MEDS Chinese Medicine (2026)
Clausius Scientific Press, Canada

DOI: 10.23977/medcm.2026.080111
ISSN 2616-1753 Vol. 8 Num. 1

Mechanisms of Protein Acetylation Modification in Chronic Heart Failure and Research Progress on Traditional Chinese Medicine Intervention

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Keywords: Heart failure, Protein acetylation, Epigenetic regulation, Histone deacetylase, Traditional Chinese Medicine

Abstract: Protein acetylation is a widely prevalent and highly dynamic post-translational modification that regulates chromatin structure, gene transcription, metabolic enzyme activity, and protein stability by reversibly adding acetyl groups to lysine residues. Acetylation is "written" by lysine acetyltransferases (KATs) and "erased" by histone deacetylases (HDACs) and the NAD^+-dependent Sirtuin family, with its dynamic equilibrium closely coupled to the metabolic state of intracellular acetyl-CoA. Chronic heart failure (CHF) patients exhibit significant protein acetylation abnormalities in myocardial tissue, particularly excessive acetylation of mitochondrial proteins, leading to impaired fatty acid oxidation, energy metabolism disorders, and myocardial remodeling. In this review, we systematically elucidate the molecular mechanisms of histone and non-histone acetylation, explore the multi-level regulatory roles of acetylation modifications in myocardial energy metabolism, contractile function, fibrosis, and inflammatory responses, and outline the pathological mechanisms by which acetylation dysregulation drives heart failure progression. Building on this, we discuss therapeutic strategies targeting acetylation, including preclinical evidence for HDAC inhibitors and the direct regulatory effects of active components in traditional Chinese medicine on acetyltransferase activity.

1. Introduction

Chronic heart failure (CHF) is a complex clinical syndrome characterized by ventricular remodeling and systolic or diastolic dysfunction, involving coordinated dysregulation of multiple cell types including cardiomyocytes, fibroblasts, immune cells, and vascular cells [1]. Its pathological process encompasses multiple levels such as energy metabolism disturbances, oxidative stress, inflammatory activation, fibrotic deposition, and calcium homeostasis imbalance [2,3]. In recent years, post-translational protein modifications, particularly lysine acetylation, have garnered increasing attention for their role in the pathogenesis of heart failure.

Post-translational modification (PTM) refers to a critical biological process where amino acid

residues of proteins are chemically modified after synthesis through covalent or enzymatic means, thereby regulating their structure, stability, localization, activity, and interactions [4]. These modifications—including phosphorylation, ubiquitination, methylation, acetylation, lactylation, glycosylation, and N-terminal acetylation—not only significantly expand the functional diversity of the proteome but also play pivotal roles in cellular signal transduction, gene expression regulation, maintenance of metabolic homeostasis, and stress responses. Among various PTM types, acetylation has garnered increasing attention due to its dual roles in epigenetic regulation and metabolic integration [5]. Advances in chemical biology tools have further revealed the modifiability of protein covalent structures and their close association with chromatin function, providing crucial support for elucidating the molecular mechanisms of PTMs [6]. Protein acetylation was initially discovered on histones, but subsequent studies have confirmed its widespread presence in non-histone substrates, constituting a key mechanism for regulating multiple cellular processes [5]. Acetylation primarily occurs on the ε-amino group of lysine residues, catalyzed by lysine acetyltransferases (KATs, also known as HATs), which transfer acetyl groups from acetyl-CoA to target proteins. Deacetylation is performed by classical histone deacetylases (HDACs) and the NAD^+-dependent Sirtuin family, collectively maintaining a reversible dynamic equilibrium of modifications [4,7]. Acetylation not only reshapes chromatin structure and regulates gene transcriptional activity, but also directly modulates the enzymatic activity, subcellular localization, and protein-protein interactions of non-histone proteins [8]. This regulatory function holds clear pathophysiological significance in the cardiovascular system: In a tachycardia-induced cardiomyopathy model, global protein acetylation levels are significantly elevated, particularly the excessive acetylation of sarcoplasmic reticulum/endoplasmic reticulum calcium ATPase leads to abnormal calcium handling, while supplementation with NAD+ can reverse this acetylation and restore myocardial function [2]. Additionally, reduced N-terminal acetylase activity caused by NAA10 gene mutations can induce cardiomyopathy, prolonged QT interval, and contractile dysfunction [9], further demonstrating the critical pathological implications of dynamic acetylation modification imbalances in cardiovascular systems.

This imbalance is particularly prominent in chronic heart failure (CHF). Patients with HFpEF exhibit global hyperacetylation of myocardial mitochondrial proteins, where the key enzyme HADHA in the fatty acid oxidation (FAO) pathway becomes inactivated after Dlat-mediated acetylation at the K728 site, leading to lipid metabolism disorders and worsening cardiac function [3,10]. Concurrently, abnormal histone acetylation levels also contribute to the regulation of pathological myocardial hypertrophy: PRMT5 enhances p300's histone acetyltransferase (HAT) activity through methylation, promoting H3K9 acetylation and thereby driving the expression of hypertrophy-related genes [10]. Conversely, HDAC6 deficiency or inhibition increases myofibrillar stiffness and exacerbates diastolic dysfunction, suggesting that deacetylases are indispensable for maintaining myocardial elasticity [11]. Given the multifaceted regulatory roles of acetylation modifications at metabolic, structural, and transcriptional levels, targeting acetylation homeostasis has emerged as a novel strategy for CHF intervention [8,12]. However, existing acetylation-targeting therapies—represented by HDAC inhibitors—face clinical translation barriers due to single-target limitations and off-target toxicity. This situation highlights the need for a therapeutic approach capable of multi-node intervention to address acetylation network dysregulation. Traditional Chinese medicine, with its characteristics of multi-component, multi-target, and multi-pathway synergistic regulation, may represent an ideal pathway for modulating acetylation homeostasis.

2. Molecular Mechanisms of Protein Acetylation Modification

2.1 Dynamic Equilibrium of Histone Acetylation

Histone acetylation is a reversible post-translational modification whose dynamic equilibrium is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), which respectively perform "writing" and "erasing" functions [13]. This modification primarily occurs on lysine residues at the N-terminal end of histones, weakening electrostatic interactions between histones and DNA through neutralization of positive charges, thereby promoting chromatin structural loosening and enhancing gene transcriptional activity. Histone acetylation levels are not only modulated by HATs/HDACs activity but also highly dependent on intracellular acetyl-CoA availability [14]. The nuclear acetyl-CoA pool is partially generated by acetyl-CoA synthetase 2 (ACSS2), which directly provides acetyl groups for histone acetylation during gene activation [15]. Under metabolic stress conditions such as carbon starvation, histone acetylation marks can be redistributed from pro-growth genes to genes related to gluconeogenesis and lipid metabolism, a process mediated by Rpd3p (HDAC) and Gcn5p (HAT), demonstrating adaptive responses of acetylation modifications to metabolic state changes [16]. In the context of cardiovascular diseases, doxorubicin-induced cardiac toxicity is closely associated with histone acetylation imbalance, involving dysregulation of HDACs/HATs in oxidative stress [8]. Combined with similar acetylation regulatory abnormalities observed in chronic heart failure (CHF), these findings collectively support the critical regulatory role of this dynamic equilibrium system in cardiovascular diseases.

2.2 Acetylation Recognition of Non-Histone Substrates

Lysine acetylation is not limited to histones but is also widely present in various non-histone proteins, influencing their stability, localization, interactions, and enzymatic activity [13]. Recognition of non-histone protein acetylation depends on lysine residues within specific sequences or structural domains, with its modification status further regulated by acetyl-CoA concentration and HATs/HDACs activity. In the context of heart failure (HF), this regulatory mechanism carries direct pathological significance: In the myocardium of patients with heart failure with preserved ejection fraction (HFpEF), mitochondrial protein Dlat acts as a transacetylase, directly mediating acetylation at the K728 site of HADHA, leading to inactivation of this fatty acid oxidation (FAO) key enzyme activity, thereby inhibiting fatty acid oxidation and promoting the HFpEF phenotype [3]. In hepatocellular carcinoma, overall downregulation of the acetyl-CoA synthesis pathway results in non-histone protein hypacetylation, indicating that non-histone protein acetylation levels are closely correlated with the availability of metabolic intermediates [17]. In plant models, lysine acetylation of ADA2 protein is regulated by GCN5, and the acetylated form can be recognized and degraded by E3 ubiquitin ligases, revealing the role of non-histone protein acetylation in protein homeostasis regulation [18]. In summary, non-histone protein acetylation exhibits substrate specificity and participates in various physiological and pathological processes by modulating target protein functions.

2.3 Classification of Acetyltransferase (HATs) Family and "Writing"

Acetyltransferases (HATs) are a class of enzymes that catalyze the transfer of acetyl groups from acetyl-CoA to the ε-amino group of lysine. Based on structure and function, they can be classified into several families including GNATs, MYSTs, p300/CBP, and nuclear hormone-associated receptor coactivators [13]. HATs regulate chromatin structure and gene expression by "writing" acetylation marks, but their functions extend far beyond histone substrates. p300 promotes histone

acetylation of pregnancy-related genes upon recruitment by STAT3, a process dependent on ACSS2-mediated acetyl-CoA biosynthesis [19]. In α-Syn overexpression models, activated p300 translocates from the nucleus to the cytoplasm, leading to reduced histone acetylation and increased acetylation of cytoplasmic substrates (e.g., raptor), which triggers excessive mTORC1 activation [20]. GCN5 not only acetylates histones but also modifies non-histone proteins such as ADA2, enhancing its own activity through ADA2 accumulation under stress conditions to maintain acetylation homeostasis [18]. In rice, HAT1 specifically mediates H4K5 and H4K16 acetylation, with its activity on H4K5 dependent on interaction with ACLA2, which participates in localized acetyl-CoA accumulation in the nucleus [21]. These studies reveal the molecular mechanisms by which HATs achieve precise "writing" through substrate recognition and utilization of localized acetyl-CoA pools across diverse biological systems.

2.4 Distribution of HDAC Subtypes and "Erasure"

Histone deacetylases (HDACs) are responsible for removing acetyl groups from lysine residues, restoring the tight binding of histones to DNA and inhibiting gene transcription. Mammalian HDACs are classified into four classes: Class I (HDAC1, 2, 3, 8), Class IIa (HDAC4, 5, 7, 9), Class IIb (HDAC6, 10), Class III (NAD^+-dependent sirtuins), and Class IV (HDAC11) [13]. Each class of HDACs exhibits tissue-specific distribution and functional distinctiveness, a characteristic particularly prominent in the cardiovascular system. HDAC6 is upregulated in the HFpEF mouse model, and its selective inhibitor TYA-018 can reverse myocardial hypertrophy, fibrosis, and mitochondrial energy metabolism disorders. In contrast, HDAC6 gene-deficient mice show no response to this drug, indicating that HDAC6 plays a critical "erasing" role in the pathological progression of HFpEF [22]. Doxorubicin-induced cardiac toxicity is also associated with HDACs/HATs imbalance, suggesting that abnormal HDAC activity may exacerbate oxidative stress injury [8]. Additionally, HDACs participate in regulating cardiac energy metabolism, and their dysregulation may serve as a potential therapeutic target for heart failure [23]. The NAD^+-dependent nature of Class III HDACs (sirtuins) tightly couples acetylation modifications with cellular energy status, further expanding the metabolic regulatory dimensions of the "erasing" mechanism [13].

2.5 Regulatory Network of Acetyl-CoA Metabolic Pathway

Acetyl-CoA serves as the sole acetyl donor in acetylation reactions, with its intracellular concentration directly determining the level of acetylation modifications, thereby constituting a core hub linking metabolic states and epigenetic outputs. Acetyl-CoA can be generated through multiple metabolic pathways, including the cleavage of citrate derived from glycolysis via ATP-citrate lyase (ACLY), fatty acid β-oxidation, amino acid catabolism, and the activation of acetic acid via acetyl-CoA synthetase (ACSS) [14]. In glioblastoma, a high-glucose environment promotes O-GlcNAcylation of ACLY via the PI3Kβ-OGT axis, enhancing acetyl-CoA production and driving histone acetylation [24]; lactate can also elevate acetyl-CoA levels through ACLY-dependent pathways, improving chromatin accessibility [25]. Conversely, BOLD-100 reduces histone acetylation by inducing acyl-CoA depletion, highlighting the central role of acetyl-CoA metabolism in epigenetic regulation [26]. In cardiac tissues, impaired cytoplasmic transport of mitochondrial acetyl-CoA leads to decreased chromatin acetylation, which can be reversed by acetic acid supplementation or restoration of CiC expression [27]. ACSS2 has been demonstrated to regulate nuclear acetyl-CoA levels in neurodegenerative diseases and gestational β-cells, thereby influencing the acetylation status of histone H3K9 and H4K12 sites [19,28]. In CHF, acetyl-CoA metabolic reprogramming and acetylation modification imbalance form a

bidirectional interactive relationship: on one hand, changes in metabolic intermediates affect acetylation levels; on the other hand, histone acetylation itself can serve as an acetic acid reservoir, retroactively regulating downstream metabolic processes [14]. This complex regulatory network tightly integrates cellular metabolic states with epigenetic outputs.

The aforementioned acetyltransferase system and acetyl-CoA metabolic network precisely maintain epigenetic homeostasis in cardiomyocytes under physiological conditions. However, in the pathological environment of chronic heart failure, systemic collapse of this network directly drives energy metabolism disorders, contractile dysfunction, myocardial hypertrophy, and fibrosis, constituting the core molecular basis for the progression of heart failure.

3. Mechanisms of Acetylation Modification in the Cardiovascular System

3.1 Acetylation Regulation of Energy Metabolism in Cardiomyocytes

Protein acetylation plays a critical regulatory role in myocardial energy metabolism, particularly in mitochondrial function and the fatty acid oxidation (FAO) pathway. Significant protein hyperacetylation has been observed in cardiac tissues of patients with heart failure with preserved ejection fraction (HFpEF), predominantly localized to mitochondria and highly enriched in FAO-related pathways [3]. Mechanistically, Dlat, as a key transacetylase, directly mediates acetylation modifications at the K728 site of HADHA protein, leading to loss of HADHA enzyme activity, which subsequently inhibits FAO and induces cardiac lipid metabolism disorders. Overexpression of Dlat exacerbates HFpEF phenotypes, whereas its knockdown effectively alleviates FAO inhibition and associated cardiac dysfunction, suggesting that abnormal mitochondrial protein acetylation levels are a significant driver of HFpEF pathogenesis. In diabetic mouse models, Sirt3 deficiency also induces mitochondrial protein hyperacetylation, disrupts the assembly of mitochondrial respiratory chain supercomplexes, impairs mitochondrial respiratory function, and increases reactive oxygen species (ROS) generation, thereby exacerbating myocardial ischemia/reperfusion injury [29]. These findings collectively demonstrate that acetylation modifications profoundly influence myocardial energy homeostasis by regulating the activity of mitochondrial metabolic enzymes.

3.2 Acetylation Modification of Cardiac Contractile-Related Proteins

Acetylation modification also directly participates in regulating the structural and mechanical properties of proteins related to cardiac contractile function. HDAC6 can modulate myocardial sarcoplasmic reticulum (SR) stiffness through deacetylation, and its deletion or pharmacological inhibition leads to a significant increase in SR stiffness in mouse myocardium, a change closely associated with hypertensive or aging-induced diastolic dysfunction [11]. In myocardial SRs of mice, rats, and humans, exogenous supplementation of HDAC6 effectively reduces SR stiffness, suggesting that the acetylation status of key contractile proteins such as titin is reversible and directly influences myocardial compliance [11]. N-terminal acetylation, as another highly conserved post-translational modification, also plays a critical role in maintaining cardiomyocyte electrophysiological stability and contractile function. The p.(Arg4Ser) mutation in the NAA10 gene reduces its enzymatic activity, leading to disturbances in late sodium currents and slow delayed rectifying potassium currents, weakened contractility, and SR structural abnormalities in cardiomyocytes, clinically manifested as prolonged QT interval and cardiomyopathy phenotypes [9]. These findings indicate that acetylation modification not only regulates the mechanical properties of myofilament proteins but also affects the electromechanical coupling process in cardiomyocytes.

3.3 Epigenetic Regulation of Myocardial Fibrosis Progression

Acetylation modification plays a central role in the epigenetic regulation of myocardial fibrosis, primarily by modulating the expression of fibroblast-activating and pro-fibrotic genes. In a stress-induced heart failure model, ATP-citrate lyase (ACLY) activates transcription of fibrosis-related genes by promoting histone H3K27 acetylation, thereby driving the differentiation of cardiac fibroblasts into myofibroblasts [30]. Genetic deletion or pharmacological inhibition of ACLY effectively reverses myofibroblast phenotypes, reduces collagen deposition, and protects cardiac function, highlighting the critical role of ACLY-mediated histone acetylation in fibrotic processes [30]. Members of the sirtuin family (e.g., SIRT1, SIRT3, SIRT6, SIRT7) inhibit pro-fibrotic signaling pathways such as TGF-β/Smad through deacetylation, thereby reducing fibroblast activation and collagen synthesis to exert anti-fibrotic effects [31]. Another study found that PDCD5 is upregulated by SMAD3 after myocardial infarction (MI) and can suppress its activity by promoting HDAC3 ubiquitination, thereby alleviating myocardial fibrosis and improving cardiac function [32]. Deng et al. [33] demonstrated that peptidase inhibitor 16 (PI16) inhibits HDAC1 expression in myocardial fibroblasts, increases histone H3 acetylation levels, and consequently suppresses fibroblast proliferation and the expression of fibrosis-related proteins, mitigating angiotensin II-induced cardiac fibrosis and hypertrophy. These findings indicate that HDAC1 plays a pathogenic role in cardiac fibrosis and may serve as a therapeutic target for anti-fibrotic treatment. The evidence suggests that acetylation modifications regulate the occurrence and progression of myocardial fibrosis through multi-level mechanisms involving dynamic equilibrium between histone and non-histone substrates.

3.4 Acetylation Regulation Mechanism of Inflammatory Response Pathways

Acetylation modification also plays a widespread role in regulating inflammatory responses within the cardiovascular system, with its mechanisms involving the activity and subcellular localization of key inflammatory transcription factors. As previously described, in a doxorubicin-induced cardiotoxicity model, protein acetylation mediates oxidative stress responses through HDACs and HATs, while SIRT activators and HDAC inhibitors demonstrate potential to mitigate cellular damage. Following myocardial infarction (MI), YAP can be acetylated at the K265 site by CBP/p300, a modification that promotes YAP binding to microtubule-associated protein TUBA4A, leading to its cytoplasmic retention. This results in suppressed nuclear transcriptional activity, impeding cardiac regeneration and potentially exacerbating inflammatory and fibrotic responses indirectly. The YAP K265R mutant, which lacks acetylation capability, significantly improves cardiac regenerative capacity [34]. In classical inflammatory pathways, AceTAG has been successfully used to chemically induce p65/RelA acetylation in living cells, enhancing their transcriptional activity [4], suggesting that acetylation can directly regulate inflammatory factor expression. Integrating existing evidence, acetylation modification exerts dual regulatory effects on cardiovascular inflammatory responses by influencing the activity and localization of key inflammatory transcription factors.

4. Abnormal Protein Acetylation and Pathogenesis of Chronic Heart Failure

4.1 Acetylation Omics Characteristics of Myocardial Tissue in Patients with Heart Failure

Patients with chronic heart failure (CHF) exhibit significant abnormal protein acetylation modifications in myocardial tissue, which constitute critical molecular signatures of heart failure. In patients with heart failure with preserved ejection fraction (HFpEF), myocardial mitochondrial

proteins demonstrate widespread hyperacetylation, particularly enriched in proteins associated with the fatty acid oxidation (FAO) pathway [3]. In a tachycardia-induced cardiomyopathy model, metabolic reprogramming leads to NAD^+ redox imbalance, resulting in excessive acetylation of multiple proteins including sarcoplasmic reticulum/endoplasmic reticulum calcium ATPase [2]. These acetylomics alterations not only impair the activity of key metabolic enzymes but also disrupt calcium homeostasis and energy supply, thereby exacerbating cardiac dysfunction.

4.2 Association between HDAC Subtype Expression Profiles and Cardiac Function

Members of the HDAC family exhibit subtype-specific expression patterns in CHF and demonstrate strong correlation with cardiac functional status. HDAC6 shows upregulated expression in HFpEF models, and its inhibition or gene knockout significantly ameliorates myocardial hypertrophy, fibrosis, and diastolic dysfunction [22]. In contrast, cardiac-specific knockout of HDAC3 in adult mice induces myocardial hypertrophy and contractile dysfunction even without dependence on its enzymatic activity under a high-fat diet, indicating that the structural function of HDAC3—rather than catalytic activity—is critical for maintaining normal cardiac function [35]. These findings suggest that distinct HDAC subtypes exhibit fundamental differences in their mechanisms of action during heart failure, necessitating subtype-specific considerations in targeted therapeutic strategies.

4.3 Mitochondrial Protein Acetylation Defects and Energy Crisis

Mitochondrial protein acetylation imbalance represents one of the core mechanisms underlying energy metabolism disorders in chronic heart failure (CHF). In the myocardium of patients with heart failure with preserved ejection fraction (HFpEF), Dlat mediates acetylation at the HADHA K728 site, leading to its inactivation and inhibition of fatty acid oxidation (FAO), which exacerbates lipid metabolism disturbances and cardiac energy supply insufficiency [3]. In type 2 diabetes model mice, downregulation of Sirt3 expression induces excessive mitochondrial protein acetylation, disrupts respiratory chain supercomplex assembly, increases reactive oxygen species (ROS) generation, and enhances susceptibility to myocardial ischemia/reperfusion injury [29]. However, nicotinamide ribosyl chloride supplementation can improve mitochondrial function, and this effect persists in SIRT3-deficient mice, suggesting that some benefits of NAD+ therapy may be independent of Sirt3-mediated deacetylation pathways [36]. These findings provide critical insights into the complexity of acetylation regulation and guide the development of therapeutic strategies.

4.4 Acetylation Regulatory Nodes in Pathological Cardiac Hypertrophy

The development of pathological myocardial hypertrophy is influenced by multiple acetylation regulatory nodes in a synergistic manner. HDAC6 regulates myosin proteins through deacetylation, thereby affecting myocardial passive stiffness; in mice lacking HDAC6, hypertensive or aging-induced diastolic dysfunction is exacerbated, indicating that HDAC6 exerts a protective role in myocardial structural remodeling [11]. NAT10-mediated RNA N4-acetylcytosine (ac4C) modification is upregulated during myocardial remodeling, promoting hypertrophic protein expression by enhancing mRNA stability and translation efficiency, and participating in myocardial hypertrophy and fibrosis processes; inhibition of NAT10 effectively alleviates cardiac dysfunction and inflammatory responses [37]. These findings reveal the critical role of multi-level acetylation regulatory networks at both protein and RNA levels in pathological myocardial hypertrophy.

In summary, acetylation imbalance in chronic heart failure involves multiple pathological aspects including mitochondrial energy metabolism, contractile function, myocardial hypertrophy, fibrosis,

and inflammation, with different HDAC subtypes playing distinct roles in these processes. Although targeted acetylation strategies represented by HDAC inhibitors have demonstrated potential to improve cardiac function in preclinical models, limitations such as single-target mechanisms, off-target toxicity, and insufficient subtype selectivity have hindered clinical translation. This situation highlights the need for a therapeutic approach capable of multi-node, holistic intervention in acetylation network dysregulation. Traditional Chinese medicine compound formulations, with their multi-component and multi-target synergistic properties, possess potential advantages in modulating the aforementioned complex acetylation regulatory networks. Recent studies have begun to reveal the direct regulatory effects of their active components on the acetyltransferase system.

5. Therapeutic Strategies of Traditional Chinese Medicine Intervention on Protein Acetylation

5.1 Regulation of Acetylation Regulatory Enzymes by Monomers of Traditional Chinese Medicine

Current studies have demonstrated that certain active monomers derived from traditional Chinese medicines can directly regulate the activity of acetylation-related enzymes. Ginsenoside Rb2 directly inhibits the activity of acetyltransferase p300, reduces the acetylation level of splicing factor SF3A2 at the K10 site, promotes alternative splicing of mitochondrial function-related genes and Fscn1 expression, ultimately improving mitochondrial respiratory function in cardiomyocytes and exhibiting significant cardioprotective effects in ischemic myocardial injury models [38]. Additionally, the exogenous HDAC inhibitor SAHA increases the acetylation level of histone H3 in the promoter region of flavonoid synthesis-related genes in licorice, promoting flavonoid accumulation, suggesting that the biosynthesis of active components in traditional Chinese medicines is itself subject to epigenetic regulation by acetylation modifications [39]. Furthermore, ligustrazine reduces biomarkers of myocardial injury and alleviates histopathological damage by enhancing the deacetylase activity of Sirt1, while inhibiting ventricular remodeling in myocardial infarction mouse models [40]. These findings provide preliminary molecular evidence for the role of traditional Chinese medicine monomers as acetylation regulators.

5.2 Synergistic Potential between Wenyang Yiqi Treatment Principle and Compound Multi-Target Regulation of Acetylation Networks

The core therapeutic principle of Traditional Chinese Medicine (TCM) for chronic heart failure (CHF), "warming yang and replenishing qi," corresponds to a pathophysiological state that exhibits high consistency with the aforementioned core pathological features of mitochondrial energy dysfunction, myocardial fibrosis, and inflammatory activation, as well as the imbalance in acetylation. In patients with heart failure with preserved ejection fraction (HFpEF), excessive acetylation of mitochondrial proteins leads to the inactivation of the HADHA K728 site, resulting in myocardial lipid metabolism disorders and energy disturbances [3]. "Yang-warming" drugs often possess effects of enhancing mitochondrial function and increasing ATP production, which may correct abnormal acetylation states by regulating the acetyl-CoA/NAD^+ ratio or influencing deacetylase activity. For example, Tongmai Yangxin Decoction exerts anti-cardiac hypertrophy effects by upregulating the expression of Sirt3 deacetylase [41]. This therapeutic principle's intrinsic connection with acetylation metabolism provides a novel epigenetic perspective for elucidating the mechanisms of TCM action.

Unlike HDAC inhibitors that typically target a single subtype, the multi-component nature of

traditional Chinese medicine formulations endows them with structural advantages to simultaneously influence multiple pathways including HATs, HDACs/Sirtuins, and acetyl-CoA metabolism. Taking the direct inhibitory effect of ginsenoside Rb2 on p300 [38] as an example, a single component can already modulate HAT activity. Meanwhile, butyrate, as a natural HDAC inhibitor, restores macrophage function by increasing H3K27ac levels during diabetic wound repair [42], suggesting that natural-derived components can intervene in the acetylation balance through "erasing" mechanisms. Compound formulations integrating multiple such active components theoretically enable synergistic regulation of the acetylation "writing-erasing" system. Notably, NAD+ supplementation improves certain effects in heart failure independently of the SIRT3-mediated deacetylation pathway [36], indicating that acetylation regulation involves Sirtuin-independent mechanisms. The multi-target profile of compound formulations precisely holds the potential to address this complexity.

However, there is currently a lack of systematic studies on compound regulation acetylation omics. The hypothesis that the "warming yang and replenishing qi" therapeutic principle exerts cardioprotective effects through acetylation networks still requires further experimental validation. This gap represents both a limitation in current research and a critical breakthrough for future integrated traditional Chinese and Western medicine studies.

Current research on traditional Chinese medicine interventions targeting acetylation modifications remains at the stage of mechanism exploration, facing core bottlenecks such as systematic validation of direct targets for active ingredients, elucidation of compound synergistic mechanisms, and lack of molecular markers for individualized medication. Overcoming these challenges relies on the synergistic advancement of emerging technologies including spatiotemporal proteomics, multi-omics integration, and AI-assisted modeling.

6. Conclusion and Prospects

6.1 Spatiotemporal Analysis Techniques for Dynamic Acetylation Modifications

Current research on protein acetylation modifications predominantly relies on static omics analysis, which fails to accurately reflect the dynamic regulatory characteristics of these modifications in cardiomyocytes across time and space. Emerging technologies are breaking through this bottleneck: AceTAG enables selective, tunable, and dynamic acetylation at specific protein sites in living cells through chemical induction of proximity principles, with its applicability validated in proteins such as histone H3.3, p65/RelA, and p53 [4]. Ketolysine (KeK), as a stable analog of acetylated lysine, allows site-specific incorporation in cells and can more stably mimic the biological effects of protein acetylation due to its resistance to deacetylase degradation [43]. Future efforts should focus on developing high spatiotemporal resolution imaging and detection technologies, combined with single-cell acetylamomics and in situ labeling strategies, to elucidate the dynamic evolution patterns of acetylation modifications across different subcellular structures during chronic heart failure (CHF).

6.2 Precision Regulation Strategies for Integrated Traditional Chinese and Western Medicine Treatment

Traditional Chinese Medicine (TCM) demonstrates unique advantages in the treatment of chronic heart failure (CHF). Qili Qiangxin Capsule (QLQX) significantly reduces cardiovascular mortality or hospitalization risk for heart failure with reduced ejection fraction (HFrEF) patients on standard therapy (HR=0.78,95% CI 0.68 – 0.90, P<0.001), with consistent efficacy across different left ventricular ejection fraction stratifications [44,45]. Ginsenoside Rb2 improves myocardial cell

respiratory function by directly inhibiting p300 acetyltransferase activity [38]. These findings suggest that individualized integrated TCM-Western medicine intervention strategies can be developed based on TCM's "syndrome differentiation and treatment" principles, combined with modern molecular subtypes (e.g., HDAC subtype expression profiles, mitochondrial acetylation status). Future prospective clinical trials are needed to clarify differential acetylation responses to specific herbal components among patients with different syndrome patterns, thereby advancing precision treatment strategies.

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