activation and subsequent neointimal hyperplasia, suggesting a complex mechanistic landscape influenced by cell-specific signaling networks and experimental conditions.

Collectively, targeted inhibition of SUV39H1 demonstrates efficacy in attenuating post-injury neointima formation, positioning it as a novel therapeutic candidate for proliferative vasculopathy including in-stent restenosis (31).

In addition, SUV39H1 is implicated in enhancing the possibility of As development in obese individuals (32). Free radicals produced by p66Shc in mitochondria affect energy metabolism and the development of obesity (33). Obesity-induced epigenetic modifications, particularly those involving the SUV39H1 methyltransferase, JMJD2C/SRC-1 demethylase and SRC-1 acetyltransferase, have the potential to lower the levels of H3K9me2/me3 while simultaneously elevating H3K9 acetylation, which binds to the p66Shc promoter (34). This leads to an overproduction of mitochondrial ROS in the visceral fat artery of obese individuals. These epigenetic changes were found not only in humans but also in the endothelial cells and aorta of obese mice. In particular, obesity-induced downregulation of SUV39H1 expression is at the heart of H3K9 modification changes, which may contribute to ROS-induced endothelial dysfunction and the development of As (34). Experiments showed that the SUV39H1, JMJD2C and SRC-1 complexes clustered in the promoter region of p66Shc. Moreover, it was

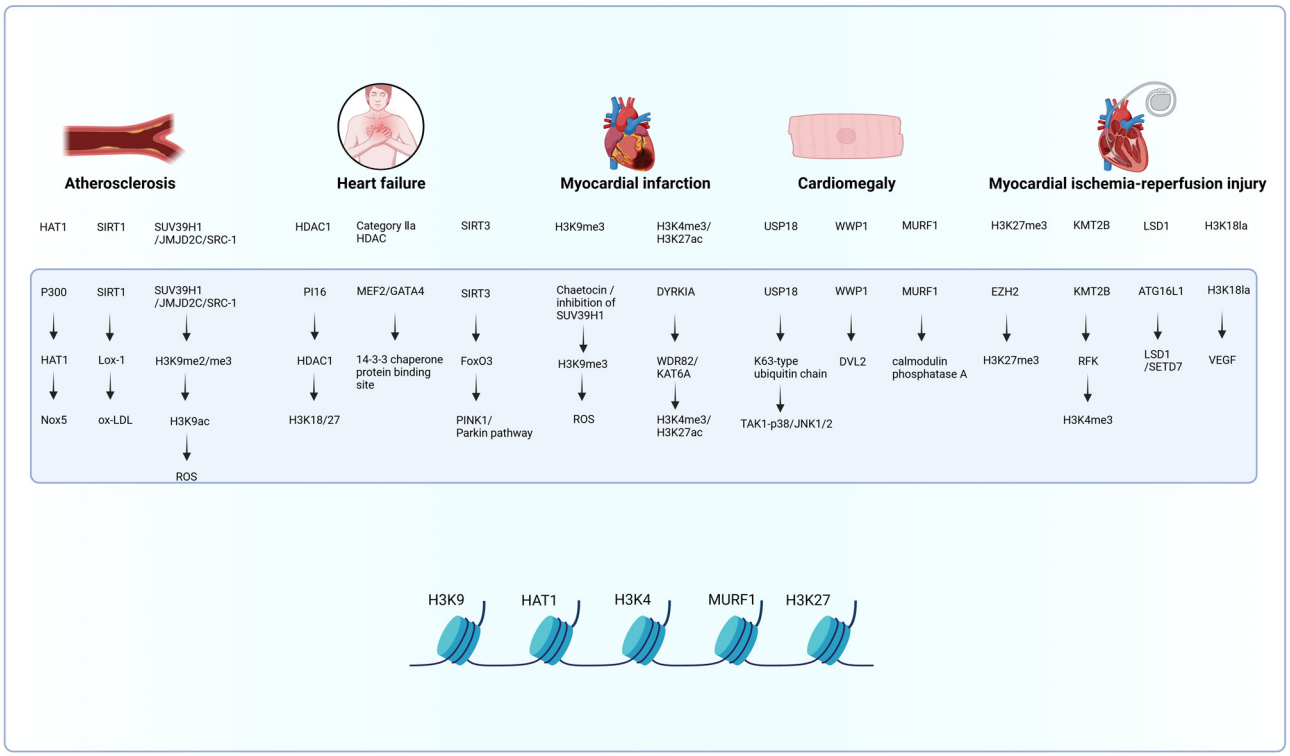


Figure 2. Specific mechanisms studied for the effects of histone modifications on cardiovascular disease . HAT, histone acetyltransferase; HDAC, histone deacetylase; ROS, reactive oxygen species; ox-LDL, oxidized low-density lipoprotein; H3K9me3, trimethylation of histone H3 at lysine 9; SIRT, silent information regulator; SUV39H1, suppressor of variegation 3-9 homolog 1; JMJD2C, jumonji domain-containing protein 2c; SRC-1, steroid receptor coactivator-1; H3K9ac, histone h3 lysine 9 acetylation; H3K4me, histone h3 lysine 4 trimethylation; H3K27ac, histone h3 lysine 27 acetylation; H3K27me3, histone h3 lysine 27 trimethylation; H3K18la, histone h3 lysine 18 lactylation; p300, e1a binding protein p300; KAT6A, lysine acetyltransferase 6a; EZH2, enhancer of zeste homolog 2; KMT2B, lysine methyltransferase 2b; LSD1, lysine specific demethylase 1; SETD7, set domain containing 7; TAK1, TGF-β activated kinase 1; PINK1, pten induced kinase 1; DYRK1A, dual-specificity tyrosine-phosphorylation regulated kinase 1a; FoxO3, forkhead box O3; MEF2, myocyte enhancer factor 2; GATA4, gata binding protein 4; USP18, ubiquitin specific peptidase 18; WWP1, ww domain containing e3 ubiquitin protein ligase 1; ATG16L1, autophagy related 16 like 1; Lox-1, lectin-like oxidized ldl receptor 1; DVL2, dishevelled segment polarity protein 2; MURF1, muscle ring finger protein 1; RFK, riboflavin kinase; WDR82, wd repeat domain 82; PI16, peptidase inhibitor 16; Nox5, NADPH oxidase 5. This figure was created with BioRender.com (https://www.biorender.com/).

observed that JMJD2C and SRC-1 did not affect the function of SUV39H1, suggesting that targeting SUV39H1 may help delay the progression of obesity-induced As. Aging is also an important risk factor for As. AMPK, known as AMP-activated protein kinase, serves a crucial role in combating aging by reducing mitochondrial oxidative stress. It functions as a cellular energy sensor, activating important proteins such as SIRT1 and PGC-1α. These proteins facilitate mitochondrial biogenesis and enhance mitochondrial function, thereby improving the cell's capacity for efficient energy production and decreasing the generation of harmful ROS. This process ultimately supports an extended lifespan. Activation of AMPK using drugs such as metformin or AICAR triggers an increase in DOT1L-mediated H3K79 trimethylation on SIRT1/SIRT3 promoters. This, in turn, results in higher levels of telomerase reverse transcriptase and the protein PGC-1α, which are important for cellular longevity and mitochondrial function. Silencing SIRT3 increases mitochondrial oxidative stress and prevents age-induced atheromatous plaque formation in ApoE knockdown mice (35). This finding indicates that the SIRT-mediated longevity of the vascular system can be promoted through DOT1L hypermethylation of H3K79. Furthermore, metformin may be a potential treatment for age-related As.

The study suggests that the development of As may be linked to specific risk factors that serve a role in influencing the methylation status of H3K9 and H3K79, as well as the oxidative stress response of mitochondria. In addition, targeted therapy against SUV39H1 and DOT1L may help delay the progression of As. It is important to note that metformin, as a commonly used anti-diabetic drug, may have a positive effect on diabetes-related As, especially during aging. In the pathological process of As, histone methylation may not only trigger the occurrence of As but also serve as a biomarker to assess the severity of the disease and participate in its development. For example, the levels of H3K4me2 in smooth muscle cells were elevated during advanced atherosclerotic plaques in the human carotid artery, compared with earlier stages. By contrast, H3K9me2 levels were observed to decline in smooth muscle cells and inflammatory cells, while H3K27me2 levels decreased specifically in inflammatory cells (36). In the advanced stages of As, the expression levels of H3K4 methyltransferase MLL2 and H3K9 methyltransferase G9a are elevated (36). Previous studies have also found that in human advanced atherosclerotic plaques, SMC and inflammatory cells lacking H3K9 methyltransferase exhibit reduced H3K9 and H3K27 methylation levels, while in SMC with elevated MLL2/4 levels, H3K4 methylation levels are increased. This

suggests that H3K4 methylation may be related to the severity of As (36,37). Nevertheless, the mechanism of atherosclerotic plaque formation, disease progression and the interaction between histone methylation and oxidative stress still need further study. These areas may represent promising avenues for future research endeavors.

Histone acetylation (involving regulators such as HDAC5 and SIRT1) modulates inflammation and endothelial dysfunction. Pan-HDAC inhibitors such as SAHA enhance KLF2 activity to suppress VCAM1, while HDAC3-selective agents specifically target endothelial-mesenchymal transition. Methylation modifiers, including SUV39H1 and DOT1L, exhibit dual roles: SUV39H1-mediated H3K9me3 drives vascular smooth muscle cell proliferation and obesity-linked oxidative stress, whereas DOT1L-driven H3K79me3 activates SIRT1/SIRT3 to mitigate age-related mitochondrial damage. Challenges persist in acetylation's isoform specificity and methylation's contextual risks. Obesity and aging exacerbate complexity. Combined strategies merging SAHA with SUV39H1 inhibition may synergize anti-inflammatory and antiproliferative pathways.

*Histone modification and heart failure*. Chronic heart failure is a widespread and potentially fatal condition notably impacting life expectancy and quality of life. It is characterized by alterations in histone acetylation, which in turn affects gene expression crucial to the progression of the disease.

Histone acetylation is a key regulator in cardiovascular disease, impacting gene expression and disease progression. This modification influences gene expression by multiple pathways, some of which are described below. First, the post-translational modification (PTM) of histone lysine alters the positive charge of the ε-amino group, which diminishes nucleosome compaction and impacts DNA-histone or histone-histone interactions. This leads to a decrease in euchromatin-nucleosome interactions but enhances the interaction between enhancers and their target promoters (38). Thus, the PTM of histones directly affects the structure of chromatin and nucleosomes. Additionally, the PTMs of lysine residues on histones can serve as epigenetic signals, either directly or indirectly, by influencing the recruitment of transcription factors that facilitate the acetylation of RNA polymerase II. The acetylation status of lysine residues is governed by the balance between the activities of HAT and HDAC (38,39). Studies have demonstrated that HDAC serves a significant regulatory role in heart failure and is closely connected to the onset and progression of the condition (40,41).

Group I HDACs may contribute to the development of heart failure by affecting ventricular remodeling. Studies have shown that histone H3 lysine trimethylation at position 27 (H3K27), micro inhibitor of ribonucleic acid-21-3p (MIR-21-3p), and HDAC 3-nuclear receptor co-inhibitory factor 2/thyrotropin receptor silencer of retinoic acid (Hdac3-NCoR/SMRT) complexes are associated with ventricular remodeling, suggesting that the development of ventricular remodeling may be related to histone acetylation at both the transcriptional and translational levels (42-44). The process of ventricular remodeling may be related to histone acetylation, and group I HDACs may also regulate myocardial fibrosis, potentially contributing to the development of chronic heart failure (45). Peptidase inhibitory protein 16 (PI16), transforming growth factor-β/mother DPP homolog (TGF-β/Smad) signaling, myofibroblast marker α-smooth muscle actin (α-SMA), and transforming growth factor-β1/mother DPP homolog 2/3 (TGF-β1/Smad2/3) were found to be closely related to myocardial fibrosis. The overexpression of PI16 results in a decrease in the nuclear level of HDAC1, which subsequently enhances histone acetylation in K18 and K27 lysine. This process also reduces myocardial collagen deposition, effectively inhibiting the proliferation of fibroblasts and fibrotic levels of related proteins, thereby preventing the occurrence of cardiac hypertrophy and cardiac fibrosis development (46). When HDAC3 is abnormally expressed, it actively suppresses the production of Klotho protein, a molecule that protects against fibrosis in the heart muscle, leading to an amplified TGF-β/Smad signaling pathway and ultimately causing the development of myocardial fibrosis (scar tissue buildup), as observed in mice (47). α-SMA, regulated by HDAC8, is highly expressed in myocardial fibrosis but less so in normal myocardium, suggesting an important role of HDAC8 in myocardial fibrosis (48).

Among HDACII, specifically, class IIa HDACs, serve a key role in suppressing the activity of cardiac-specific transcription factors such as MEF2 and GATA4 in the heart by a mechanism involving phosphorylation, which then allows the 14-3-3 chaperonin to bind and shuttle the HDACs out of the nucleus, effectively inhibiting the transcription of genes related to cardiac hypertrophy (49). This action prevents the progression to chronic heart failure, offering a protective effect on the heart (49). Conversely, HDAC class IIb affects cardiac function through non-epigenetic mechanisms, including the pathological remodeling of the ventricles and the modulation of myogenic fibers, both of which may contribute to the advancement of chronic heart failure.

Class III HDAC is a family of SIRT proteins, which are $NAD^+$-dependent HDACs involved in the pathophysiology of cardiovascular disease (50). The SIRT family serves a crucial role in managing oxidative stress, autophagy and apoptosis by lowering ROS levels. This is achieved through the activation of SIRT2, the deacetylation of hepatic kinase B1, and the promotion of the protein kinase (AMPK) pathway activation (51). According to research, failing hearts of humans, mice and pigs, the expression of SIRT1, a class III HDAC, is significantly reduced, indicating its downregulation in these conditions. SIRT1 deficiency leads to an increase in the acetylation of sarcoplasmic reticulum calcium ion ATPase (SERCA2a). By contrast, the pharmacological activation of SIRT1 facilitates the deacetylation of SERCA2a, which in turn improves cardiac dysfunction in models of heart failure (52). These findings position SIRT1 as a promising therapeutic target for heart failure. SIRT3's demethylation impacts the FoxO family by triggering autophagy-related proteins, including light chain 3 (LC3) of microtubule-associated protein 1, and the phosphorylation of BNIP3, a pro-death regulatory protein (53). An upregulation in SIRT3 expression stimulates the FoxO3/PINK1/Parkin pathway, enhancing mitochondrial autophagy and thus providing cardiac protection.

Pulmonary arterial hypertension (PAH) is an important cause of increased right ventricular loading and the eventual development of right heart failure (54). Valproic acid (VPA), an HDAC inhibitor targeting Class I enzymes, has demonstrated

therapeutic potential in preclinical models of PHA (55). CS1, an oral sustained-release formulation of sodium valproate, is currently under investigation for PAH management. Following oral administration, the compound undergoes intestinal conversion to its active metabolite, VPA, which mediates its pharmacological effects. A recent Phase II randomized clinical trial (NCT05224531) has been designed to evaluate the safety and exploratory efficacy of CS1, an HDAC inhibitor, in patients with PAH. This prospective, open-label, blinded-endpoint (PROBE-design) trial enrolled 30 patients with PAH, randomized into three dose cohorts: 480, 960 and 1,920 mg/day, with a target of 10 participants per cohort. CS1 was administered as controlled-release capsules (160 mg sodium valproate per capsule), with dose escalation guided by tolerability. The highest dose (1,920 mg/day) was selected based on effective dose ranges derived from animal models (equivalent human dose: 1,120-3,430 mg/day) and safety data from a Phase I trial in healthy volunteers (552 mg/day significantly reduced PAI-1 levels). The study incorporated continuous ambulatory monitoring of mean pulmonary arterial pressure *via* the CardioMEMS HF System, alongside right heart catheterization, cardiac magnetic resonance imaging (MRI), and biomarker profiling to enable high-resolution clinical phenotyping (56). Although results remain unpublished, this trial provides a scalable model for evaluating HDAC inhibitors in heart failure through its innovative integration of dynamic hemodynamic monitoring and multimodal assessments.

Beyond individual modifications, the functional antagonism within HDAC subfamilies underscores the complexity of epigenetic regulation in heart failure. For example, while Class I HDACs (such as HDAC1/3) promote fibrosis by suppressing antifibrotic genes, Class III HDACs (SIRT1/3) enhance mitochondrial autophagy and calcium handling. Such divergence necessitates subtype-specific interventions. Similarly, methylation dynamics reveal a paradoxical role: H3K27me3-mediated silencing of cardioprotective Klotho contrasts with H3K4me3-driven activation of pro-fibrotic TGF-β/Smad pathways. These findings advocate for combinatorial strategies [simultaneously inhibiting PRC2 (to relieve H3K27me3 repression) and enhancing H3K4me3 erasure] to restore transcriptional balance.

*Histone modifications and MI.* MI serves as a significant contributor to cardiovascular disease, exhibiting the highest rates of mortality and morbidity globally. It is typically induced by the occlusion or stenosis of coronary arteries, resulting from thrombosis linked to the degradation of atherosclerotic plaques. This condition is marked by an inflammatory response, detrimental ventricular remodeling, fibrosis and oxidative stress. Histone methylation is important in the pathogenesis of MI. Previous studies have shown that H3K9 methylation serves a role in cardiac hypertrophy and fibrosis by influencing free radical production (57,58). A previous study further confirmed that increased H3K9me2 levels can exacerbate negative ventricular remodeling after MI (59). Yang *et al* (60) found that the absence or functional inhibition of SUV39H1 can reduce the damage caused by myocardial ischemia, limit the scope of MI, improve the survival rate of mice with MI, reduce the death of cardiomyocytes, and improve left ventricular function in a SIRT1-dependent manner. Molecularly, H3K9me3 is methylated by SUV39H1 and recruited to the promoter region of SIRT1. By silencing or inhibiting SUV39H1, H3K9me3 levels on SIRT1 promoters can be reduced, thereby preventing excessive accumulation of intracellular ROS. Chaetocin is a small molecule naturally derived from the metabolites of the marine fungus genus *Chaetomium*, which primarily functions as an inhibitor of the enzymes SUV39H1 and G9a. Previous research indicates that Chaetocin exhibits multiple pharmacological functions in the context of cancer, bacterial and viral infections, as well as cardiovascular diseases. It achieves this by inhibiting processes such as apoptosis, oxidative stress, autophagy and angiogenesis (61), suggesting that Chaetocin may regulate histone methylation and oxidative stress. It has potential application prospects in the treatment of MI. Emerging evidence highlights the therapeutic potential of chaetocin in ischemic pathologies. Schweizer *et al* (62) demonstrated that the pharmacological application of chaetocin confers neuroprotection in cellular models of cerebral ischemia, concomitant with enhanced histone H3K9 acetylation at BDNF promoter regions, which mechanistically underlies the upregulation of neurotrophin transcription. This epigenetic modulation aligns with findings by Yang *et al* (60), wherein chaetocin-mediated cardioprotection against ischemic injury was attributed to SIRT1 transcriptional activation. Collectively, these studies suggest that chaetocin may functionally mimic SUV39H1 depletion in ischemia-compromised cells, implicating its role as a multimodal epigenetic modulator in hypoxic-ischemic disorders. DYRK1A, a protein kinase that has remained conserved throughout evolution, can regulate the proliferation of a wide range of cell types, including neoplastic mouse tumor cells, neural precursor cells, pancreatic islet β-cells and cardiomyocytes (63). Research indicates that the overexpression of DYRK1A can disrupt the normal cell cycle of cardiac myocytes, potentially leading to dilated cardiomyopathy. This condition is linked to congestive heart failure and may result in premature mortality in neonatal mice. These results suggest that DYRK1A may be a potent regulator of cell proliferation, even when the cell type is resistant to the stimulation of cell division or prone to excessive proliferation (64).

Recent studies have found that DYRK1A may be a potential target for promoting the cyclical circulation of cardiomyocytes and the self-repair of the heart, especially in the case of MI (65,66). It was revealed that DYRK1A, a protein kinase, regulates cardiomyocyte cell cycle activation by inhibiting the deposition of histone modifications (H3K4me3 and H3K27ac) on the promoters of cell cycle genes; it does this by phosphorylating two interacting proteins, WDR82 and KAT6A, which are key players in histone acetylation and methylation, thereby limiting their transcriptional activity and suppressing cell cycle gene expression. This finding is significant in the field of translational medicine because harmaline, a commonly used DYRK1A inhibitor, has demonstrated the ability to pharmacologically inhibit DYRK1A. This inhibition subsequently facilitates cardiac repair following a MI. In addition, complementary experiments were conducted using inhibitors that phosphorylated WDR82 or phosphorylated KAT6A to verify the role of phosphorylation of WDR82 and KAT6A in DYRK1A-mediated cardiomyocyte cycle and cardiac repair. The experimental results confirmed that

WDR82 and KAT6A are key factors in the epigenetic marks H3K4me3 and H3K27ac, which are essential for the transcriptome that promotes proliferation and activation of the cardiomyocyte cycle (65).

The functional significance of histone lactylation during MI recovery remains to be fully characterized. Emerging evidence from murine MI models indicates that circulating monocytes exhibit rapid induction of tissue-reparative transcriptional programs, accompanied by elevated histone lactylation levels during the acute injury phase, a modification that directly coordinates the expression of reparative mediators including LRG1, VEGF-A and IL-10. These lactylation-driven molecular cascades establish a cardioprotective microenvironment by exhibiting both anti-inflammatory and angiogenic properties. Notably, this epigenetic modification attenuated pathological inflammatory responses while enhancing cardiac functional recovery in post-MI hearts. Mechanistically, monocyte metabolic rewiring characterized by glycolytic flux dysregulation and MCT1-dependent lactate shuttling was identified as a critical driver of lactylation dynamics. Furthermore, IL-1β signaling was found to orchestrate lactylation patterns through GCN5 recruitment, partially mediating the activation of tissue-restorative genetic networks. Collectively, these insights position histone lactylation as both a biomarker and a tunable epigenetic mechanism governing post-ischemic myocardial repair, thereby offering translational opportunities for targeted cardiac regeneration strategies (67).

Trans-differentiation of cardiac fibroblasts into functional cardiomyocytes has previously been recognized as an innovative therapeutic strategy to repair and rejuvenate damaged myocardial tissue following injury. Previous studies have revealed a functional interplay between H3K27me3 dynamics and a miR combination (comprising miR-1, miR-133, miR-208 and miR-499) in driving direct reprogramming of cardiac fibroblasts into cardiomyocytes, offering a novel therapeutic avenue for MI (68). The miR combo remodels chromatin states through dual epigenetic modulation: It downregulates the H3K27 methyltransferase Ezh2 (a PRC2 complex component), reducing the deposition of the repressive H3K27me3 mark at cardiac gene promoters, while simultaneously upregulating the expression of demethylases Kdm6A/B to further erase H3K27me3 and activate cardiomyocyte-specific genes (such as those regulated by enhancer binding and transcription factor interactions) (69,70). Experiments demonstrated that knockdown of Kdm6A/B or pharmacological inhibition of Ezh2 activity (for instance, using 3-Deazaneplanocin A) could either reverse or mimic the reprogramming effects of miR combo, underscoring the central role of H3K27me3 homeostasis (70,71). This 'epigenetic-miR synergy' bypasses transcription factor-dependent genetic manipulation, significantly enhancing reprogramming efficiency and safety, and highlights a promising strategy for in situ cardiac repair and functional recovery post-MI.

During cardiac repair after MI, there are critical regulatory interactions between miRs and histone demethylases. For instance, Kdm3a, an epigenetic modifier that specifically removes H3K9 monomethylation/dimethylation (H3K9me1/2), is directly suppressed by miR-22-3p. Intriguingly, the long non-coding RNA H19 competitively binds miR-22-3p, thereby indirectly upregulating Kdm3a expression. Experimental evidence from animal models demonstrates that overexpression of H19 via adenoviral vectors prior to MI significantly reduces infarct size, attenuates fibrosis and inflammatory responses, and improves cardiac contractile function (72). Further investigations confirm that either knockdown of miR-22-3p using gene editing techniques or direct overexpression of Kdm3a enhances cardiomyocyte survival and ameliorates post-injury cardiac phenotypes (72). This regulatory network underscores the synergistic mechanisms by which non-coding RNAs and histone-modifying enzymes coordinate multidimensional epigenetic regulation, offering novel therapeutic insights for targeted MI intervention.

Histone modifications exhibit distinct roles in cardiovascular pathologies: H3K9me2/3 exacerbates ventricular remodeling through SUV39H1-driven ROS accumulation, whereas H3K27me3 dynamics, regulated by Ezh2/Kdm6A/B alongside miR combos, enable fibroblast-to-cardiomyocyte reprogramming. Lactylation promotes reparative angiogenesis by upregulating VEGF-A expression. The DYRK1A-WDR82/KAT6A axis drives cardiomyocyte regeneration by dynamically balancing H3K4me3 and H3K27ac levels. Pharmacologically, Chaetocin, a selective SUV39H1 inhibitor, and harmaline, targeting DYRK1A, demonstrate therapeutic potential, but studies on specificity and off-target risk remain scarce. These mechanisms underscore context-dependent interplay among oxidative stress, cell cycle control and inflammation resolution, positioning epigenetic modifiers as precision targets for myocardial repair.

*Histone modifications and cardiac hypertrophy.* Cardiac hypertrophy, often stemming from hypertension or valve diseases, is associated with specific histone modifications that impact cardiomyocyte growth. This condition ultimately leads to decreased cardiac output, increased heart failure risk, and the potential for heart failure to develop (73).

Ubiquitination, regulated by ligases and DUBs, is a critical modifier in the pathogenesis of cardiac hypertrophy (74). This process is tightly controlled by specific enzymes called E3 ubiquitin ligases and DUBs within the ubiquitin-proteasome pathway which are implicated in cardiovascular diseases (6). For example, ubiquitin-specific protease 18 (USP18) exerts a mitigating effect on cardiac hypertrophy by exclusively removing the K63-type ubiquitin chain on TAK1, which leads to inhibition of the TAK1-p38/JNK1/2 signaling pathway (75,76). In addition, calmodulin phosphatase is a protein associated with promoting cardiac hypertrophy, while atrogin-1 acts as a countermeasure by forming a complex called 'SCFatrogin-1' which, through its E3 ubiquitin ligase activity (by interacting with Skp1, Cul1 and Roc1), can target and degrade proteins such as calmodulin phosphatase, thereby inhibiting cardiac hypertrophy. When the expression level of atrogin-1 is reduced, it enhances agonist-triggered calmodulin phosphatase activity, which in turn leads to cardiomyocyte hypertrophy. It has been shown that the SCFatrogin-1 complex serves a crucial role in the regulation and inhibition of calmodulin phosphatase activity through the ubiquitination-dependent protein degradation pathway. Thus, atrogin-1 acts as a negative regulator of calmodulin phosphatase and ultimately inhibits the cardiac response to pathological stimuli, thereby attenuating symptoms of cardiac hypertrophy.

The WW structural domain E3 ubiquitin ligase 1 (WWP1) serves a key role in a variety of age-related diseases, including cardiovascular disease and cancer. According to research, the expression level of WWP1 is notably elevated in cardiac tissue samples from patients with heart failure, as well as in animal models where cardiac hypertrophy is induced by transverse aortic constriction (TAC), indicating a potential role of WWP1 in the development of pathological cardiac remodeling associated with heart failure. Notably, TAC-induced cardiac hypertrophy could be inhibited by interfering with the interaction of WWP1 with DVL2 protein. Thus, WWP1 may be a potential therapeutic target for the treatment of cardiac hypertrophy and heart failure (77). In addition, previous studies have shown that muscle-specific ring finger protein 1 (MuRF1), an E3 ubiquitin ligase, can attenuate pathological cardiac hypertrophy by promoting the degradation of calmodulin phosphatase A (6,78). These observations underscore the significant role of ubiquitination in the progression of cardiac hypertrophy and highlight the potential for developing anti-hypertrophic medications that target E3 ligases and deubiquitinating enzymes.

Sumoylation is a PTM where small ubiquitin-like modifier (SUMO) proteins are attached to lysine residues on target proteins, including histones, with the help of a cascade involving E1 activating, E2 conjugating and E3 ligase enzymes, effectively altering the function of the modified protein. This process is closely related to ubiquitination and has a decisive impact on the regulation of cardiac gene expression and cardiac development, including the differentiation process of cardiomyocytes. Previous studies have revealed the key role of SUMOisation in the maintenance of cardiac function, in particular its protective role in the heart's response to stress. UBC9 upregulation of the SUMO E2 enzyme enhances protein quality control in the heart and promotes higher levels of autophagy, suggesting that increasing UBC9-mediated SUMO may be a novel strategy to treat heart disease, improve heart function, and increase survival (79). In addition, SUMO-1-mediated SUMOylation of heat shock factor 2 (HSF2) has been shown to attenuate cardiac hypertrophy. In the presence of Ang II, increased expression of MEL-18 leads to de-SUMOisation of HSF2, which in turn increases the expression of IGF-IIR, thereby triggering cardiac hypertrophy (80). The COP9 signaling complex (CSN) modulates the function of cullin-RING ligases, with CSN8 being a crucial subunit of the CSN complex. This complex is integral to numerous biological processes, including the process of demethylation. Deletion of CSN8 not only disrupts the assembly of the CSN complex but also leads to an increase in the level of ubiquitylation of the cullin proteins, which in turn induces cardiac hypertrophy. In addition, CSN8 deficiency affects the function of the ubiquitin-proteasome system, leading to myocardial necrosis. Elevated activity of ZAK, a kinase with mixed specificity, may facilitate the development of cardiac hypertrophy. Estrogen receptor β has the capacity to interact with ZAK, inhibiting its accumulation within the nucleus by blocking SUMO-1 modification. This interaction results in a reduction of ZAK protein levels, thereby producing an antihypertrophic effect (81).

Previous findings indicate that the re-expression of the Scn5a gene in denervated skeletal muscle shares similar molecular mechanisms with those that drive Scn5a transcription in cardiac tissue. Experiments using ChIP-qPCR have demonstrated that the re-expression of Scn5a correlates with increased levels of H3K4me3 and H3K27ac histone marks, as well as the binding of the transcription factor Gata4 to the gene's promoter region. Notably, ChIP-seq analysis of H3K27ac has revealed that denervation activates a super enhancer previously identified as regulating Scn5a expression in cardiac tissue. The aforementioned data suggest that Gata4 serves a significant role in the transcriptional activation of the Scn5a gene in denervated muscle, as evidenced by a substantial increase in Gata4 expression observed through RNA-seq analysis (82). Gata4, a zinc-finger transcription factor belonging to the Gata family, is extensively expressed in both developing and mature cardiac tissue. It serves as a key regulator of transcriptional networks and is essential for cardiac differentiation and morphogenesis (83). Studies have shown that mice lacking Gata4 exhibit severe cardiac defects leading to embryonic lethality (84) while genetic mutations affecting GATA4 activity are linked to various cardiac abnormalities, such as right ventricular hypoplasia and cardiomyopathy (85). Moreover, $Gata4^{+/-}$ mice have been reported to exhibit shortened PR intervals, highlighting the critical role of Gata4 in the development of the atrioventricular cardiac conduction system (86). Mechanistically, Gata4 interacts synergistically with other transcription factors, including Nkx2-5, TBX5, and MEF2, to regulate gene expression. ChIP-seq studies have identified the co-localization of these factors with the HAT KAT3B at cardiac enhancers, revealing that Gata4 promotes gene activation through the deposition of H3K27ac (87-89).

Hypertrophic cardiomyopathy (HCM) is a genetically diverse condition primarily linked to mutations in sarcomere-related genes, leading to pathological thickening of the left ventricular wall, tissue scarring, excessive contractile activity and impaired diastolic relaxation (90,91). Previous studies have identified suppressed expression of short-chain enoyl-CoA hydratase 1 (ECHS1) and elevated histone crotonylation modifications at H3K18 and H3K12 sites in cardiac tissues of patients with HCM. Mechanistic investigations demonstrated that ECHS1 modulates crotonyl-CoA metabolic levels, orchestrates histone crotonylation dynamics, and regulates the NFATc3 signaling pathway, thereby contributing to cardiomyocyte maturation and homeostatic stability. These findings suggest that targeting epigenetic regulation of histone crotonylation may represent a promising therapeutic approach for pediatric patients harboring ECHS1 mutations associated with HCM (92,93).

Ubiquitination is not the only epigenetic driver of cardiac hypertrophy. Comparative studies highlight SUMOylation as a counterregulatory mechanism: SUMO1 conjugation to HSF2 attenuates hypertrophy by blocking IGF-IIR signaling, whereas ubiquitination, exemplified by the WWP1-DVL2 axis, accelerates pathological remodeling. This antagonistic interplay underscores the imperative for selective modulation of distinct PTM pathways. Additionally, non-canonical modifications such as H3K12/H3K18 crotonylation, which are regulated by ECHS1 in HCM, reveal metabolic-epigenetic crosstalk distinct from acetylation. Unlike H3K27ac, which broadly enhances transcription, crotonylation fine-tunes NFATc3 activation, urging a re-evaluation of metabolic interventions in hypertrophy.

*Histone modifications and MIRI*. Ischemic heart disease (IHD) is considered the most prevalent form of cardiovascular disease, and it is significantly linked to the highest rates of morbidity and mortality globally (94). While reperfusion therapy, which aims to restore blood flow to the heart during a heart attack (IHD), is the standard treatment, the process of re-establishing blood flow can paradoxically cause further damage to the heart muscle, known as MIRI, due to cellular dysfunction and tissue damage that occurs when blood flow returns after a period of ischemia (95). MIRI contributes to cardiomyocyte apoptosis, myocardial damage, the no-reflow phenomenon and microvascular endothelial injury, significantly impacting patient prognosis and increasing follow-up care costs (96).

Histone modifications significantly impact MIRI pathology by controlling the expression of genes related to cardiac damage and the repair mechanisms that follow ischemia/reperfusion (I/R), essentially acting as an epigenetic regulator that influences the cellular response to injury and recovery process. A research investigation has identified epigenetic alterations in cardiac cells following I/R injury by integrating transcriptomic and epigenetic information regarding histone modifications. Particularly at 24 and 48 h after the onset of I/R injury, the investigators observed disease-associated histone marker changes in the regions of genes modified by H3K27me3, H3K27ac and H3K4me1. These differentially modified genes are involved in biological processes such as immune function, cardiac electrophysiology or muscle contraction, cytoskeletal structure and vascular neogenesis. After I/R injury, there is an observed increase in the expression of H3K27me3 and its associated methyltransferase complex, PRC2, within the myocardium. However, selective inhibition of EZH2, the principal catalytic subunit of PRC2, leads to a decrease in H3K27me3 levels. This intervention results in the activation of protective gene expression, enhancement of cardiac function, promotion of neovascularization, and a reduction in fibrosis in mice. Further studies showed that EZH2 inhibition enhanced angiogenesis *in vitro* and *in vivo* by modulating the modification of multiple angiogenesis-related genes by H3K27me3 (97). In I/R injury, lactate accumulation drives pathological angiogenesis through H3K18 lactylation (H3K18la)-mediated activation of VEGF transcriptional programs. Concurrently, H3K27 trimethylation (H3K27me3) works in conjunction with DNA hypermethylation to inhibit antioxidant defense mechanisms, such as the silencing of SOD2, thereby exacerbating oxidative damage. Dual therapeutic strategies targeting both lactate metabolic pathways (via LDH-A inhibition) and epigenetic modifiers such as EZH2 inhibitor may synergistically mitigate these maladaptive responses (98,99). However, research has indicated that the use of GSK126, an EZH2 inhibitor, is associated with elevated arterial rigidity and breakdown of elastin fibers, suggesting potential negative impacts on cardiovascular health (100).

Lysine-specific methyltransferase 2B (KMT2B), commonly referred to as MLL2, is a substantial protein composed of 2,715 amino acids. Its primary role is to facilitate the trimethylation modification (specifically, H3K4me3) of the lysine 4 residue on histone H3 within the promoter regions of specific genes (101). The KMT2 family encompasses the H3K4 methyltransferases found in six mammalian species, including KMT2A,KMT2B, KMT2C, KMT2D, KMT2F and KMT2G. These KMT2 family members regulate the transcriptional activity of target genes through H3K4 methylation. Nonetheless, the role of KMT2B in regulating histone modifications, especially in terms of its association with abnormal responses in iron metabolism, has been relatively limited.

Iron death, also known as ferroptosis, is a specific form of cell death heavily reliant on iron and characterized by excessive lipid peroxidation, which is considered a key contributor to I/R injury and subsequent organ failure due to the uncontrolled oxidative damage it causes when blood flow is restored to previously ischemic tissue; this process involves the release of free iron, which can trigger a chain reaction of lipid peroxidation leading to cell death. Iron death, through the modulation of glutathione peroxidase activity, whether directly or indirectly, results in the peroxidation of cellular membrane lipids. This phenomenon is attributed to a disturbance in intracellular redox homeostasis and an excessive generation of ROS, ultimately culminating in the disruption of the cell membrane (102). This finding provides a new strategy for the prevention of MIRI. The aforementioned study demonstrated that reducing the expression of KMT2B can attenuate the injury of cardiomyocytes under hypoxia/reoxygenation (H/R) conditions and reduce the occurrence of iron death, which can reduce the area of MI in MIRI rats. In addition, the study revealed the potential mechanism by which KMT2B affects iron death. KMT2B was able to recruit H3K4me3 in the promoter region of the RFK gene to promote the transcription of the RFK gene. The RFK protein further interacted with the p22 subunit of the NOX2 complex and with FOX and TRADD (103).

In addition, KMT2B has been recognized as an activator of the RFK gene through H3K4me3. Studies have noted increased RFK levels in individuals experiencing acute MI (AMI). The overexpression of RFK counteracts the suppressive impact of KMT2B reduction on ROS generation and iron death during H/R. RFK can interact with TRADD and p22phox. Moreover, blocking TNF-α has been observed to enhance MIRI by elevating mouse lipocalin levels (104). The TNF-α antagonist ETA mitigates MIRI, reduces infarct size, and enhances cardiac performance by inhibiting the overproduction of gp91phox, another NOX2 subunit, and superoxide (105). A decrease in NOX2 or NOX4 levels significantly reverses TNF-α-induced ROS overproduction and decreases IL-1β and IL-6 accumulation in cardiomyocytes (106). Consistent with multiple studies, the NOX2 inhibitor apocynin alleviates H/R-induced ROS accumulation and the release of pro-inflammatory cytokines, thus preventing iron death (107,108). *In vivo* studies have shown that NOX2 inhibitors reduce MIRI and infarct size when KMT2B is present, which is partially consistent with the results presented by Wang *et al* (109). Their study indicated that the NOX2 inhibitor Vas2870 or NOX2 silencing via small interfering RNA improved MIRI in diabetic rats by inhibiting oxidative stress, apoptosis, pyroptosis and iron death in cardiomyocytes under high-glucose conditions. Another study found that NOX2 expression is significantly increased in cardiomyocytes following AMI and its downregulation reduces superoxide production and apoptosis in these cells. Pharmacological interventions that partially inhibit ROS production due to NOX2 deficiency have

shown potential for post-I/R recovery, suggesting a therapeutic strategy for MIRI (110,111). These results suggest that KMT2B may promote iron death by activating the TNF-α/RFK/NOX2 signaling pathway.

Research suggests that Lysine-specific demethylase 1 (LSD1) can interact with autophagy-related 16-like 1 protein, serving a role in the cellular response to H/R conditions, which can lead to apoptosis (programmed cell death). This interaction can directly influence SETD7 and LSD1, reversing the apoptotic process and mitigating myocardial damage caused by H/R (112). In a mouse cardiomyocyte cell line that underwent H/R treatment, a decrease in LSD1 protein expression was observed. The study revealed that elevated levels of LSD1 expression can suppress the transcriptional activity of the SOX9 gene by decreasing the H3K4 trimethylation (H3K4me3) in the promoter region of the SOX9 gene. This mechanism serves a role in mitigating apoptosis triggered by H/R conditions in cardiomyocytes (113). Furthermore, other key members of the KDM family closely associated with cardiovascular functions predominantly belong to the JmjC domain family (114). Research has shown that KDM6A expression is upregulated in rat models of AMI and hypoxia-induced cardiomyocytes. The lack of KDM6A results in elevated H3K27 trimethylation at the Ncx gene promoter, which subsequently results in decreased Ncx expression and a decrease in calcium influx into cardiac muscle cells (115). This indicates that members of the JmjC family may serve as new regulatory factors in the protection of ischemic cardiomyopathy.

In addition to methylation and lactylation, acetylation is also strongly associated with cardiac I/R injury. Whether HDAC inhibitors exert cardioprotective effects by limiting infarct size in cardiac IR injury has previously been investigated. Available studies suggest that the core therapeutic window for the selective HDAC6 inhibitor ACY1215 corresponds to the reperfusion phase, particularly during the peak oxidative stress and inflammatory response in the early phase of reperfusion. Modulation of ROS-related pathways, peroxiredoxin 1, and hypoxia-inducible factor-1α (HIF-1α) signaling through HDAC6 inhibition may represent a potential strategy to attenuate reperfusion injury. However, the specific role of HIF-1α and the optimal timing for administering HDAC6 inhibitors still require thorough validation (116).

The competing roles of methylation marks in MIRI underscore the challenge of selective targeting. EZH2 inhibitors, such as GSK126 enhance angiogenesis but risk vascular stiffness, whereas KMT2B knockdown reduces iron death but may impair other H3K4me3-dependent pathways. By contrast, lactylation and acetylation modifiers operate within metabolic constraints: Lactate-driven H3K18la requires glycolytic activity, while HDAC6 inhibitors like ACY1215 depend on HIF-1α signaling. This metabolic contextuality necessitates patient stratification; for instance, diabetic patients with impaired glycolysis may benefit less from lactylation-focused therapies.

*Histone modifications as biomarkers in cardiovascular diseases*. The dynamic and disease-specific nature of histone modifications has shown great potential as biomarkers in the diagnosis, prognostic assessment and efficacy monitoring of cardiovascular diseases. For instance, elevated plasma homocysteine levels have been shown to enhance abnormal DNA methylation and upregulate the expression of N-methyl-D-aspartate receptor-1 (NMDAR1), DNA (cytosine-5)-methyltransferase-1 (DNMT1), and matrix metalloproteinase-9 (MMP-9). This regulatory mechanism is driven by H3K9 acetylation and suppression of HDAC1. These proteins (NMDAR1, DNMT1 and MMP-9) serve as indicative markers for heart failure, with experimental evidence from cardiomyocyte studies confirming their direct association with disease pathogenesis (117).

Previous studies have identified plasma levels of S-adenosylhomocysteine (SAH) as a key biomarker of As, and its concentration is significantly and positively associated with atherosclerotic plaque volume and the pathological course of hyper-homo-cysteinemia. Research reveals that excessive SAH accumulation disrupts epigenetic regulation by suppressing histone H3 lysine 9 trimethylation (H3K9me3), thereby markedly upregulating endoplasmic reticulum (ER) stress markers, including glucose-regulated protein 78 and C/EBP homologous protein. This mechanistic pathway underscores the pivotal role of SAH in driving As development through ER dysfunction, solidifying its utility as a biomarker for disease diagnosis and progression monitoring (118).

Super enhancers (SEs) are emerging as pivotal biomarkers for cardiac remodeling following MI. Integrative analysis of SEs and RNA sequencing (RNA-seq) data identified 76 differentially expressed genes (DEGs) linked to H3K27ac-enriched SEs in MI, with functional enrichment primarily in angiogenesis-related pathways. Notably, SEs unassociated with DEGs showed significant involvement in actin filament dynamics and cell migration. These SE-regulated genes may maintain a transcriptionally poised state during early MI and contribute to pathological cardiac remodeling in later disease stages (119).

Similarly, ATP2A2/SERCA2a, a cardiomyocyte-specific calcium transporter critical for regulating myocardial contraction and relaxation, has emerged as a potential biomarker for HCM. Integrated multi-omics analyses, encompassing ChIP-seq, RNA-seq and proteomics, revealed significantly reduced mRNA and protein expression levels of ATP2A2/SERCA2a in HCM cardiac tissues compared with controls. This suppression was further validated in hiPSC-derived cardiomyocyte models. The observed downregulation strongly correlates with hallmark HCM pathological features, such as diastolic dysfunction, specifically impaired myocardial relaxation, indicating its role as a molecular indicator of disease progression (120).

In summary, methylation, acetylation, ubiquitination, crotonylation and lactylation modifications of histones can regulate a wide range of genes in patients with cardiovascular disease, with different modifications or levels of modification exhibiting different associated effects.

## 4. Conclusions and prospects

Cardiovascular diseases are predominantly chronic conditions requiring long-term management, such as hypertension, coronary heart disease and heart failure. Patients are often required to adhere to prolonged medication regimens, as pharmacological treatments can only manage the disease's progression and

have limited efficacy and numerous adverse effects. However, advancements in high-throughput sequencing have revolutionized traditional disease research paradigms through the field of epigenetics. New research has uncovered a substantial link between cardiovascular ailments and their associated risk factors with alterations in histone proteins.

Histone modifications serve a critical role in the development and progression of various cardiovascular diseases, particularly histone acetylation and methylation, making them potential therapeutic targets due to their ability to regulate gene expression and cellular function within the cardiovascular system. These modifications regulate gene expression, influencing processes such as cardiomyocyte apoptosis, proliferation, inflammatory responses, oxidative stress and fibrosis. They are also intricately associated with cardiac remodeling, inflammation and vascular function. Notably, the modification states of histones H3K9 and H3K27 correlate significantly with the onset and progression of cardiovascular diseases. These findings offer new insights into the molecular mechanisms underlying cardiovascular conditions.

Despite the progress made in understanding the relationship between histone modifications and cardiovascular diseases, several limitations persist. First, most studies have primarily focused on specific histone modifications, such as acetylation and methylation, while research on other crucial changes, including phosphorylation and ubiquitination, remains limited. This narrow focus hampers a comprehensive understanding of the overall network of histone modifications. Moreover, there is a scarcity of relevant literature providing detailed statistics on the prevalence and incidence of specific histone modifications in cardiovascular diseases, which limits our understanding of their epidemiological significance. Second, current research predominantly relies on animal models or *in vitro* cellular experiments, with few clinical studies validating histone-modifying drugs' therapeutic efficacy and safety in human cardiovascular diseases. For instance, while preclinical studies highlight the potential of HDAC inhibitors such as SAHA, EZH2 inhibitors such as GSK126, and SUV39H1 inhibitors such as Chaetocin in attenuating As, MI, or hypertrophy, these findings have yet to be translated into clinical trials targeting cardiovascular indications (100,121). However, the Phase II trial of CS1 (NCT05224531), a sustained-release HDAC inhibitor for PAH, has completed enrollment and preliminary evaluations (56), but clinical results are still not available. This lack of transparency hampers the translation of preclinical epigenetic discoveries into validated therapeutic strategies. Furthermore, the intricate dynamics of histone modifications and their multifaceted interactions with other epigenetic mechanisms remain inadequately investigated, which complicates the accurate evaluation of their specific contributions to cardiovascular diseases.

Future research should focus on the dynamic changes in histone modifications and their interactions with other epigenetic mechanisms, such as non-coding RNAs and DNA methylation. This focus holds vast potential for applications in diagnosing and treating cardiovascular diseases. For example, the hematopoietic DNA demethylase TET2 has been shown by Walsh's and Ebert's laboratories (122,123), respectively, to prevent As by inhibiting the increased levels of gene expression of pro-inflammatory cytokines and chemokines as well as the activation of inflammatory vesicles. In addition, the expression level of miR-1 in non-coding RNAs directly affects cardiac function. Studies have shown that miR-1 can mitigate the pathological effects of cardiomyopathy by regulating cardiomyocyte transformation while inhibiting cell reproduction and growth (124,125). In addition, circRNA CDR1as could enhance HDAC4 expression and promote cardiac hypertrophy by adsorbing miR-7, whereas lactate-mediated lactylation could modify circRNA-binding proteins to form a metabolic-epistatic-noncoding RNA interaction axis (98,126). A critical yet understudied aspect is the therapeutic time window of histone-modifying agents. For example, while SAHA's anti-inflammatory effects may be most effective in early As, Chaetocin's ability to suppress H3K9me3 could target advanced ischemic injury. Systematic evaluation of these agents across distinct disease stages-including acute injury, chronic progression, and tissue repair phases-is imperative to establish precision therapeutic regimens. Emerging technologies, such as optical imaging, are revolutionizing our ability to visualize epigenetic dynamics *in vivo*. For example, activatable two-photon fluorescent probes (127) applied in HeLa cells were able to dynamically monitor HDAC activity at cellular resolution. This finding provides a potential technological crossover and future research direction for cardiovascular disease research. Advancements in these areas could significantly reduce mortality rates among cardiovascular patients, enhance the quality of life for a lot of individuals, and propel research and clinical applications in the field forward. Additionally, the gap in clinical research underscores a critical bottleneck in translational research. Off-target effects and long-term safety profiles of epigenetic drugs, which are well-documented in oncology (128), require rigorous evaluation in cardiovascular cohorts. For example, EZH2 inhibitors such as GSK126, though promising in preclinical models for enhancing post-ischemic angiogenesis, may pose risks such as vascular stiffness, as observed in experimental settings (100). Thus, future clinical studies must prioritize dose optimization, patient stratification, and comprehensive monitoring of adverse effects to ensure therapeutic viability. By integrating clinical studies with foundational science, the authors anticipate uncovering the potential applications of histone modifications in cardiovascular diseases. This approach aims to offer new perspectives for early diagnosis and personalized treatment, ultimately contributing significantly to the understanding and management of human cardiovascular conditions.

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**Authors' contributions**

QQ revised the manuscript regarding intellectual content. YDZ performed literature research. LL performed data analysis. QQ and HL were responsible for the editing of the manuscript. YDZ revised and validated the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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**Competing interests**

The authors declare that they have no competing interests.

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