MEDS Chinese Medicine (2026)
Clausius Scientific Press, Canada

DOI: 10.23977/medcm.2026.080107
ISSN 2616-1753 Vol. 8 Num. 1

The Post-Translational Code of Myocardial Fibrosis: From Signaling Circuitry to Epigenetic Consolidation

Weijun Li[1,a], Zhixi Hu[1,b,*]

[1] *Hunan University of Chinese Medicine, Changsha, Hunan, 410208, China*
[a]*l010514334@163.com*, [b]*003405@hnucm.edu.cn*
**Corresponding author*

Keywords: Myocardial fibrosis; post-translational modifications (PTMs); transforming growth factor-β/Smad signaling pathway; lysine lactylation; cross-regulation and competitive interactions; metabolic-epigenetic axis; cardiac remodeling

Abstract: The onset and progression of heart failure (HF) are primarily driven by myocardial fibrosis (MF), a key pathological process. However, previous studies have largely focused on interventions targeting single signaling pathways, yielding limited clinical efficacy and highlighting the limitations of conventional therapies. Currently, the academic community is shifting its focus to "post-translational modifications"—deep regulatory mechanisms that transcend the genomic template—which are considered key factors contributing to the complexity and irreversibility of MF. This article first explores the mechanisms underlying MF signaling in a layered manner: centered on the TGF-β/Smad core axis, various signaling pathways—including MAPK, PI3K/AKT, and NF-κB—interact to form a highly integrated signaling network, rather than targeting a single pathway. Building on this foundation, we conduct an in-depth analysis of the critical role of site-specific post-translational modifications (PTMs) in this process. Phosphorylation, acetylation, ubiquitination, and the emerging lactylation (Kla) are no longer merely biochemical modifications; rather, they interact with one another to jointly determine protein function and fate. By analyzing synergistic or antagonistic interactions at key lysine residues (e.g., SERCA2a K480, α-MHC K1897), this study proposes the "metabolic epigenetic imprinting" model. This model provides a rational explanation for how "transient stress" is converted into permanent cardiac structural fibrosis through "biochemical imprinting." Finally, we summarize the shift from traditional drug therapy to precision PTM editing as a therapeutic approach and, based on the PTM profile, elucidate how to achieve better therapeutic outcomes, aiming to provide a substantial theoretical foundation for subsequent research on reversing cardiac remodeling.

1. Introduction

Heart failure (HF) is not a clinical event resulting from a single pathological change, but rather

an end-stage syndrome caused by multifaceted pathological alterations, the core feature of which is systemic tissue hypoperfusion resulting from impaired cardiac pumping function[1].Although over the past three decades, the “golden triangle” regimen—centered on neurohumoral inhibition (ACEIs/ARBs and beta-blockers) and metabolic modulation (SGLT2 inhibitors)—has significantly reduced patients’ hemodynamic burden[2].However, millions of patients worldwide are still hospitalized each year due to worsening symptoms, and the five-year mortality rate is as high as 50%[3,4].This discrepancy between clinical benefit and long-term prognosis suggests that current treatment strategies primarily focus on functional compensation while neglecting structural changes. Myocardial fibrosis (MF), as a key pathological milestone in the progression of heart failure (HF), involves programmed cell death of cardiomyocytes, abnormal activation of interstitial fibroblasts, and pathological remodeling of the extracellular matrix (ECM)[5].Once the myocardial fraction crosses the threshold of decompensation, increased ventricular wall stiffness and electrical conduction heterogeneity become irreversible pathological changes.

For a long time, MF has been simplified as excessive collagen deposition following the transdifferentiation of fibroblasts into myofibroblasts. However, the application of multi-omics technologies has revealed that MF undergoes highly dynamic changes in both spatial and temporal dimensions[6].In the spatial dimension, immune cells, endothelial cells, and fibroblasts form a complex network of interactions through paracrine pathways. In the temporal dimension, reparative fibrosis in the early stages of injury (which mitigates the risk of rupture) and pathological fibrosis in the later stages (which leads to functional failure) exhibit fundamental differences in their transcriptional programs. The molecular basis for this heterogeneity lies in how cells process complex signaling inputs. Although the transforming growth factor β (TGF-β) signaling axis is a key pathway in MF, clinical trials targeting only the ligand or receptor have largely failed. This suggests that, at a level above the transcriptional level, there exists a more refined and dynamic regulatory mechanism for integrating environmental stress.

In recent years, post-translational modifications (PTMs) have been recognized as a key link between environmental stress and cellular phenotypic remodeling. These enzymatic chemical modifications confer a complexity on the proteome that far exceeds that of the genome by altering protein conformational stability, subcellular localization, and molecular interaction properties[7,8]. PTMs serve not only as "switches" for signal transduction but also as the cell's "molecular memory" of pathological stimuli. The intensity of TGF-β signaling depends not only on its phosphorylation levels, but is also influenced by the degradation rate resulting from ubiquitination at specific sites, as well as the nuclear translocation efficiency regulated by acetylation[9,10].This multidimensional regulatory network, comprising phosphorylation, glycosylation, ubiquitination, acetylation, and lactylation, determines the balance or imbalance of ECM metabolism[11].Therefore, a thorough analysis of the regulatory mechanisms of PTMs in myocardial fibrosis is not only aimed at identifying new biomarkers but also at providing new avenues for targeted interventions in heart failure.

2. Myocardial Fibrosis: Signal Interaction Networks and Cardiac Remodeling

The nature of MF extends far beyond simple pathological accumulation of ECM; it represents systemic pathological changes occurring in the heart under stress. Epidemiological data reveal that fibrosis-related conditions are profoundly affecting approximately one-quarter of the global population, and the high mortality rate is primarily due to irreversible destruction of normal organ structure and functional failure[12-14].In the heart, MF is a hallmark terminal pathological manifestation of various cardiovascular diseases that have progressed to the decompensated stage[15].

Traditional models of single-pathway signaling are no longer sufficient to explain the complexity of MF formation. Whether induced by myocardial ischemia/reperfusion injury (MI/RI) or chronic stress overload, oxidative stress and inflammatory responses jointly remodel the cardiac microenvironment, thereby activating CFs[16,17].As the primary components of the ECM, the transdifferentiation of fibroblasts into myofibroblasts in response to environmental stimuli serves as the core driving force of the myofibroblastic process[18].The pathogenesis of MF does not rely on a single pathway but involves multiple signaling pathways, including TGF-β, PI3K/AKT, MAPK, and NF-κB[19].These pathways not only have the ability to reprogram normal fibroblasts into a fibrogenic phenotype or even cancer-associated fibroblasts (CAFs), but also induce HF by causing cardiac chamber dilation, myocardial hypertrophy, and apoptosis[20,21].From another perspective, these signaling pathways do not operate in a simple parallel manner but exhibit a distinct “logic gate” effect. In this model, the TGF-β/Smad pathway plays a central role in initiating fibrosis, while the PI3K/AKT and MAPK pathways serve as hubs and transducers, dynamically regulating the pulse frequency and duration of signaling in real time based on the cell’s metabolic state and the intensity of stress.

2.1 Core: TGF-B/Smad Pathway

As a central signaling pathway in MF, TGF-β1 converts extracellular stress signals into transcriptional reprogramming via the classical Smad pathway. Activated TGF-β family members bind to high-affinity receptors, triggering TGF-β receptor I (TβRI) to phosphorylate R-Smads (Smad2/3). The key site is the C-terminal SSXS sequence of Smad2/3; this phosphorylation event is a prerequisite for the recruitment of Smad4 to form a heterodimeric complex and facilitate nuclear translocation[22,23].This direct signaling is subject to complex regulation by PTMs. Studies have shown that inhibiting this pathway significantly reduces fibrosis, such as by disrupting the signaling loop through NUAK1 knockout[24,25].In addition, Smad proteins not only directly promote ECM production but also influence myofibroblast formation by regulating the epithelial-mesenchymal transition (EMT) mechanism[26].The negative feedback protein Smad7 acts as a threshold for regulating this pathway. Studies have shown that aloe-emodin activates the regulatory potential of this pathway by upregulating Smad7[27].In contrast, circPTEN1 physically blocks the binding of Smad4 to Smad2/3 by binding to the MH2 domain of Smad4, thereby inhibiting downstream fibrosis-related genes[28].Existing targeted strategies, such as Trabedersen (which inhibits mRNA) or SRK-181 (which targets the latent complex), essentially attempt to inhibit the activation of this core axis at its source[29-31].

2.2 Signal Transduction: MAPK (JNK/ERK) and NF-κB Pathways

The core function of this pathway lies in its ability to detect fluctuations in external physical stress and the inflammatory microenvironment in real time, thereby inducing cardiac remodeling through a dual “apoptosis-fibrosis” mechanism. Within the regulatory network governing MF formation, JNK signaling (JNK1/2/3) plays a critical role as a stress responder. Abnormal activation of JNK not only mediates massive cardiomyocyte apoptosis during MI/RI but also leads to pathological differentiation of cardiomyocytes through high-frequency oscillations of the JNK/c-Jun axis[32].During the late stages of CHF, the ferroptosis mechanism triggered by the JNK/p53 axis represents a critical turning point in the progression from stress overload to fibrosis[33].Unlike the stress feedback loop involving JNK, the ERK pathway regulates mitochondrial homeostasis and transcriptional activity through site-specific phosphorylation. Studies have shown that ERK1/2 specifically phosphorylates the mitochondrial protein Drp1 at Ser616, thereby impairing mitochondrial fission and releasing fibrogenic signals into the

cytoplasm[34, 35].At the same time, it regulates cardiac hypertrophy and ECM gene expression by modulating GATA4 phosphorylation[36].The NF-κB pathway is a key signaling pathway in the inflammatory microenvironment. When myocardial damage leads to the massive release of damage-associated molecular patterns (DAMPs), the TLR/NLRP3-NF-κB axis is rapidly activated, inducing a surge in the secretion of pro-inflammatory factors such as TNF-α[37].The underlying mechanism lies in the synergistic interaction between Wnt2/4 and β-catenin/NF-κB, which further permanently transforms transient acute inflammatory signals into chronic fibrotic scarring[38].

Given the strong synergistic interaction between members of the MAPK family and NF-κB, the development of multi-target intervention strategies offers significant advantages. Natural products such as tabersonine or apocynin, by precisely targeting and inhibiting TAK1 or ASK1, can simultaneously suppress the two key signaling pathways—JNK and NF-κB—thereby curbing the onset and progression of fibrosis at the systemic level[39, 40].

2.3 Key Pathway: PI3K/AKT Pathway

As a hub integrating growth factors and immune signals, the PI3K/AKT axis plays a dominant role in mediating the phenotypic evolution and metabolic remodeling of CFs. This phosphorylation event leads to the downstream phosphorylation (inactivation) of GSK3β (Ser9) and the phosphorylation (nuclear translocation) of FOXO1/3, thereby lifting the endogenous constraints on the cell's pro-fibrotic gene programs[41-43].The PI3K/AKT pathway does not operate in isolation but forms a tightly regulated network with the TGF-β/Smad and mTOR pathways. It has been demonstrated that the ERK/JNK pathway can lead to AKT-induced fibronectin synthesis, thereby forming a closed loop that promotes fibrosis[44].Furthermore, CRAMP or ginsenoside F2 demonstrates the pivotal role of this hub in multi-pathway repair by simultaneously regulating the PI3K/AKT and innate immune/antioxidant pathways[45, 46].The anti-fibrotic effects of SGLT2 inhibitors (such as dapagliflozin) in alleviating CHF are largely attributable to their inhibition of AKT-related signaling pathways[47].This reversal of pathological structural changes, achieved through improvements in metabolic homeostasis, profoundly reveals the central role of the PI3K/AKT axis in coordinating the transition of the heart from "abnormal energy expenditure" to "uncontrolled structural remodeling."

3. Molecular Rearrangements Induced by PTMs: From Transient Signal Switching to Epigenetic Imprinting

3.1 Kinetic Triggering: Phosphorylation-Mediated Signal Pulses and Calcium Transport Homeostasis

As the fastest and most precise PTMs within cells, phosphorylation confers instantaneous conformational dynamics on proteins by introducing a negative charge at serine/threonine/tyrosine (Ser/Thr/Tyr) residues. In the evolution of MF, this "phosphorylation pulse" serves not only as an initiator of signaling pathways but also as a regulatory hub for maintaining cardiac calcium homeostasis and electromechanical coupling[48, 49].

3.1.1 Site-Specific Regulation of Signaling Hubs: Logical Polarization of Smad and AKT

The regulation of fibrotic signaling by phosphorylation is not a simple "on/off" switch, but rather exhibits significant site-specific functional branches. This residue-specific polarization determines the ultimate phenotypic outcome of cardiac cells under stress. In CFs, TGF-β receptor-induced C-terminal (Ser423/425) phosphorylation of Smad3 serves as the "pass" for its translocation into

the nucleus and promotion of the fibrotic program[50].However, this process is strongly influenced by the modification status of its linker region (Ser204/208/213). Phosphorylation of the Smad3 linker region (Ser204/208/213) catalyzed by JNK or ERK exhibits distinctly different effects: it may either inhibit the nuclear translocation effect of C-terminal phosphorylation through steric hindrance, or recruit an E3 ligase to induce Smad degradation[51].This “site-specific antagonism” within the same protein acts as an endogenous rate-limiting factor for the intensity of fibrotic signaling. In CMs, AKT phosphorylation at Thr308 and Ser473 not only determines the fibroblast proliferative phenotype but also, by modulating the phosphorylation status of GSK3β (Ser9), lifts the endogenous repression of the pro-fibrotic transcription factor GATA4, thereby activating the transcription of pro-fibrotic genes[41, 42].Studies have demonstrated that blocking PI3K/Akt phosphorylation using osteopontin (OPN) aptamers can effectively inhibit pathological ECM deposition, providing a theoretical basis for achieving structural reversal by targeting specific phosphorylation sites[52].

3.1.2 "Dysfunction" of the Calcium Cycle Pump: From Phosphorylation Homeostasis to Heart Failure

The significant increase in myocardial stiffness observed in CHF is essentially due to a synergistic dysfunction of the calcium pump (SERCA2a) and the release channel (RyR2) caused by a phosphorylation imbalance, resulting in the heart losing its inherent biomechanical compliance[53-55].Under pathological stress conditions, abnormally high phosphorylation of RyR2 (Ser2808/Ser2814) by PKA or CaMKII significantly increases the channel’s open probability, thereby inducing arrhythmogenic spontaneous calcium leakage. Studies have shown that long-term administration of dantrolene can reverse this pathological phosphorylation, recalibrate calcium homeostasis, and effectively halt the progression of fibrosis[56, 57].At the same time, the phosphorylation levels of cardiac myosin-binding protein-C (cMyBP-C) are influenced by PP1/PP2A, which directly regulates the sliding velocity of myofilaments[55].When this phosphorylation homeostasis is disrupted in a CHF environment, ventricular diastolic compliance undergoes a precipitous decline. This deterioration in mechanical properties is not only a marker of functional impairment but also a key mechanical signal driving the transition of tissue toward pathological fibrosis.

3.2 Regulation of Stability: Steady-State Selection between Ubiquitination and SUMOylation at Lysine Sites

Within the complex post-translational regulatory network of proteins, lysine (Lys) residues, due to their unique chemical properties, have become the most functionally diverse and fiercely competitive hub of modifications. The dynamic regulation of ubiquitination and sumoylation at the same specific lysine site essentially constitutes a “life-or-death switch” that determines the fate of proteins. It antagonizes degradation signals by inducing subtle adjustments in protein conformation and creating physical steric hindrances, or by reshaping subcellular localization to maintain functional homeostasis[58-60].This modification-induced polarization at a single residue provides a precise molecular mechanism by which the heart rapidly adjusts its proteome homeostasis under pathological stress.

3.2.1 Ubiquitination-Mediated Loss: Ion Channel Rearrangement and Signal Termination

During the MF process, the regulation of structural proteins and signaling molecules by the ubiquitination system is the primary cause of reduced protein abundance and loss of function. By inducing ubiquitination at this site, it forcibly initiates the endocytic degradation pathway of the

channel, ultimately leading to a depletion of membrane surface expression and a pathological reduction in sodium current density[61].This modification-driven rearrangement of ion channels constitutes the molecular basis for the transition from physiological electrical activity to a malignant arrhythmia phenotype during ventricular remodeling. Furthermore, E3 ligases such as WWP2 and RNF207 exhibit bidirectional regulatory properties in the progression of MF. Studies have shown that specific deletion of WWP2 significantly downregulates PARP1 ubiquitination, thereby amplifying isoproterenol-induced myocardial hypertrophy and fibrogenic signaling by enhancing downstream PARylation modification[62, 63].Furthermore, the UCHL1-mediated deubiquitination process, through its interaction with the endoplasmic reticulum stress protein GRP78, provides an additional layer of degradation control for the regulation of fibrosis following myocardial infarction[64].

3.2.2 SUMO-Modified "Protective Barriers": Inhibiting Degradation and Enhancing Function

SUMOylation does not merely act as a passive antagonist to ubiquitination in molecular regulation; rather, through precise and efficient synergistic or competitive mechanisms, it confers superior structural stability and functional diversity on target proteins. As the driving force behind calcium cycling, SUMOylation at Lys480 and Lys585 in SERCA2a is a critical site for maintaining its structural integrity. This biochemical event significantly enhances protein stability, thereby improving calcium cycling function.In the pathological progression of CHF, the level of SUMOylation of SERCA2a is significantly downregulated; conversely, gene therapy to restore SUMO1 effectively counteracts pump failure induced by abnormal acetylation or ubiquitination, thereby promoting a pathological reversal of cardiac function at the molecular level[65, 66].In the signal transduction network of CFs, SUMOylation and phosphorylation exhibit synergistic effects. Studies have revealed that SUMOylation significantly enhances the extent of Smad2 phosphorylation and its transcriptional activity, exponentially amplifying the TGF-β-regulated pro-fibrotic signals[67].This "modulatory coupling" explains how, within a complex fibrotic microenvironment, fibrogenic signals overcome the constraints of endogenous degradation to maintain a sustained and highly active state.

4. Summary and Outlook

Over the past two decades, the core of CHF treatment has focused on reducing hemodynamic load and modulating the neurohumoral system. However, even with interventions using first-line medications such as ACEIs/ARBs and ARNIs, the progression of MF continues to exhibit a significant “stress escape” phenomenon. This study provides an in-depth analysis of the central role of post-translational modifications (PTMs) in this process, revealing that the essence of myocardial fibrosis is not the excessive activation of a single signaling pathway, but rather a multidimensional “protein functional remodeling.” We observed that site competition among phosphorylation, acetylation, and SUMOylation on individual proteins (such as SERCA2a or Smad3) constitutes a logical gatekeeper for cellular fate. Phosphorylation acts as a “transient switch” responsible for immediate stress responses, while methylation and lactylation function as “long-term memory” units that consolidate pathological stimuli into permanent tissue remodeling. This hierarchical regulatory logic explains why short-term interventions often fail to achieve long-term reversal of fibrosis.

Although PTMs hold promising therapeutic potential, their translation into clinical practice faces two major bottlenecks: “spatial heterogeneity” and “regulatory specificity.” Traditional kinase inhibitors or deacetylase agonists are often associated with broad-spectrum toxicity. We propose the

development of novel drugs based on PROTACs (Protein Degradation Targeting Assemblies) or LYTACs to achieve “surgical-like” interventions at the molecular level by precisely targeting pathological proteins in specific PTM states (e.g., acetylated SERCA2a). By integrating single-cell proteomics and modificationomics, we aim to establish serum/tissue PTM profiles for heart failure patients at different stages. This approach not only provides highly sensitive biomarkers for disease progression but also guides “subtype-stratified therapy” in clinical practice. The various natural products discussed in this article (such as puerarin and danphenolic acid) often exhibit characteristics of “multi-modification regulation.” This multi-target, soft-regulation model may be better suited to the robustness requirements of the complex cardiac system than single, potent inhibitors.

As the "ultimate interpretive layer" linking gene expression to phenotypic remodeling, the complexity of post-translational modifications (PTMs) underlies the adaptability of cardiac function and serves as the root cause of its pathological failure. In the future, through in-depth decoding of the PTM code, we hope to transition from "slowing disease progression" to "structural reversal" in the treatment of CHF, ushering in a new era of precision medicine for the heart.

References

[1] McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021. 42(36): 3599-3726.

[2] Greene SJ, Butler J, Fonarow GC. Contextualizing Risk Among Patients With Heart Failure. JAMA. 2021. 326(22): 2261-2262.

[3] Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. Circulation. 2021. 143(8): e254-e743.

[4] Taylor CJ, Ordóñez-Mena JM, Roalfe AK, et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. BMJ. 2019. 364: l223.

[5] Bacmeister L, Schwarzl M, Warnke S, et al. Inflammation and fibrosis in murine models of heart failure. BASIC RESEARCH IN CARDIOLOGY. 2019. 114(3).

[6] Ghazal R, Wang M, Liu D, Tschumperlin DJ, Pereira NL. Cardiac Fibrosis in the Multi-Omics Era: Implications for Heart Failure. Circ Res. 2025. 136(7): 773-802.

[7] Cui XK, Wang JX, Li K, Lv BS, Hou BK, Ding ZJ. Protein post-translational modifications in auxin signaling. Journal of Genetics and Genomics. 2024. 51(3): 279-291.

[8] Wethekam LC, Moore JK. Microtubule cytoskeleton: Revealing new readers of the tubulin code. Curr Biol. 2022. 32(18): R960-R962.

[9] Miao RR, Wang LB, Chen ZG, et al. Advances in the study of nicotinamide adenine dinucleotide phosphate oxidase in myocardial remodeling. Frontiers in Cardiovascular Medicine. 2022. 9.

[10] Wu D, Liu T. Studying Reversible Protein Post-translational Modification through Co-translational Modification. CHEMBIOCHEM. 2023 .

[11] Campbell SL, Philips MR. Post-translational modification of RAS proteins. Curr Opin Struct Biol. 2021. 71: 180-192.

[12] Zhao X, Kwan J, Yip K, Liu PP, Liu FF. Targeting metabolic dysregulation for fibrosis therapy. Nat Rev Drug Discov. 2020. 19(1): 57-75.

[13] Wu X, Yang Y. Neutrophil extracellular traps (NETs) and fibrotic diseases. Int Immunopharmacol. 2024. 133: 112085.

[14] Kania G, Lindner D, Zuppinger C. Editorial: Myocardial fibrosis: What we know now. Frontiers in Cardiovascular Medicine. 2023. 9.

[15] Chen TT, Xiao F, Li N, et al. Inflammasome as an Effective Platform for Fibrosis Therapy. J Inflamm Res. 2021. 14: 1575-1590.

[16] Frangogiannis NG. Cardiac fibrosis. Cardiovasc Res. 2021. 117(6): 1450-1488.

[17] Zhang YL, Li PB, Han X, Zhang B, Li HH. Blockage of Fibronectin 1 Ameliorates Myocardial Ischemia/Reperfusion Injury in Association with Activation of AMP-LKB1-AMPK Signaling Pathway. Oxid Med Cell Longev. 2022. 2022: 6196173.

[18] Zhang QJ, He Y, Li YN, Liao J, Zang QS, Liu ZP. Matricellular Protein Cilp1 Promotes Myocardial Fibrosis In Response To Myocardial Infarction. CIRCULATION RESEARCH. 2022. 131.

[19] Henderson NC, Rieder F, Wynn TA. Fibrosis: from mechanisms to medicines. Nature. 2020. 587(7835): 555-566.

[20] Buechler MB, Pradhan RN, Krishnamurty AT, et al. Cross-tissue organization of the fibroblast lineage. Nature. 2021. 593(7860): 575-579.
[21] Yoshida GJ. Regulation of heterogeneous cancer-associated fibroblasts: the molecular pathology of activated signaling pathways. J Exp Clin Cancer Res. 2020. 39(1): 112.
[22] Morikawa M, Derynck R, Miyazono K. TGF-β and the TGF-β Family: Context-Dependent Roles in Cell and Tissue Physiology. Cold Spring Harb Perspect Biol. 2016. 8(5): a021873.
[23] Peng D, Fu M, Wang M, Wei Y, Wei X. Targeting TGF-β signal transduction for fibrosis and cancer therapy. Mol Cancer. 2022. 21(1): 104.
[24] Modi SJ, Kulkarni VM. Discovery of VEGFR-2 inhibitors exerting significant anticancer activity against CD44+ and CD133+ cancer stem cells (CSCs): Reversal of TGF-β induced epithelial-mesenchymal transition (EMT) in hepatocellular carcinoma. Eur J Med Chem. 2020. 207: 112851.
[25] Zhang T, He X, Caldwell L, et al. NUAK1 promotes organ fibrosis via YAP and TGF-β/SMAD signaling. Sci Transl Med. 2022. 14(637): eaaz4028.
[26] Alyaseer A, de Lima M, Braga TT. The Role of NLRP3 Inflammasome Activation in the Epithelial to Mesenchymal Transition Process During the Fibrosis. Front Immunol. 2020. 11: 883.
[27] Yu J, Zhao X, Yan X, et al. Aloe-emodin ameliorated MI-induced cardiac remodeling in mice via inhibiting TGF-β/SMAD signaling via up-regulating SMAD7. Phytomedicine. 2023. 114: 154793.
[28] Zheng L, Liang H, Zhang Q, et al. circPTEN1, a circular RNA generated from PTEN, suppresses cancer progression through inhibition of TGF-β/Smad signaling. Mol Cancer. 2022. 21(1): 41.
[29] Deng Z, Fan T, Xiao C, et al. TGF-β signaling in health, disease, and therapeutics. Signal Transduct Target Ther. 2024. 9(1): 61.
[30] Martin CJ, Datta A, Littlefield C, et al. Selective inhibition of TGFβ1 activation overcomes primary resistance to checkpoint blockade therapy by altering tumor immune landscape. Sci Transl Med. 2020. 12(536): eaay8456.
[31] Cully M. TGF β1-specific antibody spurs anti-tumour immunity. Nat Rev Drug Discov. 2020. 19(5): 310.
[32] Singh R, Kaundal RK, Zhao B, Bouchareb R, Lebeche D. Resistin induces cardiac fibroblast-myofibroblast differentiation through JAK/STAT3 and JNK/c-Jun signaling. Pharmacol Res. 2021. 167: 105414.
[33] Wang J, Deng B, Liu Q, et al. Pyroptosis and ferroptosis induced by mixed lineage kinase 3 (MLK3) signaling in cardiomyocytes are essential for myocardial fibrosis in response to pressure overload. Cell Death Dis. 2020. 11(7): 574.
[34] Sun Z, Ji Z, Meng H, et al. Lactate facilitated mitochondrial fission-derived ROS to promote pulmonary fibrosis via ERK/DRP-1 signaling. J Transl Med. 2024. 22(1): 479.
[35] Chen W, Zhao H, Li Y. Mitochondrial dynamics in health and disease: mechanisms and potential targets. Signal Transduct Target Ther. 2023. 8(1): 333.
[36] Meng H, Du Z, Lu W, et al. Baoyuan decoction (BYD) attenuates cardiac hypertrophy through ANKRD1-ERK/GATA4 pathway in heart failure after acute myocardial infarction. Phytomedicine. 2021. 89: 153617.
[37] Suthahar N, Meijers WC, Silljé H, de Boer RA. From Inflammation to Fibrosis-Molecular and Cellular Mechanisms of Myocardial Tissue Remodelling and Perspectives on Differential Treatment Opportunities. Curr Heart Fail Rep. 2017. 14(4): 235-250.
[38] Yin C, Ye Z, Wu J, et al. Elevated Wnt2 and Wnt4 activate NF-κB signaling to promote cardiac fibrosis by cooperation of Fzd4/2 and LRP6 following myocardial infarction. EBioMedicine. 2021. 74: 103745.
[39] Dai C, Luo W, Chen Y, et al. Tabersonine attenuates Angiotensin II-induced cardiac remodeling and dysfunction through targeting TAK1 and inhibiting TAK1-mediated cardiac inflammation. Phytomedicine. 2022. 103: 154238.
[40] Ding W, Feng H, Li WJ, et al. Apocynin attenuates diabetic cardiomyopathy by suppressing ASK1-p38/JNK signaling. Eur J Pharmacol. 2021. 909: 174402.
[41] Huang J, Chen L, Wu J, et al. Targeting the PI3K/AKT/mTOR Signaling Pathway in the Treatment of Human Diseases: Current Status, Trends, and Solutions. J Med Chem. 2022. 65(24): 16033-16061.
[42] Qin W, Cao L, Massey IY. Role of PI3K/Akt signaling pathway in cardiac fibrosis. Mol Cell Biochem. 2021. 476(11): 4045-4059.
[43] Zhang T, Li L, Mo X, et al. Matairesinol blunts adverse cardiac remodeling and heart failure induced by pressure overload by regulating Prdx1 and PI3K/AKT/FOXO1 signaling. Phytomedicine. 2024. 135: 156054.
[44] Chen X, Zhang Z, Zhang X, et al. Paeonol attenuates heart failure induced by transverse aortic constriction via ERK1/2 signalling. Pharm Biol. 2022. 60(1): 562-569.
[45] Wang X, Chen L, Zhao X, et al. A cathelicidin-related antimicrobial peptide suppresses cardiac hypertrophy induced by pressure overload by regulating IGFR1/PI3K/AKT and TLR9/AMPK α. Cell Death Dis. 2020. 11(2): 96.
[46] Cui Y, Wu J, Wang Y, et al. Protective effects of ginsenoside F(2) on isoproterenol-induced myocardial infarction by activating the Nrf2/HO-1 and PI3K/Akt signaling pathways. Phytomedicine. 2024. 129: 155637.
[47] Alsereidi FR, Khashim Z, Marzook H, et al. Dapagliflozin mitigates cellular stress and inflammation through

PI3K/AKT pathway modulation in cardiomyocytes, aortic endothelial cells, and stem cell-derived β cells. Cardiovasc Diabetol. 2024. 23(1): 388.
[48] Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. NATURE REVIEWS MOLECULAR CELL BIOLOGY. 2012. 13(4): 251-262.
[49] Bilbrough T, Piemontese E, Seitz O. Dissecting the role of protein phosphorylation: a chemical biology toolbox. Chem Soc Rev. 2022. 51(13): 5691-5730.
[50] Li C, Meng X, Wang L, Dai X. Mechanism of action of non-coding RNAs and traditional Chinese medicine in myocardial fibrosis: Focus on the TGF-β/Smad signaling pathway. Front Pharmacol. 2023. 14: 1092148.
[51] Huang S, Chen B, Humeres C, Alex L, Hanna A, Frangogiannis NG. The role of Smad2 and Smad3 in regulating homeostatic functions of fibroblasts in vitro and in adult mice. Biochim Biophys Acta Mol Cell Res. 2020. 1867(7): 118703.
[52] Li JH, Yousefi K, Ding W, Singh J, Shehadeh LA. Osteopontin RNA aptamer can prevent and reverse pressure overload-induced heart failure. CARDIOVASCULAR RESEARCH. 2017. 113(6): 633-643.
[53] Traub J, Otto M, Monoranu CM, et al. Increasing Phosphorylated Tau Protein Serum Levels in the Course of Chronic Heart Failure. JACC Heart Fail. 2024. 12(8): 1494-1496.
[54] Pizzo E, Cervantes DO, Ketkar H, et al. Phosphorylation of cardiac sodium channel at Ser571 anticipates manifestations of the aging myopathy. Am J Physiol Heart Circ Physiol. 2024. 326(6): H1424-H1445.
[55] Kampourakis T, Ponnam S, Campbell KS, Wellette-Hunsucker A, Koch D. Cardiac myosin binding protein-C phosphorylation as a function of multiple protein kinase and phosphatase activities. Nat Commun. 2024. 15(1): 5111.
[56] Dobrev D, Wehrens XH. Role of RyR2 phosphorylation in heart failure and arrhythmias: Controversies around ryanodine receptor phosphorylation in cardiac disease. Circ Res. 2014. 114(8): 1311-1319.
[57] Schmeckpeper J, Kim K, George SA, et al. RyR2 inhibition with dantrolene is antiarrhythmic, prevents further pathological remodeling, and improves cardiac function in chronic ischemic heart disease. JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY. 2023. 181: 67-78.
[58] Sun M, Zhang X. Current methodologies in protein ubiquitination characterization: from ubiquitinated protein to ubiquitin chain architecture. Cell Biosci. 2022. 12(1): 126.
[59] Varejão N, Lascorz J, Li Y, Reverter D. Molecular mechanisms in SUMO conjugation. Biochem Soc Trans. 2020. 48(1): 123-135.
[60] Sheng Z, Zhu J, Deng YN, Gao S, Liang S. SUMOylation modification-mediated cell death. Open Biol. 2021. 11(7): 210050.
[61] Wright KM, Nathan S, Jiang H, et al. NEDD4L intramolecular interactions regulate its auto and substrate Na(V)1.5 ubiquitination. J Biol Chem. 2024. 300(3): 105715.
[62] Zhang N, Zhang Y, Qian H, Wu S, Cao L, Sun Y. Selective targeting of ubiquitination and degradation of PARP1 by E3 ubiquitin ligase WWP2 regulates isoproterenol-induced cardiac remodeling. Cell Death Differ. 2020. 27(9): 2605-2619.
[63] Yuan L, Bu S, Du M, et al. RNF207 exacerbates pathological cardiac hypertrophy via post-translational modification of TAB1. Cardiovasc Res. 2023. 119(1): 183-194.
[64] Lei Q, Yi T, Li H, et al. Ubiquitin C-terminal hydrolase L1 (UCHL1) regulates post-myocardial infarction cardiac fibrosis through glucose-regulated protein of 78 kDa (GRP78). Sci Rep. 2020. 10(1): 10604.
[65] Samuel TJ, Rosenberry RP, Lee S, Pan Z. Correcting Calcium Dysregulation in Chronic Heart Failure Using SERCA2a Gene Therapy. Int J Mol Sci. 2018. 19(4): 1086.
[66] Hu W, Xu T, Wu P, et al. Luteolin improves cardiac dysfunction in heart failure rats by regulating sarcoplasmic reticulum Ca(2+)-ATPase 2a. Sci Rep. 2017. 7: 41017.
[67] Su Q, Chen X, Ling X, et al. SUMOylation of Smad2 mediates TGF-β-regulated endothelial-mesenchymal transition. J Biol Chem. 2023. 299(10): 105244.