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Regulatory Mechanisms of Histone Modifications in Myocardial Ischemia-Reperfusion Injury: A Narrow Review

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Abstract

Myocardial ischemia-reperfusion injury (MIRI) remains a critical bottleneck limiting the clinical efficacy of treatments for ischemic heart disease. Its pathological progression involves oxidative stress, mitochondrial dysfunction, inflammation, and multiple forms of regulated cell death. Conventional single-target therapeutic strategies generally show limited success in clinical translation, making the identification of novel therapeutic targets an urgent need in this field. As a core mechanism of epigenetic regulation, histone modification can translate ischemia-reperfusion-induced stress signals into transcriptional reprogramming at the chromatin level, thereby serving as a key epigenetic driver of the occurrence and progression of MIRI. This review systematically describes the biological basis and core regulatory framework of histone modifications, with a particular focus on the pathological regulatory mechanisms of acetylation, methylation, phosphorylation, and other emerging acylation modifications in MIRI. It further analyzes the crosstalk network among different histone modifications and summarizes current intervention strategies and research progress targeting histone modifications in MIRI, aiming to provide a systematic theoretical reference for studies on the epigenetic mechanisms and clinical translation of MIRI.

Keywords

Myocardial Ischemia-Reperfusion Injury, Histone Modification, Epigenetics, Transcriptional Regulation

1. Introduction

Myocardial ischemia-reperfusion injury (MIRI) remains a major challenge in cardiovascular medicine. Ischemic heart disease (IHD) is the leading cause of cardiovascular mortality worldwide, causing more than 9 million deaths and affecting 197 million people in 2019, according to the Global Burden of Disease study [1]. Although timely reperfusion by percutaneous coronary intervention or thrombolysis is essential for treating acute myocardial infarction, reperfusion itself can induce additional cardiomyocyte death and substantially contribute to the final infarct size [2]. MIRI also occurs during cardiac surgery and heart transplantation, yet validated targeted therapies remain limited [3], highlighting the urgent need for new cardioprotective targets.

Epigenetic regulation has emerged as a key mechanism in cardiovascular disease. Without altering DNA sequences, epigenetic modifications regulate chromatin accessibility and gene expression through DNA methylation, histone modification, and non-coding RNAs [4]. Among them, histone modification is one of the best-characterized mechanisms, including acetylation, methylation, phosphorylation, ubiquitination, crotonylation, and lactylation. Through the "writers-readers-erasers" paradigm, histone modifications precisely control myocardial gene expression. During MIRI, the histone modification landscape is markedly remodeled; for instance, H3K27me3, H3K27ac, and H3K4me1 show disease-specific changes within 24 - 48 h after ischemia-reperfusion, affecting genes involved in immune responses, myocardial contraction and conduction, cytoskeletal organization, and angiogenesis [5]. Ischemia also induces H3/H4 deacetylation, while histone deacetylase inhibitors can significantly reduce infarct size even when administered within 1 hour after reperfusion [6], suggesting an important therapeutic window.

Therefore, this review summarizes the regulatory mechanisms and functional consequences of histone acetylation, methylation, phosphorylation, and emerging modifications such as crotonylation and lactylation in MIRI. It also discusses modification crosstalk, integration with upstream signaling pathways, and the translational potential and challenges of histone modification-targeted cardioprotective strategies.

2. Core Pathological Mechanisms of Myocardial Ischemia-Reperfusion Injury

The pathological process of MIRI consists of two linked but distinct phases: ischemia and reperfusion [2]. During ischemia, coronary blood flow interruption shifts the myocardium to anaerobic metabolism, causing ATP depletion, lactate accumulation, intracellular acidosis, Na^+ overload via Na^+/H^+ exchanger activation, and subsequent Ca^{2+} overload through reverse Na^+/Ca^{2+} exchange, resulting in early cardiomyocyte dysfunction [2]. Upon reperfusion, restored oxygen supply abruptly reactivates the mitochondrial electron transport chain, while xanthine oxidase, NADPH oxidase, and other pathways trigger a burst of reactive oxygen

species (ROS), leading to severe oxidative stress [2] [3]. ROS and sustained Ca^{2+} overload promote mitochondrial permeability transition pore (mPTP) opening, oxidative phosphorylation uncoupling, mitochondrial swelling, and cardiomyocyte death [2]. Meanwhile, damage-associated molecular patterns (DAMPs) activate NF-κB signaling, inducing inflammatory cell infiltration and the release of IL-1β, IL-6, TNF-α, and other cytokines, thereby amplifying injury [3]. In addition to apoptosis and necrosis, ferroptosis and pyroptosis have emerged as important contributors to reperfusion-induced cardiomyocyte loss, with complex crosstalk among these death pathways [7].

These pathological events are accompanied by dynamic remodeling of myocardial gene expression, involving stress-response, pro-inflammatory, and pro-survival genes. Histone modifications act as key chromatin-level switches in this transcriptional reprogramming, making them important entry points for understanding MIRI pathogenesis and identifying new cardioprotective targets.

3. Overview of Histone Modifications

3.1. Structural Basis of Nucleosomes and Histones

In eukaryotic cells, the genome exists in the form of chromatin, whose basic structural unit is the nucleosome. In 1997, Luger *et al*. elucidated in detail the crystal structure of the nucleosome core particle, revealing for the first time at the atomic level that approximately 147 bp of DNA wraps around the outer surface of a histone octamer composed of four core histones—H2A, H2B, H3, and H4, with two copies of each—in 1.65 turns of a left-handed superhelix [8]. These four histones all possess flexible amino-terminal tails protruding outward from the nucleosome. These histone tails are enriched with enzymatically modifiable residues, such as lysine, arginine, and serine, and serve as the principal platform for the writing and reading of epigenetic information [8] [9].

3.2. Major Types of Histone Modifications

To date, more than 20 chemical types of histone modifications have been identified, involving hundreds of specific modification sites [9]. As key epigenetic mechanisms regulating chromatin structure and gene expression, histone modifications mainly include acetylation, methylation, phosphorylation, ubiquitination, and emerging acylation modifications. Each type of modification has its own regulatory system and functional tendency. Acetylation is "written" by histone acetyltransferases (HATs) and "erased" by histone deacetylases (HDACs), with its core function being to relax chromatin by neutralizing the positive charge of histones, thereby promoting transcriptional activation. The "writing" and "erasing" of methylation are mediated by histone methyltransferases (HMTs) and histone demethylases (KDMs), respectively; its effect on transcription may be activating or repressive, depending on the modification site and the degree of methylation. Phosphorylation is "written" by kinases and "erased" by phosphatases, mainly participating in mitotic regulation and DNA damage responses. Ubiquitination is

"written" by E3 ubiquitin ligases and "erased" by deubiquitinases (DUBs), with its core functions focused on transcriptional regulation and DNA repair. Emerging acylation modifications are "written" by metabolic enzymes or acyltransferases, and their central role is to sense cellular metabolic states and directly couple epigenetic regulation with cellular energy balance. These various modifications act cooperatively to form a precise and complex regulatory network of histone modifications [9]. Among them, lactylation is a novel histone modification reported by Zhang *et al.* in Nature in 2019. It is derived from the metabolic product lactate and can directly activate the transcription of target genes on chromatin, making it particularly important in the context of hypoxia and metabolic reprogramming [10].

3.3. The Writer-Reader-Eraser Regulatory Mode

Histone modifications are dynamically regulated by three classes of functional proteins, forming the "writer-reader-eraser" regulatory mode [9]. Writers catalyze the covalent addition of modification groups, such as acetyltransferases (HATs) and lysine methyltransferases (KMTs). Readers recognize and bind specific modifications through specialized domains, such as bromodomains, which recognize acetylated lysine, and chromodomains, which recognize methylated lysine, thereby recruiting effector complexes to alter chromatin states. Erasers remove modifications, such as histone deacetylases (HDACs) and lysine demethylases (KDMs). This reversible and adjustable dynamic system enables cells to mount rapid transcriptional responses to stress signals and constitutes the molecular basis for gene expression remodeling in MIRI.

4. Role of Histone Acetylation

4.1. General Overview

Histone acetylation is one of the core mechanisms of epigenetic regulation. It is mediated by histone acetyltransferases (HATs), which catalyze the addition of acetyl groups, and histone deacetylases (HDACs), which catalyze the removal of acetyl groups. The dynamic balance between these two enzyme classes determines the degree of chromatin openness and the activity of gene transcription [9] [11]. Granger *et al.* [6] first demonstrated that myocardial ischemia can significantly induce an increase in HDAC enzymatic activity, resulting in global deacetylation of histones H3 and H4, whereas HAT activity does not undergo a corresponding change. This indicates that the decline in acetylation levels during ischemia is mainly caused by abnormal activation of HDAC activity. This finding reveals that ischemia-reperfusion is not only a metabolic and oxidative stress event, but also a profound process of epigenetic reprogramming.

Eighteen HDACs have been identified in mammalian cells and are classified into four groups according to structural and functional characteristics. Class I HDACs, including HDAC1, HDAC2, HDAC3, and HDAC8, are mainly localized in the nucleus and regulate gene transcription. Class II HDACs, including HDAC4,

HDAC5, HDAC7, and HDAC9, can shuttle between the nucleus and cytoplasm, sensing stress signals and transmitting them to the chromatin level. Class III HDACs are the Sirtuin family, including SIRT1-7, which are NAD^+-dependent deacetylases that tightly couple cellular metabolic status with epigenetic regulation. Class IV contains only HDAC11 [12]. In the myocardium, all of these HDAC classes are expressed, but their roles in MIRI differ substantially.

4.2. Cardioprotective Effects of HDAC Inhibitors

Given the detrimental effect of ischemia-induced global deacetylation on the myocardium, the cardioprotective potential of HDAC inhibitors (HDACi) has attracted extensive attention. In a mouse I/R model, Granger *et al.* [6] found that trichostatin A (TSA), even when administered 1 hour after ischemia, could still reduce infarct size by approximately 50%. Xie *et al.* [13] further confirmed in a rabbit I/R model that SAHA, also known as vorinostat, among HDAC inhibitors, significantly reduced infarct size when administered at the time of reperfusion. The underlying mechanism involved the induction of cardiomyocyte autophagy to remove damaged proteins and mitochondria. In addition, Zhang *et al.* [14], by generating cardiomyocyte-specific HDAC4-overexpressing transgenic mice, directly demonstrated that sustained activation of HDAC4 aggravates ventricular dysfunction and infarct expansion after I/R, thereby validating the rationale for HDAC inhibition. Selective inhibition of class I HDACs has also been shown to produce cardioprotective effects [12], suggesting that different HDAC subclasses contribute unequally to I/R injury. Therefore, future precise intervention strategies targeting specific HDAC isoforms may have important translational value.

4.3. Figures and Tables

As class III HDACs, the Sirtuin family directly links cellular energy metabolism with deacetylation regulation through its NAD^+ dependence. Several family members play key cardioprotective roles in myocardial ischemia-reperfusion (I/R) injury. SIRT1 is the most extensively studied cardioprotective Sirtuin. Using SIRT1 knockout mice and transgenic models, Hsu *et al.* [15] demonstrated that SIRT1 can directly protect the myocardium from I/R injury through deacetylation. Mechanistically, SIRT1 activates the FOXO3a transcription factor through deacetylation, thereby upregulating the expression of antioxidant enzymes such as manganese superoxide dismutase (MnSOD) and catalase, ultimately reducing oxidative damage and apoptosis [16] [17]. SIRT3 is the major mitochondrial deacetylase, and its role in I/R injury has received increasing attention. Parodi-Rullán *et al.* [18] found that SIRT3 knockout mice exhibited significantly poorer cardiac functional recovery after I/R compared with wild-type mice, accompanied by increased mitochondrial ROS production and reduced SOD2 activity. Mechanistically, SIRT3 activates SOD2 through deacetylation, enhancing the clearance of superoxide anions within mitochondria [19]. In addition, Hafner *et al.* [20] revealed that SIRT3 deacetylates cyclophilin D (CypD) at lysine 166, thereby inhibiting abnormal opening of the

mitochondrial permeability transition pore (mPTP) and maintaining mitochondrial membrane potential stability. Functional synergy also exists between SIRT1 and SIRT3. The study by Liao *et al.* [21] showed that abnormalities in the SIRT1-SIRT3 axis can induce ferroptosis by silencing the PINK1/Parkin signaling pathway, thereby aggravating myocardial ischemia-reperfusion injury (MIRI). As a nuclear Sirtuin member, SIRT6 exerts multiple protective functions in myocardial I/R injury. Wang *et al.* [22] demonstrated using SIRT6 heterozygous knockout mice that SIRT6 deficiency aggravates myocardial injury and oxidative stress after I/R, whereas restoration of SIRT6 expression upregulates MnSOD and catalase expression by activating the AMPK-FOXO3α axis. In addition, SIRT6 regulates glycolytic gene expression through deacetylation and participates in DNA damage repair, thereby maintaining genomic stability [23]. In terms of agonists, the natural polyphenolic compound resveratrol is a classic SIRT1 activator and has been shown to alleviate myocardial I/R injury by activating the Sirt1/Sirt3-FoxO pathway, restoring the balance between mitochondrial fusion and fission, recovering autophagic flux, and promoting mitochondrial biogenesis [24].

4.4. Involvement of HATs

Corresponding to HDACs, the role of HATs in MIRI should also not be overlooked. p300/CBP-associated factor (PCAF) is an important member of the GCN5-related N-terminal acetyltransferase family and possesses histone acetyltransferase activity. Qiu *et al.* [25] found that MIRI significantly upregulates PCAF expression in the myocardium, whereas downregulation of PCAF can inhibit excessive autophagy by activating the PI3K/Akt/mTOR signaling pathway, thereby reducing myocardial infarct size in rats. Further studies showed that PCAF downregulation can also alleviate cardiomyocyte apoptosis, inflammatory responses, and oxidative stress by suppressing the NF-κB signaling pathway [26]. As a large acetyltransferase, p300 is closely associated with cardiac development and pathological remodeling. Under ischemic stress, p300 can be activated and acetylate cardiac transcription factors such as GATA4, participating in myocardial hypertrophy and remodeling [27]. These findings indicate that the imbalance between HATs and HDACs jointly drives epigenetic disorders in MIRI, and HATs may also serve as potential intervention targets.

5. Role of Histone Methylation

5.1. Overview

Histone methylation has a unique "positional code" characteristic: different degrees of methylation on the same lysine residue, including mono-, di-, or trimethylation, can produce markedly different functional consequences. For example, H3K4me3 usually marks active gene promoters, whereas H3K27me3 and H3K9me3 are closely associated with gene silencing [28]. This precise regulation, which couples modification sites with methylation degree, makes the role of histone methylation in MIRI highly complex. By integrating transcriptomic data with

histone modification epigenomic data, Ni *et al.* [5] first mapped the genome-wide histone modification landscape after myocardial I/R injury. They found that within 24 and 48 hours after I/R, disease-specific changes in histone marks were mainly concentrated in regions marked by H3K27me3, H3K27ac, and H3K4me1. The differentially modified genes involved were associated with key processes such as immune responses, cardiac conduction and contraction, cytoskeletal organization, and angiogenesis.

5.2. Activating Methylation Marks

H3K4me3 is a hallmark histone modification associated with transcriptional activation. The KMT2 family, also known as the MLL family, is the major methyltransferase family responsible for catalyzing H3K4 trimethylation. Cao *et al.* [29] found that KMT2B was significantly upregulated in the peripheral blood of patients with acute myocardial infarction and in I/R myocardial tissues. KMT2B promotes the transcription of the riboflavin kinase (RFK) gene by catalyzing H3K4me3 modification, thereby activating the TNF-α/NOX2 inflammatory signaling pathway, aggravating oxidative stress and ferroptosis, and expanding myocardial infarct size. Knockdown of KMT2B can significantly alleviate these injuries. This finding suggests that H3K4me3 does not always play a protective role in MIRI. Instead, its ultimate biological effect depends on the spectrum of target genes whose transcription it promotes. When H3K4me3 is enriched at the promoters of pro-inflammatory and pro-death genes, it can instead aggravate injury.

5.3. Repressive Methylation Marks

H3K27me3 is catalyzed by polycomb repressive complex 2 (PRC2), in which EZH2 serves as the core catalytic subunit. Ni *et al.* [5] showed that H3K27me3 levels and PRC2 expression are significantly upregulated in myocardial tissue after I/R, whereas selective inhibition of EZH2 improves cardiac function, promotes angiogenesis, and reduces fibrosis. The mechanism involves relieving the repressive H3K27me3 modification at the promoters of multiple pro-angiogenic genes. However, EZH2 does not play a purely detrimental role in myocardial injury. Peng *et al.* [30] found that mesenchymal stem cell-derived exosomes reduce EZH2 and H3K27me3 levels in cardiomyocytes by delivering miR-25-3p, thereby derepressing the expression of protective genes such as eNOS and SOCS3 and alleviating post-infarction apoptosis and inflammation. Another study showed that lncRNA JPX can reduce H3K27me3 modification in the SERCA2a promoter region by binding to EZH2, restoring SERCA2a expression to alleviate calcium overload and thereby attenuating I/R injury [31]. Therefore, the role of EZH2 in MIRI is clearly target gene-dependent and dual-sided. In addition, H3K9me2/3 is also an important mark of heterochromatin formation and gene silencing. Using cardiac-specific G9a knockout mice combined with genome-wide ChIP-seq analysis, Papait *et al.* [32] revealed that the histone methyltransferase G9a maintains transcriptional homeostasis in adult cardiomyocytes by preserving H3K9me2 modifications

at key gene regions in cardiomyocytes. Loss of G9a causes abnormal reactivation of the fetal gene program and induces myocardial hypertrophy. Thienpont *et al.* [33] further confirmed that H3K9me2 serves as a key repressive epigenetic modification regulating cardiomyocyte differentiation homeostasis. In a heart failure model, Yan *et al.* [34] also found that G9a is highly expressed in heart failure and can silence BDNF expression by mediating repressive H3K9me2 modification in the BDNF promoter region, thereby blocking the downstream TrkB signaling pathway and further aggravating cardiomyocyte apoptotic injury and heart failure progression.

5.4. Role of Histone Demethylases (KDMs)

Corresponding to methyltransferases, histone demethylases (KDMs) also play certain roles in MIRI. He *et al.* [35] found that the histone demethylase KDM1A/LSD1 can suppress SOX9 transcription by reducing H3K4me3 modification in the SOX9 promoter region, thereby inhibiting hypoxia/reoxygenation-induced cardiomyocyte apoptosis. However, under myocardial ischemia-reperfusion injury conditions, downregulation of KDM1A relieves this inhibitory effect and aggravates cardiomyocyte apoptosis. Zhang *et al.* [36] reported that KDM3A, an H3K9me2-specific demethylase, is upregulated in the myocardium after pressure overload and promotes myocardial hypertrophy and fibrosis by activating Timp1 transcription; the pan-KDM inhibitor JIB-04 can effectively suppress this process. These studies indicate that the dynamic balance between the "writing" and "erasing" enzymes of methylation modifications is critical for maintaining myocardial homeostasis, and disruption of this balance can aggravate pathological remodeling after MIRI.

6. Role of Histone Phosphorylation

6.1. H2AX Phosphorylation

Phosphorylation of the histone variant H2AX at serine 139, known as γH2AX, is a classic marker of DNA double-strand breaks (DSBs) and plays an important role in MIRI. Corbucci *et al.* [37] demonstrated in patients undergoing cardiac valve surgery that ischemia can induce extensive γH2AX formation in the human left ventricular myocardium. As a specific substrate of ATM kinase and a core marker of myocardial DNA double-strand breaks, γH2AX phosphorylation is significantly increased during myocardial ischemia. It represents a key node in ischemia-induced DNA damage response activation and can drive downstream activation of the p53/p21 pathway. After reperfusion, TUNEL staining is reduced, but ATM activation persists, indicating that reperfusion provides a time window for DNA repair, and the outcome of this repair directly determines cardiomyocyte survival [37].

6.2. H3S10/H3S28 Phosphorylation

Phosphorylation of histone H3 at serine 10 (H3S10) and serine 28 (H3S28) is a key epigenetic mark that rapidly transmits extracellular stress signals to the

chromatin level [38]. MSK-mediated phosphorylation of histone H3S28 is a core epigenetic regulatory event in macrophages under inflammatory stimulation and can directly activate p300/CBP-dependent transcription of inflammatory genes. MSK1/2 can amplify inflammatory transcriptional programs at the chromatin level through this histone phosphorylation modification and can also drive pathological transcriptional upregulation of the mast cell growth factor SCF under inflammatory conditions by phosphorylating NF-κB p65 at Ser276. Thus, MSK1/2 acts as a central hub linking epigenetic regulation by histone phosphorylation with the NF-κB inflammatory pathway [39] [40]. In the cardiac field, Robinson *et al.* [41] showed that MAPK pathway-activated MSK-mediated H3S28 phosphorylation is required for the induction of immediate early genes (IEGs) during myocardial hypertrophy. pH3S28 initiates gene expression programs by recruiting the BRG1 subunit of the BAF60 chromatin remodeling complex. Blocking MSK activity and IEG induction can suppress the hypertrophic response. Considering the key role of p38 MAPK in reperfusion injury, the MSK1/2-H3S10/S28 phosphorylation axis is likely to play an important role in inflammatory responses and gene reprogramming in MIRI [42].

6.3. H3T11 Phosphorylation

Pyruvate kinase M2 (PKM2) is a rate-limiting enzyme in glycolysis, but its non-canonical function—as a protein kinase that catalyzes phosphorylation of histone H3 at threonine 11 (H3T11)—has attracted widespread attention in recent years [43]. In myocardial ischemic injury, the metabolic reprogramming function of PKM2 has been shown to be of great importance. PKM2 tetramers protect the myocardium from ischemic injury by promoting pyruvate oxidation and ATP production, whereas PKM2 dimers promote the entry of glycolytic intermediates into the pentose phosphate pathway to support cardiomyocyte proliferation and regeneration [44]. Magadum *et al.* [45] demonstrated in a mouse myocardial infarction model that cardiomyocyte-specific expression of PKM2 promotes myocardial regeneration and cardiac functional recovery. Recent research has also found that MTX2 regulates cardiac glucose metabolic flux by promoting PKM2 tetramerization; loss of MTX2 aggravates I/R injury, whereas the PKM2 activator TEPP-46 can reverse this metabolic defect [46]. These findings suggest that PKM2-mediated H3T11 phosphorylation and glucose metabolic reprogramming may constitute an important epigenetic-metabolic coupling mechanism in the adaptive response of ischemic myocardium.

7. Role of Other Emerging Histone Modifications

In recent years, with advances in mass spectrometry, a series of emerging histone acylation modifications derived from metabolic intermediates have been discovered. These modifications directly couple cellular metabolic status with epigenetic regulation, opening a new perspective for understanding the pathological mechanisms of MIRI.

Histone crotonylation uses crotonyl-CoA as a substrate and is catalyzed by acyltransferases such as p300/CBP. In the cardiovascular field, Tang *et al.* [47] found that the levels of H3K18cr and H2BK12cr were significantly increased in the myocardium of patients with hypertrophic cardiomyopathy, and that short-chain enoyl-CoA hydratase ECHS1 can suppress histone crotonylation by regulating intracellular crotonyl-CoA levels. Proteomic analysis further revealed that acute myocardial I/R injury can trigger extensive changes in protein crotonylation, involving proteins closely related to cardiomyocyte contractile function, such as those associated with mitochondria, the cytoskeleton, the sarcoplasmic reticulum, and gap junctions [48].

Histone succinylation is closely related to succinyl-CoA, a metabolite of the mitochondrial tricarboxylic acid cycle. SIRT5, as the major mitochondrial desuccinylase, has been preliminarily shown to exert protective effects in cardiac I/R. Exogenous NAD^+ alleviates I/R-induced oxidative injury in rat hearts through the Sirt5-succinate dehydrogenase-succinate pathway [49]. Mitochondrial dysfunction during ischemia leads to abnormal succinate accumulation, which may affect cardiomyocyte fate by altering the protein succinylation landscape. However, the specific role of histone-level succinylation in MIRI remains to be further elucidated.

Histone lactylation is a novel modification first reported by Zhang *et al.* in Cell in 2019. It uses lactate, a glycolytic product, as a substrate and is catalyzed by p300 [10]. A study published by Wang *et al.* [50] showed that after myocardial infarction, monocyte-macrophages undergo metabolic reprogramming, and elevated lactate levels drive enhanced H3K18la modification. Through an IL-1β-dependent GCN5 recruitment mechanism, this promotes the transcriptional activation of reparative genes such as Lrg1, VEGF-a, and IL-10, thereby exerting dual anti-inflammatory and pro-angiogenic effects. This study also confirmed similar dynamic changes in H3K18la and its repair-promoting role in a reperfused myocardial infarction model. Notably, HSPA12A regulates cardiomyocyte H3K56la levels by maintaining aerobic glycolytic homeostasis during reperfusion, thereby exerting cardioprotective effects [51]. However, lactylation can also promote myocardial fibrosis by enhancing Snail1 lactylation and activating the TGF-β/Smad2 endothelial-to-mesenchymal transition pathway [52], suggesting that lactylation has both protective and injurious roles in MIRI.

8. Conclusions and Perspectives

In summary, histone acetylation, methylation, phosphorylation, and emerging acylation modifications such as lactylation and crotonylation reshape chromatin states and transcriptional programs through the dynamic "writer-reader-eraser" regulatory system. These modifications are extensively involved in the core pathological processes of myocardial ischemia-reperfusion injury, including oxidative stress, sterile inflammation, mitochondrial dysfunction, and multiple forms of regulated cell death. They serve as key epigenetic hubs mediating myocardial stress

responses and injury repair. A variety of intervention strategies targeting histone modifications have demonstrated clear cardioprotective effects in preclinical models.

In the future, single-cell epigenomic technologies may be used to clarify the differences in histone modifications among different cardiac cell types during myocardial ischemia-reperfusion. *In vivo* monitoring technologies with high spatiotemporal resolution should also be developed to dynamically track the entire process of histone modification changes in real time, thereby identifying key intervention windows. In addition, multi-target synergistic "epigenetic cocktail" combination strategies may help overcome the poor clinical translation of single-target therapies. Meanwhile, artificial intelligence can be applied to establish predictive models linking histone modification profiles with patients' clinical phenotypes, thereby facilitating precise and individualized myocardial protection therapy.

A comprehensive analysis of the crosstalk networks among histone modifications will provide new theoretical support and target directions for overcoming the clinical translational bottleneck of myocardial ischemia-reperfusion injury and for developing precise cardioprotective therapies.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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