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Review

Recent Advances in The Molecular Regulation of Cardiac Hypertrophy Related to Heart Failure

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ABSTRACT: Cardiac hypertrophy is a prevalent adaptive response to hemodynamic and neurohormonal stress, but its persistence often leads to maladaptive remodeling and heart failure. This review integrates recent advances in the molecular regulation of hypertrophy, encompassing classical signaling cascades—including phosphoinositide 3-kinase (PI3K)–Ak strain transforming (Akt)–mammalian target of rapamycin (mTOR), mitogen-activated protein kinases (MAPKs), G protein-coupled receptors (GPCRs), AMP-activated protein kinase (AMPK), Hippopotamus–Yes-associated protein (Hippo–YAP), and Wingless-related integration site/Beta-catenin (Wnt/β-catenin) pathways—alongside metabolic reprogramming, epigenetic control, and organelle dynamics. Recent findings emphasize the role of transcriptional and post-transcriptional regulation, mitochondrial quality control, and post-translational modifications in modulating cardiomyocyte structure and function. One of the special focuses is on the gut–heart axis, emphasizing the emerging role of the gut microbiota as a pivotal systemic regulator of cardiac remodeling. While significant strides have been made in delineating the molecular underpinnings of cardiac hypertrophy, critical gaps remain in early detection, mechanistic specificity, and therapeutic translation. Moving forward, integrative, multi-omics approaches and improved experimental models will be essential to unravel the complexity of hypertrophic signaling networks. Based on the current evidence, a detailed understanding of the molecular regulation of cardiac hypertrophy may ultimately enable the development of targeted interventions to prevent or reverse pathological remodeling of cardiac hypertrophy related to heart failure.

Keywords: Cardiac hypertrophy, molecular signaling pathways, epigenetic regulation, metabolic remodeling, gut–heart axis

1. Introduction

Cardiac hypertrophy and heart failure represent two closely interlinked pathological stages within the progression of cardiovascular disease [1-3]. Hypertrophy initially develops as a compensatory mechanism in response to elevated hemodynamic stress, allowing the heart to preserve output by increasing cardiomyocyte size and ventricular wall thickness [4, 5]. However, when the stress persists, this adaptive remodeling becomes maladaptive, disrupting myocardial architecture and impairing function, ultimately leading to heart failure [2]. Understanding the molecular and cellular mechanisms that govern this transition is crucial for identifying intervention points that could delay or prevent disease progression [6].

In contrast, pathological hypertrophy arises due to chronic hemodynamic overload and can be further classified based on the nature of the load. Conditions involving pressure overload, including systemic hypertension and aortic stenosis, typically result in concentric hypertrophy, characterized by wall thickening

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with preserved chamber size [7]. In comparison, volume overload, as observed in mitral or aortic valve regurgitation, leads to eccentric hypertrophy, featuring chamber dilation along with wall thickening. Initially, the hypertrophied heart compensates through mechanisms including sarcomere assembly and activation of neurohormonal pathways involving catecholamines and components of the renin–angiotensin–aldosterone system [8]. Over time, however, sustained overload leads to maladaptive changes such as mitochondrial dysfunction, metabolic reprogramming from fatty acid oxidation to glycolysis, impaired calcium handling, fibrotic remodeling, and reduced microvascular density [9-11]. Molecular hallmarks of this transition include the reactivation of fetal genes—such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and β-myosin heavy chain (β-MHC)—as well as pathological phosphorylation of calcium-handling proteins like ryanodine receptor 2 (RyR2) [12, 13].

At the molecular level, several signaling pathways contribute to the hypertrophic response. Mechanical stress activates the integrin–focal adhesion kinase (FAK)–PI3K/Akt/mTOR axis, which promotes protein synthesis and cardiomyocyte growth. Chronic stimulation of this axis has been shown to suppress autophagy and induce proteotoxic stress, thereby representing a potential therapeutic target. Another pivotal pathway is the calcium–calcineurin–nuclear factor of activated T-cells (NFAT) cascade, which regulates both hypertrophic and inflammatory responses [14]. Modulation of this pathway may allow for selective attenuation of maladaptive gene expression without broadly affecting immune function [15]. Epigenetic regulation also plays a key role. For example, nuclear export of histone deacetylases (HDAC4 and HDAC5) permits activation of myocyte enhancer factor 2 (MEF2), highlighting potential roles for HDAC inhibitors in preventing transcriptional reprogramming [16]. MicroRNAs, including miR-133 and members of the miR-195 family, negatively regulate hypertrophy and represent promising candidates for targeted molecular therapies.

Organelle-level dysfunction further amplifies pathological remodeling. Mitochondrial imbalance—manifesting as altered fission and fusion dynamics, impaired mitophagy, ATP deficiency, and excessive reactive oxygen species (ROS) generation—disrupts cardiac energy homeostasis and promotes cellular injury [17]. Strategies to correct mitochondrial dysfunction, such as targeting fission/fusion proteins such as Dynamin-related protein 1 (DRP1) and Optic atrophy 1 (OPA1), enhancing PINK1–Parkin-mediated mitophagy, or restoring sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) function, have demonstrated cardioprotective effects in preclinical studies [18-20]. Concurrently, maladaptive extracellular matrix remodeling *via* transforming growth factor-β (TGF-β) signaling and insufficient angiogenesis contribute to progressive fibrosis and ischemia, suggesting additional avenues for intervention.

In parallel, post-translational modifications (PTMs) have emerged as critical modulators of the hypertrophic response [21]. These chemical alterations allow proteins to dynamically respond to cellular stress, extending regulatory capacity beyond the genome. Lysine acylations—including acetylation, succinylation, malonylation, and crotonylation—have drawn attention for their dual roles in transcriptional and mitochondrial regulation. Lysine acetylation, governed by histone acetyltransferases such as E1A binding protein p300/CREB binding protein (EP300/CBP) and deacetylases like SIRT1 and SIRT3, influences both nuclear transcription factors and mitochondrial enzymes. For instance, acetylation of GATA binding protein 4 (GATA4) and MEF2 enhances the expression of hypertrophic genes, whereas SIRT3-mediated deacetylation of enzymes such as succinate dehydrogenase A (SDHA) and isocitrate dehydrogenase 2 (IDH2) supports oxidative phosphorylation and mitigates oxidative stress. Similarly, succinylation and malonylation—derived from intermediates of the tricarboxylic acid cycle—have been implicated in respiratory chain dysfunction and elevated ROS production [22]. Although crotonylation remains less studied, emerging evidence suggests it may modulate chromatin accessibility and influence anti-hypertrophic gene expression [21]. These findings position PTMs as both sensors and effectors of metabolic and stress signaling, offering new possibilities for therapeutic targeting.

Beyond intracellular processes, recent research has underscored the systemic regulatory role of the gut microbiota in cardiovascular pathology, including cardiac hypertrophy [23]. The gastrointestinal tract hosts a complex microbial ecosystem that contributes to nutrient metabolism, immune modulation, and the production of bioactive metabolites. Alterations in gut microbial composition, termed dysbiosis, can compromise intestinal barrier integrity and facilitate the translocation of bacterial components such as lipopolysaccharide (LPS) into systemic circulation. This initiates chronic low-grade inflammation and promotes pathological myocardial remodeling through cytokine signaling, oxidative stress, and immune cell activation [24]. Animal models of cardiac hypertrophy and heart failure frequently exhibit increased gut permeability and elevated circulating LPS levels, which precede detectable cardiac dysfunction.

The emerging framework of the "gut–heart axis" describes a bidirectional relationship in which cardiac

dysfunction impairs intestinal perfusion and promotes dysbiosis, while microbial metabolites and inflammatory mediators feed back to influence myocardial structure and function. Among these metabolites, trimethylamine N-oxide (TMAO), produced from dietary choline and carnitine by gut bacteria, has been shown to activate profibrotic signaling pathways, including nuclear factor kappa B (NF-κB) and MAPKs, thereby exacerbating cardiac hypertrophy [25]. By contrast, short-chain fatty acids (*SCFAs*) such as butyrate and propionate appear to have protective effects by modulating immune responses and preserving vascular function, although their roles may vary depending on the disease context [26, 27]. The modulation of host tryptophan metabolism through the kynurenine pathway further adds to the complexity of gut-mediated effects on cardiac pathology.

These multilayered insights—ranging from intracellular signaling and post-translational regulation to systemic influences of the gut microbiota—underscore the complexity of cardiac hypertrophy as a disease process. A comprehensive understanding of how these mechanisms interact to govern the transition from adaptive remodeling to decompensated heart failure is essential. In the following sections, we will systematically review recent advances in molecular and metabolic regulation, highlight emerging therapeutic targets, and explore how integrating epigenetic and microbiota-based strategies may open new avenues for precise and effective intervention in cardiac hypertrophy and its progress.

2. Molecular Basis of Cardiac Hypertrophy

2.1 Molecular Pathways in Physiological and Pathological Hypertrophy

Cardiac hypertrophy is a complex adaptive response to mechanical or neurohumoral stimuli. While physiological hypertrophy, as seen in athletes or during pregnancy, is typically adaptive and reversible, pathological hypertrophy—induced by conditions such as hypertension, valvular disease, or myocardial infarction—is often maladaptive and associated with cardiac dysfunction and increased risk of heart failure. These phenotypic differences are underpinned by distinct molecular pathways.

2.1.1 Cardiomyocyte Hypertrophic Programming and Gene Regulation

In both forms of hypertrophy, increased protein synthesis and sarcomere remodeling are critical features. However, the underlying transcriptional regulation differs markedly. Physiological hypertrophy is primarily governed by the PI3K-Akt-mTOR pathway, promoting coordinated cell growth without fibrosis or contractile dysfunction [28, 29].

In contrast, pathological hypertrophy is characterized by reactivation of the fetal gene program, which includes the upregulation of Myosin heavy chain 7 (MYH7, β-myosin heavy chain), Natriuretic peptide A (NPPA, atrial natriuretic peptide), and Natriuretic peptide B (NPPB, brain natriuretic peptide), alongside downregulation of adult isoforms such as MYH6 and ATP2A2 (SERCA2a) [30]. This switch is considered a hallmark of maladaptive remodeling.

Epigenetic mechanisms play a key role in the reprogramming of this gene. For instance, chromatin remodeling complexes like SWI/SNF, and histone modifiers, have been shown to interact at promoters of fetal genes such as MYH7, NPPA, and NPPB in pressure-overload models, promoting their transcriptional reactivation [30]. Moreover, suppression of HDAC activity via inhibitors like Trichostatin A (TSA) can reverse fetal gene activation and reduce cardiomyocyte hypertrophy, indicating a potential therapeutic avenue.

2.1.2 Structural Reorganization and Calcium Homeostasis in Cardiomyocytes

In pathological hypertrophy, the architecture of cardiomyocytes is significantly altered, including disorganized sarcomeres and disrupted cytoskeletal integrity. Proteins such as α-actinin, desmin, and titin may become misaligned or cleaved, contributing to contractile dysfunction.

A key feature is the dysregulation of calcium-handling proteins. The expression and function of SERCA2a (sarcoplasmic reticulum Ca^{2+}-ATPase) are significantly reduced, while phospholamban (PLN)—a negative regulator of SERCA2a—is often hyperphosphorylated or aberrantly expressed [31, 32]. These changes impair calcium reuptake into the sarcoplasmic reticulum, prolonging cytosolic calcium transients and contributing to impaired relaxation (diastolic dysfunction) and arrhythmogenesis.

Additionally, the calcineurin-NFAT signaling pathway is activated in pathological hypertrophy, promoting the transcription of hypertrophic genes via nuclear translocation of NFAT [14]. Interactions between nuclear signaling and chromatin modifiers further exacerbate maladaptive transcriptional changes [30].

In contrast, physiological hypertrophy preserves normal calcium cycling and contractility. SERCA2a levels are maintained or even upregulated, and no significant reactivation of fetal genes is observed [28]. The structural remodeling in physiological hypertrophy involves symmetric cardiomyocyte enlargement with preserved sarcomere alignment and no significant

fibrosis. Figure 1 describes the molecular pathways in physiological and pathological hypertrophy (Fig. 1).

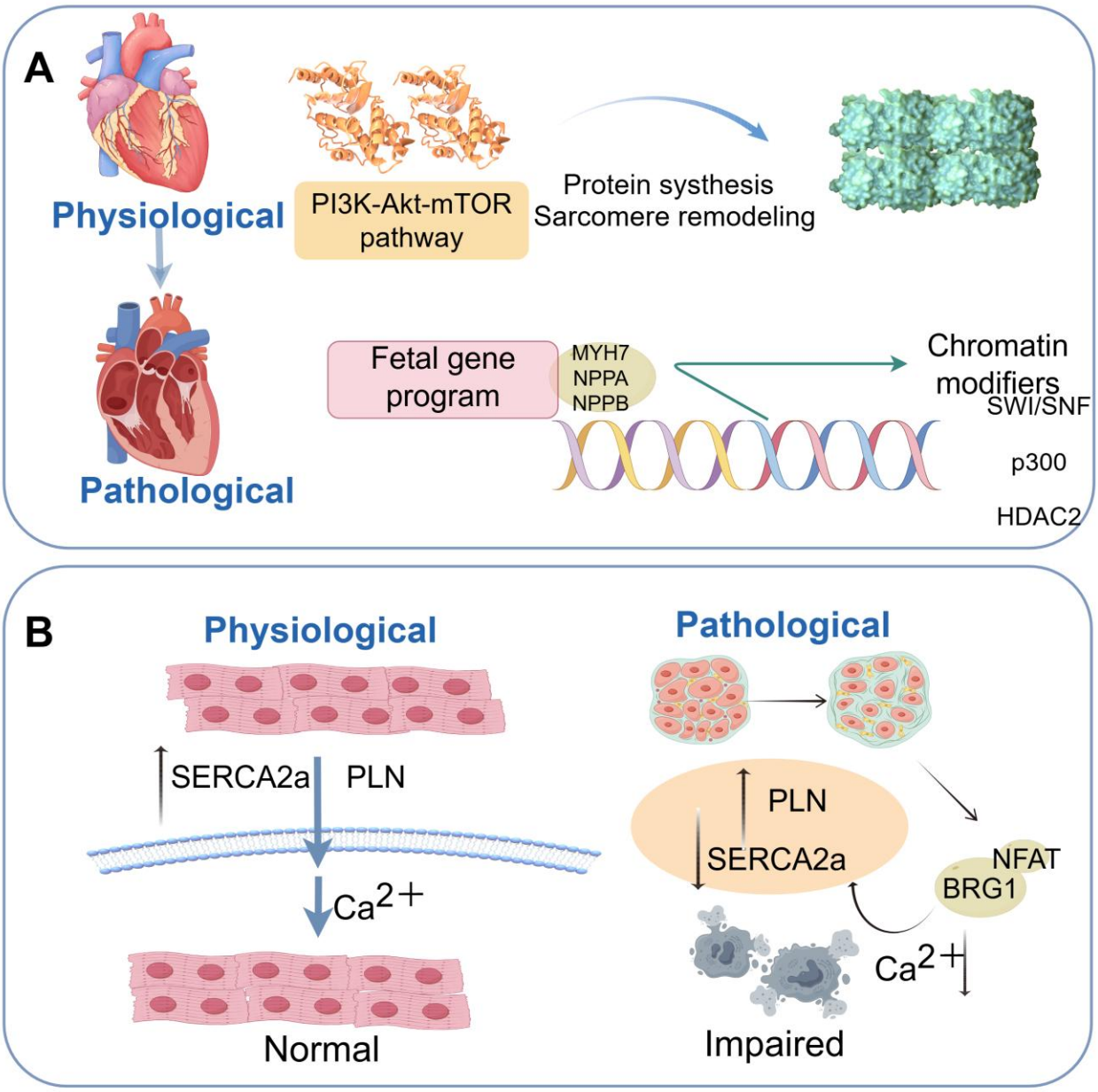

Figure 1. Molecular pathways in physiological and pathological hypertrophy. (A) Cardiomyocyte hypertrophy programming and gene regulation; **(B)** Structural reorganization and calcium homeostasis in cardiomyocytes.

2.2 Mechanistic Basis of Pathological Cardiac Remodeling

2.2.1 Sarcomere Disarray and Mechanotransduction

In maladaptive hypertrophy, sarcomere dysfunction extends beyond the general disorganization described in Section 2.1. Increasing evidence indicates that impaired mechanotransduction plays a central role. Mechanical stretch normally activates integrin-linked kinases and FAK, which coordinate sarcomere assembly and cytoskeletal tension. Dysregulation of these pathways disrupts Z-disc integrity and sustains the expression of fetal sarcomeric genes such as MYH7 (β-MHC), thereby exacerbating contractile inefficiency [30, 33].

2.2.2 Fine-Tuned Calcium Cycling Regulation

Altered calcium handling is a defining feature of pathological hypertrophy. In addition to the reduction of SERCA2a expression and imbalance in the

SERCA2a/PLN ratio outlined in Section 2.1, post-translational modifications of PLN provide an additional level of regulation. Phosphorylation of PLN at Ser16 by PKA or Thr17 by CaMKII alleviates its inhibitory effect on SERCA2a, whereas insufficient phosphorylation in hypertrophic hearts results in persistent SERCA2a suppression. This defect prolongs cytosolic calcium transients, delays relaxation, and predisposes to arrhythmias. Therapeutic approaches aimed at restoring calcium homeostasis, including AAV-mediated SERCA2a gene transfer and PLN-targeted inhibitory peptides, have shown promising results in preclinical studies, improving diastolic function and limiting maladaptive remodeling [34].

2.2.3 Epigenetic Intersection with Calcineurin–NFAT Signaling

The calcineurin–NFAT signaling axis, a well-established driver of hypertrophic gene reprogramming, also engages in extensive crosstalk with epigenetic regulators. Pathological stimuli trigger intracellular Ca^{2+} influx and activate calmodulin, which in turn stimulates the calcineurin–NFAT signaling cascade. Activated calcineurin dephosphorylates NFAT, promoting its nuclear translocation and interaction with MEF2 and GATA4 to induce the expression of hypertrophic genes such as ANP, BNP, and MYH7. Under stress conditions, elevated HDAC activity, accompanied by reduced histone acetyltransferase (HAT) function, results in histone deacetylation and chromatin condensation, thereby reshaping the epigenetic landscape. These changes facilitate the activation of fibrosis-related genes and act synergistically with NFAT-driven hypertrophic transcription to accelerate maladaptive cardiac remodeling. Class IIa HDACs, including HDAC4 and HDAC5, further modulate this process by suppressing MEF2 activity under basal conditions; upon hypertrophic stimulation, their nuclear export relieves repression and enhances MEF2-dependent gene transcription. Collectively, this coordinated regulatory network underscores the integration of calcium-dependent signaling and chromatin remodeling in coupling stress-induced transcriptional reprogramming with the structural and functional deterioration of the myocardium (Fig. 2) [30, 35].

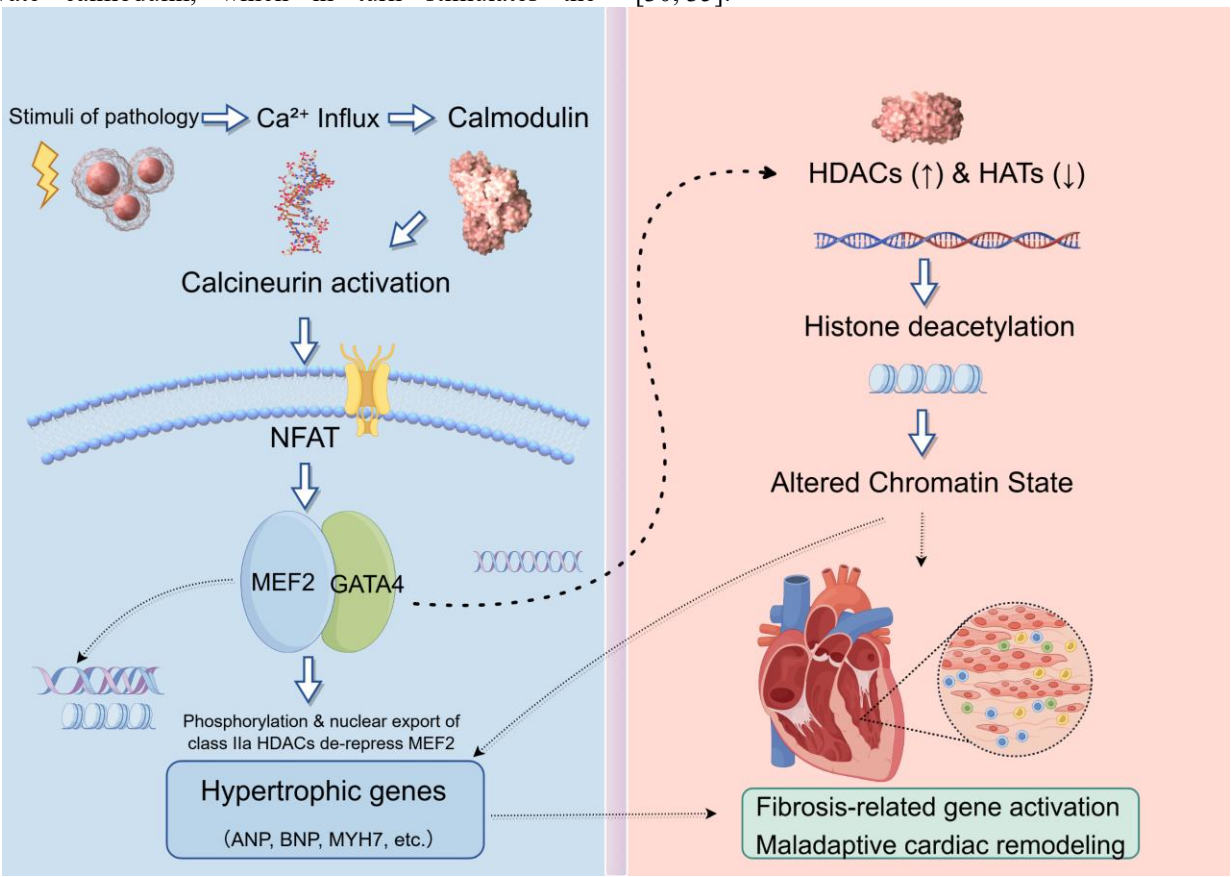

Figure 2. Calcineurin–NFAT and HDACs in cardiac hypertrophy: Pathological Ca^{2+} influx activates calcineurin, leading to NFAT dephosphorylation and nuclear translocation. NFAT cooperates with MEF2 and GATA4 to induce hypertrophic genes (ANP, BNP, MYH7). Simultaneously, increased HDAC activity and decreased HAT function promote histone deacetylation and chromatin condensation, facilitating fibrosis-related gene expression.

2.3 Canonical Signaling Pathways

2.3.1 PI3K–AKT–mTOR Axis

The PI3K–AKT–mTOR signaling axis plays a key role in physiological cardiac hypertrophy [36]. This pathway is typically activated by growth factors such as insulin-like growth factor-1 (IGF-1) or mechanical stimuli from exercise. Ligand binding to receptor tyrosine kinases recruits PI3K, which then generates phosphatidylinositol (3,4,5)-triphosphate, activating AKT. AKT subsequently phosphorylates various downstream targets, including glycogen synthase kinase-3β (GSK-3β) and the tuberous sclerosis complex 1/2 (TSC1/2), culminating in the activation of mTOR complex 1 (mTORC1) [37]. This cascade enhances protein synthesis through S6 kinase (S6K) and 4E-binding protein-1 (4E-BP1), thereby promoting cardiomyocyte growth while maintaining functional integrity [38].

Physiological hypertrophy via this pathway is generally reversible and non-fibrotic, with preserved or even enhanced cardiac function. In experimental models, constitutively active AKT increases cell size without impairing systolic performance, while inhibition of PI3K disrupts exercise-induced hypertrophic adaptation. Furthermore, this signaling axis supports mitochondrial biogenesis and oxidative metabolism through its interaction with Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and AMP-activated protein kinase (AMPK) pathways, ensuring energy supply meets increased cardiac demand. However, sustained or dysregulated PI3K–AKT–mTOR signaling can shift toward maladaptive remodeling. Chronic activation of mTORC1 suppresses autophagy, induces proteotoxic stress, and contributes to pathological hypertrophy [39]. Pharmacological inhibitors of mTOR, such as rapamycin, have demonstrated efficacy in reversing adverse remodeling in preclinical models [40]. Therefore, this pathway represents a double-edged sword: essential for adaptive growth under controlled activation, but pathogenic when chronically stimulated.

2.3.2 MAPK Signals

The MAPK family, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38, integrates multiple stress and growth cues in the regulation of cardiac hypertrophy. Each component plays a context-dependent role in either supporting physiological adaptation or promoting pathological remodeling. ERK1/2 is typically associated with adaptive hypertrophy, being activated through the Rat sarcoma virus- Rapidly accelerated fibrosarcoma-MAP kinase/ERK kinase (Ras–Raf–MEK) cascade. It supports cell survival and moderate hypertrophic growth via transcriptional regulation involving Elk-1 and GATA4 [41]. Moderate ERK activation enhances cardiomyocyte contractility and confers resistance to apoptosis during transient stress exposure. In contrast, JNK and p38 pathways are more commonly linked to stress-induced maladaptive remodeling. These kinases respond to stimuli such as mechanical overload, oxidative stress, and pro-inflammatory cytokines. Sustained activation leads to increased cell death, fibrosis, and contractile dysfunction, in part by modulating ATF-2 and NF-κB transcriptional programs [42].

Additionally, both JNK and p38 disrupt mitochondrial function and elevate ROS, contributing to energetic failure. Importantly, MAPK pathways exhibit extensive crosstalk with other signaling systems. ERK may synergize with PI3K–AKT to sustain adaptive growth, while JNK and p38 intersect with TGF-β pathways to drive fibrosis [43]. Although inhibitors targeting p38 or JNK show therapeutic promise in preclinical studies, translating these findings to clinical use is complicated by the ubiquitous roles of MAPKs in diverse physiological processes.

2.3.3 GPCR-Mediated Signals

GPCRs form a crucial signaling hub in neurohormonal regulation of pathological cardiac hypertrophy [44-46]. Principal ligands such as angiotensin II, endothelin-1, and catecholamines signal through Gq-coupled GPCRs, which activate phospholipase Cβ (PLCβ). PLCβ catalyzes the production of diacylglycerol (DAG) and inositol trisphosphate (IP3), initiating downstream signaling cascades involving protein kinase C (PKC) and calcium-dependent pathways. In animal models, targeting G protein-coupled receptors has been shown to reduce remodeling and delay the progression of heart failure [47, 48].

Moreover, GPCR signaling modulates other stress-responsive systems. PKC isoforms influence cytoskeletal remodeling, mitochondrial function, and extracellular matrix deposition. Excessive adrenergic stimulation can desensitize β-adrenergic receptors, further impairing contractile performance [1]. Additionally, Gq signaling amplifies TGF-β-mediated fibrosis and ROS production, reinforcing structural and oxidative damage.

Clinically, GPCR-targeted therapies such as ACE inhibitors, ARBs, and β-blockers have demonstrated robust benefits in managing hypertrophy and preventing heart failure. Newer strategies focus on downstream effectors like PKC or calcineurin to increase specificity and minimize systemic side effects [49].

2.3.4 AMPK Signals

AMPK is a master regulator of energy homeostasis and plays a protective role in the hypertrophied heart. It becomes activated in response to increases in the AMP/ATP ratio or via upstream kinases such as Liver kinase B1 (LKB1) during energetic stress. Once activated, AMPK shifts cellular metabolism towards energy production by enhancing catabolic processes and inhibiting energy-consuming anabolic pathways [50]. In cardiac cells, AMPK activation counters hypertrophy through several mechanisms. It inhibits mTORC1 activity, thereby reducing protein synthesis. It also stimulates autophagy and mitophagy, maintaining cellular quality control [51]. Furthermore, AMPK promotes glucose uptake and fatty acid oxidation, restoring metabolic balance in energy-deficient myocardium.

Pathological suppression of AMPK activity contributes to mitochondrial dysfunction, oxidative stress, and maladaptive remodeling [52]. Pharmacological AMPK activators such as metformin and Amino imidazole carboxamide ribonucleotide (AICAR) have shown potential in preclinical models by limiting hypertrophic progression and improving functional outcomes [53]. These findings suggest that AMPK acts as a metabolic checkpoint in cardiac hypertrophy, offering a promising target for therapeutic intervention.

2.3.5 Hippo–YAP Pathway

The Hippo–YAP pathway, initially identified in organ size control, has emerged as a key player in regulating cardiac growth and structural adaptation. Core components of this cascade include the Macrophage stimulating 1/2 (MST1/2) and large tumor suppressor 1/2 kinases (LATS1/2), which phosphorylate and inhibit the transcriptional co-activator Yes-associated protein (YAP). When Hippo signaling is suppressed, YAP translocates to the nucleus and promotes gene expression associated with cell growth and survival [54, 55].

In the heart, controlled YAP activity can support the survival and regenerative responses of cardiomyocyte. However, sustained or excessive YAP activation has been associated with maladaptive remodeling, including fibrosis, cellular disarray, and arrhythmias. Studies have shown that chronic nuclear localization of YAP in transgenic models induces dilated cardiomyopathy and functional decline [56].

The Hippo–YAP axis illustrates the need for context-dependent modulation. While transient activation may facilitate repair, chronic stimulation may drive disease [57]. Therapeutically, targeting this pathway requires careful tuning to enhance regenerative capacity while avoiding fibrotic transformation.

2.3.6 Wnt/β-Catenin Signals

The Wnt/β-catenin pathway, essential in embryonic heart development, is reactivated during pathological cardiac remodeling. Canonical Wnt signaling stabilizes β-catenin, allowing it to accumulate in the nucleus and initiate transcriptional programs that promote hypertrophic gene expression and extracellular matrix deposition [58]. In models of pressure overload, activation of this pathway has been linked to increased cardiomyocyte size, interstitial fibrosis, and re-expression of fetal cardiac genes. In contrast, inhibition of Wnt signaling has shown beneficial effects in reducing hypertrophy and improving cardiac function. Additionally, this pathway interacts with other pro-fibrotic mechanisms, such as TGF-β, amplifying adverse remodeling [59].

Interestingly, transient Wnt activation may also support cardiac regeneration, highlighting the dual role of this pathway. Ongoing studies are exploring pharmacological Wnt modulators, including porcupine inhibitors and agents targeting β-catenin, for potential therapeutic use [60, 61].

Taken together, these signaling pathways illustrate the multifaceted regulation of cardiac hypertrophy, involving not only growth and survival signals but also metabolic and stress response networks. While classical pathways such as PI3K–AKT–mTOR, MAPKs, and GPCRs remain central to the hypertrophic process, newer pathways like AMPK, Hippo–YAP, and Wnt/β-catenin add critical layers of regulatory complexity (Fig. 3). Understanding these mechanisms is essential for developing precise, context-sensitive interventions that can prevent or reverse pathological hypertrophy without disrupting physiological adaptation.

2.4 Transcriptional and Epigenetic Regulation

Cardiac hypertrophy is orchestrated not only by signaling cascades and metabolic shifts but also by finely tuned transcriptional and epigenetic regulation. These regulatory mechanisms dictate gene expression patterns underlying structural remodeling, sarcomere reorganization, and cellular stress adaptation. Key transcription factors, non-coding RNAs, and chromatin modifiers coordinate the activation of hypertrophic gene programs, particularly through the reactivation of fetal gene expression—a hallmark of pathological cardiac remodeling.

2.4.1 Transcription Factors

A core set of cardiac transcription factors mediates the hypertrophic gene response. GATA4, a zinc finger transcription factor, is activated by mechanical and

hormonal stimuli and drives expression of genes such as ANP and BNP. It interacts with other transcriptional regulators, including NKX2.5 and MEF2, to form synergistic complexes that enhance cardiac gene expression [62]. MEF2, particularly MEF2C and MEF2D isoforms, plays a central role in sarcomeric gene transcription and is activated by calcium-dependent signals through calcineurin and Ca^{2+}/calmodulin-dependent kinase (CaMK) pathways [63].

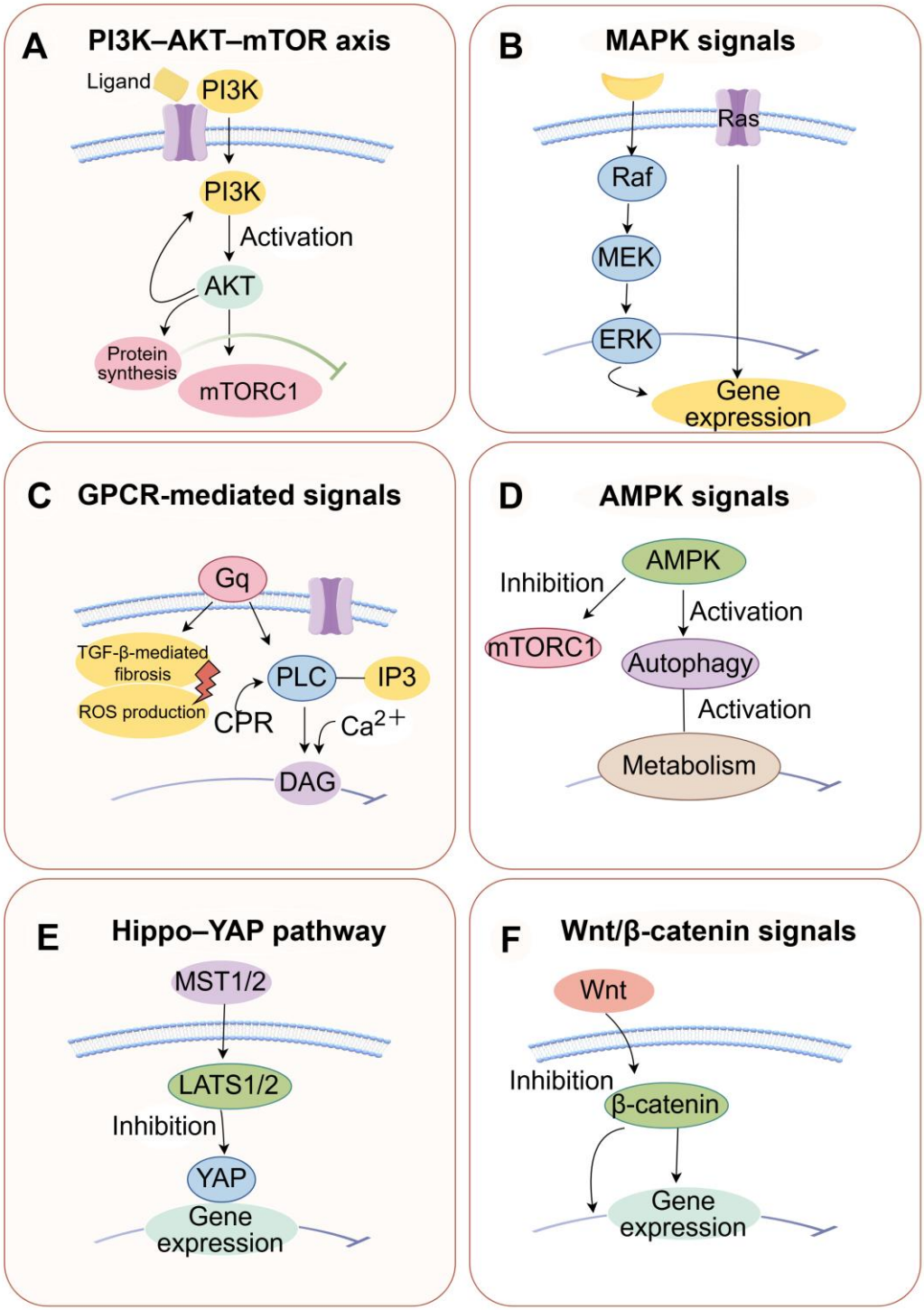

Figure 3 Canonical signaling pathways in cardiac hypertrophy. (A) PI3K–AKT–mTOR axis; **(B)** MAPK signals; **(C)** GPCR-mediated signals; **(D)** AMPK signals; **(E)** Hippo–YAP pathway; **(F)** Wnt/β-catenin signals.

2.4.2 Non-Coding RNAs

Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are pivotal post-transcriptional regulators in cardiac hypertrophy. miR-222 has been identified as a protective regulator during physiological hypertrophy, such as that induced by exercise, promoting cardiomyocyte survival and proliferation without triggering fibrosis [64]. Conversely, miR-21 is consistently upregulated in pathological hypertrophy and promotes fibrosis by targeting phosphatase and tensin homolog (PTEN) and modulating ERK-MAPK signaling.

miR-208a, encoded within the α-MHC gene, regulates the expression of β-MHC and is crucial for the switch to fetal gene expression in diseased hearts. Inhibition of miR-208a has been shown to attenuate hypertrophy and improve cardiac function in preclinical models [65]. LncRNAs such as cardiac hypertrophy–associated transcript (CHAST) and myosin heavy chain–associated RNA transcript (Mhrt) have also been implicated. CHAST promotes hypertrophic remodeling by repressing autophagy-related genes, while Mhrt antagonizes Brama-related gene 1 (Brg1), a chromatin remodeling factor that drives pathological gene expression [66, 67]. These findings underscore the complexity and specificity of non-coding RNA-mediated regulation in hypertrophy.

2.4.3 Epigenetic Modifiers

Epigenetic regulation, defined as heritable modifications to chromatin structure without changes to the DNA sequence, plays a central role in reactivating fetal gene programs during cardiac hypertrophy. Among histone-modifying enzymes, the methyltransferase enhancer of zeste homolog 2 (EZH2) catalyzes the addition of three methyl groups to histone H3 at lysine 27 (H3K27me3), generating a repressive chromatin mark that silences gene expression. Interestingly, EZH2 appears to exert dual context-dependent roles: it may initially suppress pro-hypertrophic gene activation, but in later stages, its activity promotes fibroblast proliferation and myocardial fibrosis [68, 69].

In parallel, DNA methylation changes accompany the hypertrophic process, as methylation at promoter regions of key cardiac genes influences their transcriptional stability and responsiveness to stress. Moreover, chromatin remodeling complexes, such as those containing Brg1 within the SWI/SNF family, reposition nucleosomes to regulate the accessibility of hypertrophy-related loci. Through these mechanisms, epigenetic modifiers dynamically shape the transcriptional landscape of the hypertrophied heart.

By integrating extracellular cues with nuclear transcriptional machinery, these regulatory systems serve as critical mediators between signaling and gene expression. Consequently, targeting epigenetic enzymes, such as histone methyltransferases, deacetylases, and chromatin remodelers, represents a promising precision strategy for reversing maladaptive cardiac remodeling by restoring balanced gene activity.

2.5 PTMs

PTMs serve as a critical regulatory layer that dynamically modulates protein conformation, enzymatic activity, interaction networks, and subcellular distribution [70] (Table 1). Among these, lysine acylations—including acetylation, malonylation, succinylation, crotonylation, and emerging modifications such as lactylation and β-hydroxybutyrylation—have garnered increasing attention for their pivotal roles in cardiovascular pathophysiology, particularly cardiac hypertrophy [21].

Lysine acetylation is the most extensively characterized form of acylation, modifying the ε-amino group of lysine residues on both histone and non-histone proteins [71]. In cardiomyocytes, acetylation homeostasis is maintained by the opposing actions of acetyltransferases such as EP300/CBP and deacetylases including members of the sirtuin family (SIRT1 and SIRT3). Disruption of this balance perturbs multiple hypertrophic signaling pathways. For example, EP300-mediated acetylation of GATA4 enhances its transcriptional activity, reactivating fetal gene expression and promoting pathological growth. In contrast, SIRT3 deacetylates mitochondrial enzymes such as IDH2 and PDH, thereby preserving oxidative phosphorylation, reducing reactive oxygen species (ROS) accumulation, and limiting maladaptive remodeling.

Beyond acetylation, other acylations—including succinylation and malonylation—originate from tricarboxylic acid (TCA) cycle intermediates, succinyl-CoA and malonyl-CoA, respectively [72]. These modifications introduce substantial structural and charge alterations to lysine residues. Succinylation of SDHA impairs complex II activity, elevates mitochondrial ROS production, and disrupts cellular bioenergetics, thereby amplifying stress responses [73]. Similarly, malonylation of metabolic enzymes such as Carnitine Palmitoyltransferase 1A (CPT1A) and Glyceraldehyde-3-phosphate Dehydrogenase (GAPDH) compromises fatty acid oxidation and glycolysis, particularly under diabetic or ischemic conditions.

Crotonylation, a more recently identified modification, has emerged as a chromatin mark associated with transcriptional activation. In the hypertrophic heart, reduced crotonylation at promoters of anti-hypertrophic

genes correlates with their repression, suggesting a role in energy-dependent transcriptional control. Cardiac overload or metabolic stress triggers a global increase in lysine acylation, influencing not only nuclear transcription factors but also metabolic enzymes such as ATP synthase, PDH, and CPT1A. These findings underscore the pivotal role of PTMs in coupling cellular energy state to structural remodeling [74].

Table 1. Summary of lysine acylation types, regulatory enzymes, roles in cardiac hypertrophy, representative inhibitors/modulators, translational implications, and references.

Acylation Type	Key Enzymes (Writers/Erasers)	Representative Inhibitors/Modulators	Function in cardiac hypertrophy	Translational Implications	Refs.
Acetylation	Writers: EP300/CBP, KAT2A Erasers: HDAC family, SIRT1–SRT7),	EP300 inhibitor C646; HDAC inhibitors; SIRT1 activators	Enhances GATA4 activity and fetal gene expression; SIRT3 protects mitochondria via deacetylation	HDAC inhibition and SIRT1 activation reduce pathological hypertrophy and fibrosis through epigenetic remodeling of hypertrophic genes.	[75, 76]
Succinylation	Writers: KAT2A, EP300 Erasers: SIRT5, SIRT7	SIRT5 activator (CPD12); EP300 inhibitor (C646)	Succinylation of SDHA impairs complex II, increases ROS (hypothesis supported in metabolic disorders, indirect cardiac link)	Regulation of succinylation restores mitochondrial redox balance and prevents maladaptive cardiac remodeling.	[21, 77]
Malonylation	Writers: EP300–CBP Erasers: SIRT5	SIRT5 activators (CPD12); Nicotinamide (vitamin B3)	Alters GAPDH/IDH2 activity; contributes to metabolic dysregulation (evidence in metabolic context)	Targeting malonylation via SIRT5 improves cardiac energetics and mitigates stress-induced metabolic inflexibility.	[21, 78]
Crotonylation	Writers: KAT2A, EP300/CBP Erasers: SIRT1–3, HDACs	HDAC inhibitors; SIRT1 activator (Resveratrol)	Linked to active gene transcription; potential role in stress responses	Epigenetic modulation of histone crotonylation may promote adaptive cardiac gene expression under stress.	[21, 79]
Lactylation	Writers: EP300, KAT7 Erasers: HDAC1–3	EP300 inhibitor A-485; HDAC inhibitor (Panobinostat)	Regulates stress-response genes under hypoxia; involved in cardiac remodeling	Targeting histone lactylation may modulate hypoxia-induced transcriptional programs and limit pathological hypertrophy.	[80, 81]
β-Hydroxybutyrylation	Writers: EP300/CBP Erasers: SIRT3, HDAC2	SIRT3 activators (Honokiol); HDAC inhibitors (SAHA)	Modifies histones; involved in diabetic cardiac stress via β-OHB pathway	SIRT3 activation attenuates β-OHB–driven histone modification and prevents diabetic cardiomyopathy.	[82]
Propionylation	Writers: KAT7, EP300 Erasers: SIRT1–3	SIRT1 activator (Resveratrol); EP300 inhibitor (C646)	Impacts SOD2 activity, may affect ROS homeostasis (no direct cardiac data yet)	May regulate ROS and improve redox homeostasis in hypertrophic myocardium.	[21, 83]
Myristoylation	Writers: NMT1, NMT2 Erasers: SIRT6, IpaJ	NMT inhibitor DDD85646; SIRT6 activator MDL-800	Affects calcium signaling and membrane targeting through MARCKS regulation	NMT inhibition may correct calcium dysregulation, and SIRT6 activation confers anti-hypertrophic effects.	[84, 85]

Importantly, acyl modifications are reversible, offering potential therapeutic opportunities. Pharmacological interventions—such as Nicotinamide Adenine Dinucleotide (NAD^+) precursors, sirtuin activators, or HDAC inhibitors—have shown promise in restoring mitochondrial function and normalizing cardiac architecture in experimental models. For instance, Trichostatin A (TSA) suppresses myocardial fibrosis and fetal gene re-expression, whereas SIRT3 activators enhance mitochondrial respiration and reduce infarct size following ischemic injury. Despite these advances, the cardiac "acylome"—the complete set of acylated proteins in the diseased myocardium—remains incompletely characterized. Recent proteomic profiling has revealed

novel lysine acylation sites on sarcomeric, cytoskeletal, and calcium-handling proteins, implicating these modifications in contractile regulation and mechano-transduction.

In summary, protein acylation represents an integrative molecular mechanism linking metabolic cues to gene expression and structural remodeling in cardiac hypertrophy (Fig. 4). Future study of mapping PTM networks and identifying acylation-specific biomarkers may open up a new way for accurate cardiology.

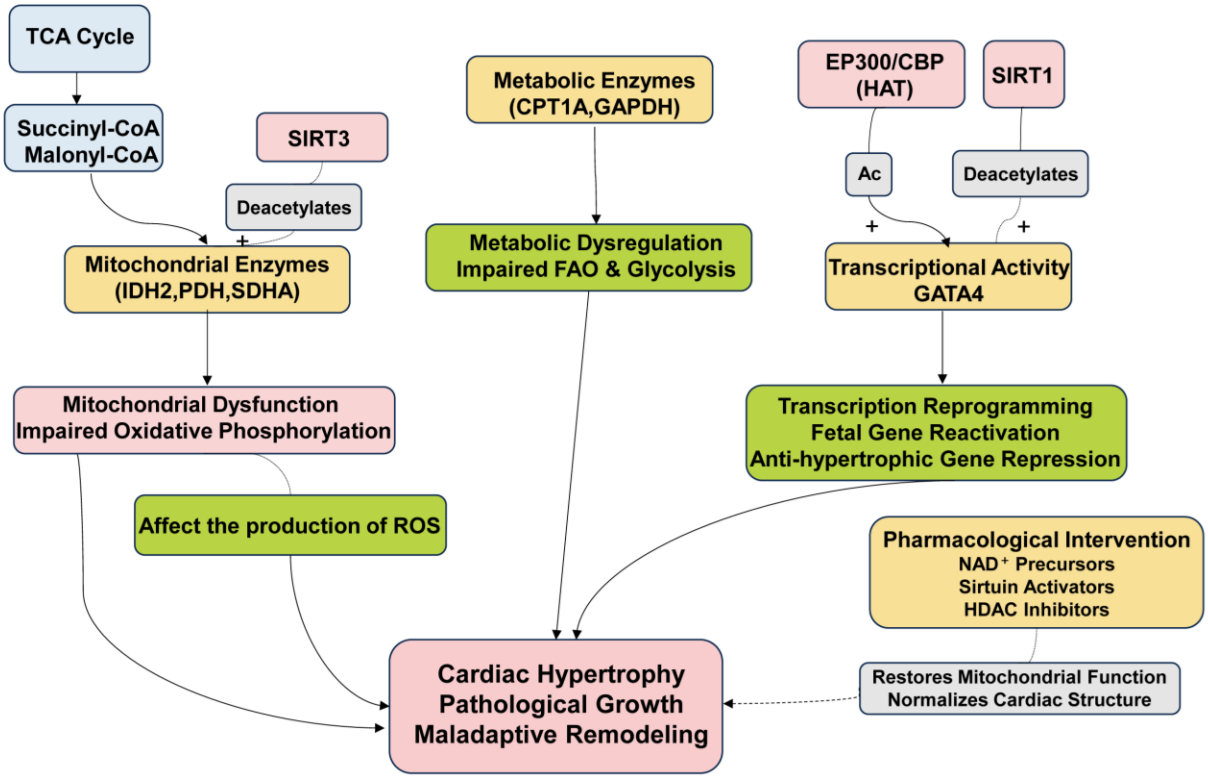

Figure 4. Post-translational modifications drive metabolic and transcriptional dysregulation in cardiac disease, revealing potential therapeutic targets.

3. Metabolic Remodeling and Signal Integration

Cardiac hypertrophy is tightly linked to metabolic remodeling, whereby energy production pathways are reprogrammed to meet altered bioenergetic demands [86]. This reorganization distinguishes physiological hypertrophy, which maintains or improves metabolic efficiency, from pathological hypertrophy, characterized by energy deficiency and mitochondrial dysfunction.

3.1 Substrate Utilization Reprogramming

In the healthy adult heart, fatty acid oxidation (FAO) supplies 60–70% of ATP, while glucose oxidation contributes the remainder. During physiological hypertrophy, such as that induced by exercise or pregnancy, metabolic flexibility is preserved or enhanced. Cardiomyocytes upregulate mitochondrial biogenesis and shift toward balanced utilization of glucose and fatty acids, optimizing ATP production. In contrast, pathological hypertrophy induces a maladaptive metabolic switch. FAO is downregulated, and glycolysis is upregulated, but mitochondrial glucose oxidation fails to match increased glycolytic flux, leading to accumulation of metabolic intermediates and reduced energy efficiency. Ketone bodies may also be increasingly utilized as alternative substrates in failing hearts, though their role in early hypertrophy remains under investigation [87]. This substrate reprogramming reflects an attempt to adapt to stress but ultimately contributes to energetic insufficiency.

3.2 Mitochondrial Function and Energetics

Mitochondria are central to cardiac bioenergetics and play a pivotal role in hypertrophic remodeling. PGC-1α is a master regulator of mitochondrial biogenesis and oxidative metabolism. In physiological hypertrophy,

PGC-1α expression is elevated, supporting increased mitochondrial capacity. However, in pathological states, downregulation of PGC-1α leads to impaired mitochondrial replication and function [88]. AMPK, an energy sensor activated under low ATP conditions, enhances mitochondrial biogenesis and autophagy, promoting metabolic homeostasis. Dysregulation of AMPK exacerbates mitochondrial dysfunction and contributes to hypertrophy progression. Mitochondrial dynamics—including fusion (mediated by OPA1, Mitofusin 1/2 (MFN1/2)) and fission (regulated by DRP1)—are essential for maintaining mitochondrial integrity [89, 90]. Imbalanced dynamics lead to fragmented or dysfunctional mitochondria, impairing energy production and increasing ROS.

3.3 Metabolite-Mediated Signals

Beyond their bioenergetic role, metabolic intermediates act as signaling molecules that regulate gene expression through epigenetic mechanisms. Acetyl-CoA serves as a substrate for histone acetylation, linking nutrient availability to chromatin remodeling and transcriptional activation of hypertrophic genes. NAD^+, a cofactor for sirtuins, modulates deacetylation of transcription factors and mitochondrial enzymes, affecting hypertrophic growth and oxidative stress. α-ketoglutarate (α-KG), a TCA cycle intermediate, regulates dioxygenase activity involved in DNA and histone demethylation, influencing gene expression in cardiac remodeling [91, 92]. Thus, metabolic rewiring not only reflects altered energy demands but also integrates with transcriptional programs to shape the hypertrophic phenotype.

4. Gut Microbiota–Heart Axis in Cardiac Remodeling

4.1 Gut-Heart Axis: Pathophysiology

Cardiac hypertrophy, previously regarded as an intrinsic cellular response to mechanical overload and neurohormonal activation, is now understood as a multifactorial condition involving extensive systemic communication. Among emerging systemic regulators, the gut microbiota has gained recognition as a critical modulator of cardiovascular structure and function. This diverse microbial ecosystem, comprising bacteria, archaea, fungi, and viruses, performs essential physiological roles in nutrient absorption, immune system modulation, and metabolic regulation [93-95].

The gut–heart axis concept encapsulates the bidirectional interaction between the intestinal and cardiac systems [96]. In pathological states such as heart failure or hypertensive cardiac remodeling, reduced cardiac output compromises mesenteric perfusion, leading to intestinal ischemia, edema, and increased epithelial permeability. This disruption allows translocation of bacterial components—notably LPS, peptidoglycans, and flagellin—into the bloodstream, initiating systemic inflammation and oxidative stress. These responses exacerbate cardiac remodeling, stimulate fibrosis, and alter energy metabolism.

Recent human studies support this model. For example, Cao et al. (2024) reported gut microbial dysbiosis in patients with left ventricular hypertrophy (LVH), characterized by elevated abundance of pro-inflammatory taxa like *Turicibacter* and *Erysipelotrichaceae UCG-003* [97]. Concurrently, altered bile acid metabolism and increased circulating LPS and Interleukin-6 (IL-6) were positively correlated with left ventricular mass index (LVMI) [98]. These findings indicate a mechanistic link between microbial composition, systemic inflammation, and maladaptive hypertrophy.

Moreover, gut-derived signals have been implicated in modulating endothelial barrier function, thereby influencing vascular stiffness and afterload. Elevated levels of zonulin and intestinal fatty acid-binding protein (I-FABP)—markers of gut barrier dysfunction—have been detected in patients with cardiac hypertrophy, suggesting a clinically significant gut-derived pro-hypertrophic signal [99].

4.2 Microbial Metabolites in Hypertrophy

Microbial metabolites serve as key intermediaries in the gut–heart axis. Among them, TMAO has been extensively characterized. Generated via hepatic oxidation of trimethylamine (TMA)—a product of microbial metabolism of choline and carnitine—TMAO exerts deleterious cardiovascular effects. It induces fibroblast activation, endothelial dysfunction, and cardiomyocyte hypertrophy by activating NF-κB, MAPK, and TGF-β1/Smad3 signaling pathways. Elevated plasma TMAO levels are consistently associated with left ventricular hypertrophy and worse outcomes in patients with heart failure [100, 101].

In contrast, *SCFAs*—primarily acetate, propionate, and butyrate—exert protective cardiovascular effects. These *SCFAs* are end-products of microbial fermentation of dietary fibers and act on host cells through G-protein coupled receptors such as GPR41, GPR43, and HDAC inhibition, leading to reduced pro-inflammatory cytokine production, enhanced Treg activation, and improved gut barrier integrity [102]. Butyrate has also been shown to enhance mitochondrial biogenesis and oxidative phosphorylation in cardiomyocytes, thereby mitigating pressure overload-induced dysfunction [103].

Emerging evidence identifies other metabolites as contributors. Kynurenine, a product of tryptophan catabolism by gut microbes, promotes hypertrophy through aryl hydrocarbon receptor (AHR) signaling [104, 105]. In murine models, inhibition of AHR or microbiota depletion attenuates hypertrophic remodeling, highlighting its role as a therapeutic target [106]. Similarly, secondary bile acids interact with FXR and TGR5, influencing lipid metabolism and mitochondrial integrity in the heart [107].

4.3 Experimental and Clinical Evidence

Preclinical models have elucidated causal relationships between gut microbiota and cardiac hypertrophy. Germ-free (GF) mice, lacking a microbiome, exhibit blunted hypertrophic responses to pressure overload or angiotensin II infusion, suggesting that microbial cues are essential for full pathological remodeling [108]. Recolonization of GF mice with fecal material from hypertrophic donors restores the phenotype, confirming microbiota's sufficiency in driving organization remodeling [109].

Inhibition of TMA production using 3,3-dimethyl-1-butanol (DMB)—a microbial enzyme inhibitor—attenuates pressure overload-induced hypertrophy, validating TMAO as a modifiable risk factor [110]. Similarly, *SCFAs* supplementation in rodent models restores intestinal barrier function, reduces macrophage infiltration, and improves cardiac output under hypertrophic stress.

Human data support these findings. Patients with hypertensive heart disease exhibit reduced microbial diversity and depletion of beneficial commensals such as *Faecalibacterium prausnitzii* and *Roseburia*, alongside an enrichment of pro-inflammatory taxa like *Enterobacteriaceae* and *Campylobacter* [111]. These shifts are linked to elevated circulating IgA and IgM, directed against bacterial antigens, implying immune-mediated myocardial damage. Moreover, gut microbial profiles influence pharmacokinetics and treatment response, potentially explaining interindividual variability in outcomes to RAAS inhibitors or β-blockers. A Mendelian randomization study in European cohorts revealed causal associations between certain gut microbial taxa (e.g., *Flavonifractor*, *Ruminococcus gnavus*) and increased heart failure risk, suggesting that genetic factors shaping microbial communities may contribute to cardiac remodeling. These findings highlight the need to integrate microbiome profiling into cardiovascular risk stratification frameworks.

4.4 Therapeutic Strategies and Challenges

The gut microbiota offers a promising therapeutic target for cardiac hypertrophy. Interventions aimed at restoring microbial homeostasis include high-fiber diets, probiotics, prebiotics, and fecal microbiota transplantation (FMT) [112]. For example, supplementation with *Lactobacillus rhamnosus* has demonstrated antihypertrophic effects in pressure overload mouse models by reducing systemic inflammation and downregulating TGF-β [113]. Similarly, in a study using angiotensin II-induced hypertensive mice, oral administration of propionate significantly reduced cardiac hypertrophy, perivascular fibrosis, and endothelial dysfunction, effects associated with increased colonic regulatory T cells and lower circulating inflammatory cytokines [114].

In pharmacological approaches, inhibitors of microbial TMA formation (e.g., DMB) or FMO3 inhibitors targeting hepatic conversion to TMAO, have demonstrated efficacy in preclinical studies [115]. Notably, TMAO-lowering interventions not only reduce LV mass but also improve mitochondrial membrane potential and ATP synthesis, implicating metabolic rejuvenation as a core mechanism.

*SCFA*s-enhancing strategies—such as resistant starch or inulin supplementation—restore epithelial integrity and modulate gut-brain-cardiac signaling, leading to reduced sympathetic tone and cardiac workload. Moreover, new molecules like N,N,N-trimethyl-5-aminovaleric acid (TMAVA) have been identified as microbiota-derived inhibitors of carnitine metabolism and FAO [116]. Targeting TMAVA with carnitine supplementation or gut microbial editing has been proposed as a novel means to reverse energetic impairment in the hypertrophic heart.

Nevertheless, several challenges remain: identification of causal microbial strains and functional metabolites; individualized responses to microbial therapy due to host-genetic and environmental variability; and establishing long-term safety and regulatory standards for microbial-based therapeutics.

In summary, the gut microbiota functions as a dynamic modulator of cardiac remodeling, influencing inflammation, mitochondrial energetics, and neurohumoral balance (Fig. 5). Therapeutic targeting of the microbiota and its metabolites offers a transformative opportunity for precision cardiology, with the potential to shift paradigms in hypertrophy management. Future studies should emphasize multi-omics integration, longitudinal cohort studies, and microbial consortia-based therapies tailored to patient-specific cardiovascular phenotypes.

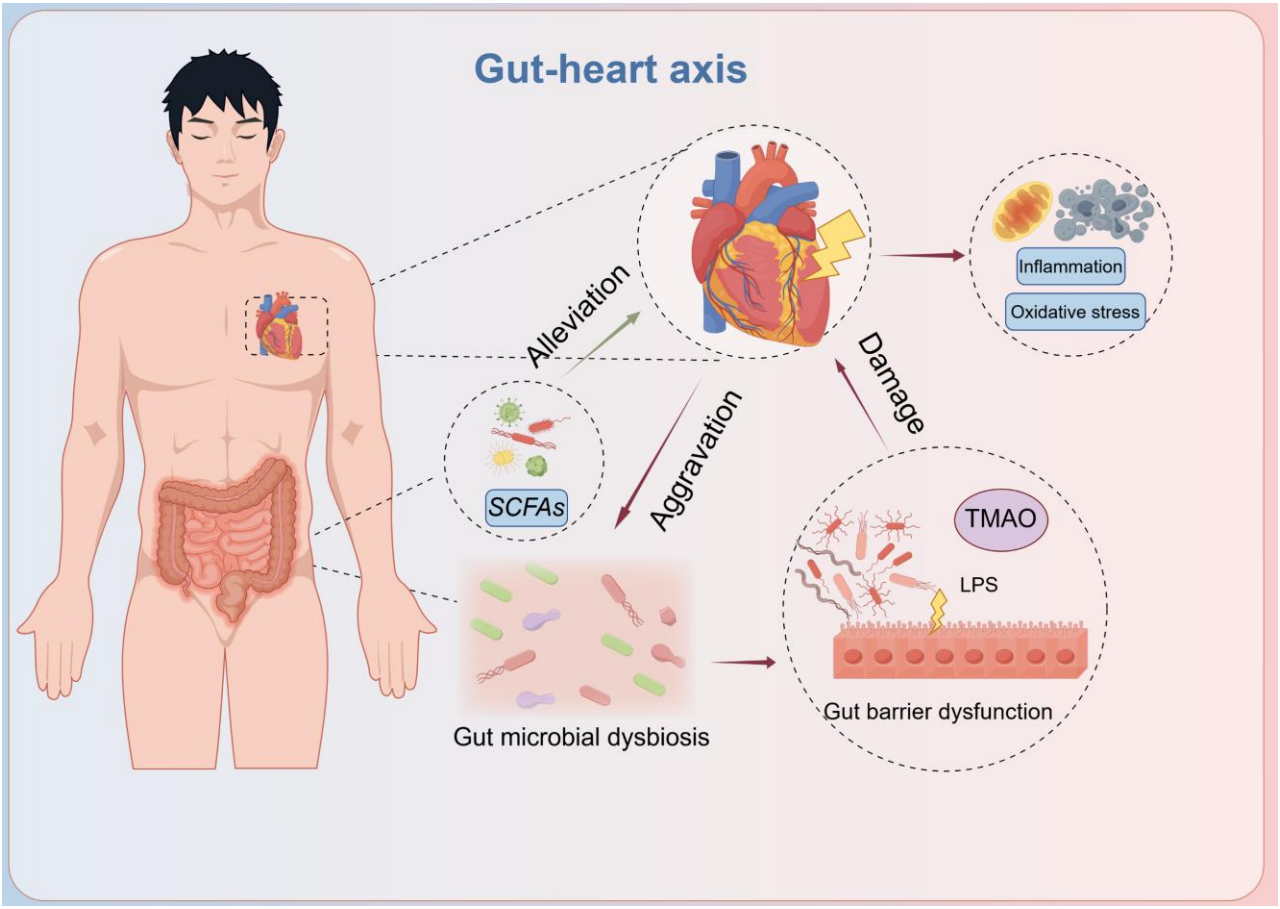

Figure 5. Gut–heart axis in cardiac remodeling. Beneficial microbial metabolites, such as *SCFAs*, alleviate cardiac risk, whereas detrimental products, including TMAO and LPS, aggravate disease progression. These factors collectively promote inflammation and oxidative stress. Dysregulation is initiated by gut microbial dysbiosis, which impairs intestinal barrier integrity, further amplifying the release of harmful metabolites into circulation and driving a vicious cycle that contributes to cardiovascular pathology.

5. Tissue Microenvironment and Translational Perspectives

5.1 Cell-cell Crosstalk and Microenvironmental Factors

Cardiac hypertrophy is not solely a cardiomyocyte-autonomous event, rather, it is a tissue-level process involving extensive communication between cardiac cells and their microenvironment. Crosstalk among endothelial cells, fibroblasts, immune cells, and cardiomyocytes shapes the structural and functional remodeling of the heart.

5.1.1 Endothelial and Angiogenic Signals

Angiogenesis is crucial for maintaining oxygen and nutrient delivery in hypertrophied hearts. Vascular endothelial growth factor (VEGF), regulated by hypoxia-inducible factor-1 alpha (HIF-1α), promotes capillary proliferation in response to increased cardiac workload [117]. In physiological hypertrophy, VEGF expression is upregulated, preserving capillary density and preventing ischemia. Nitric oxide (NO), produced by endothelial nitric oxide synthase (eNOS), enhances vasodilation and inhibits hypertrophic signaling. In pathological hypertrophy, reduced VEGF and NO bioavailability contribute to capillary rarefaction and microvascular dysfunction, exacerbating hypoxia and fibrosis.

5.1.2 Fibroblasts and Extracellular Matrix Remodeling

Cardiac fibroblasts regulate ECM composition and respond dynamically to biomechanical and inflammatory cues. In hypertrophy, fibroblasts are activated and secrete profibrotic factors such as TGF-β, connective tissue growth factor (CTGF), and periostin [118]. These mediators stimulate collagen I and III deposition, leading to myocardial stiffening and diastolic dysfunction.

Excessive ECM remodeling disrupts myocardial architecture and impairs electrical conduction, contributing to arrhythmogenesis. The fibrotic response is tightly linked to hypertrophic signaling, as pathways like Angiotensin II and endothelin-1 promote both cardiomyocyte growth and fibroblast activation.

5.1.3 Immune Cells and Inflammatory Mediators

Inflammation is increasingly recognized as a key contributor to maladaptive cardiac remodeling. Immune cells, including macrophages, T-cells, and dendritic cells, infiltrate the myocardium in response to injury or stress. Pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and IL-6 amplify local inflammation and drive hypertrophic signaling. Activation of the NLRP3 inflammasome further promotes IL-1β release and pyroptosis, exacerbating tissue injury. Immune-mediated effects also influence fibroblast behavior and vascular function, reinforcing a pro-remodeling microenvironment [119].

Altogether, metabolic adaptation and intercellular communication are fundamental to the pathogenesis of cardiac hypertrophy (Fig. 6). Understanding these integrative processes provides a broader perspective on disease progression and reveals new targets for therapeutic modulation.

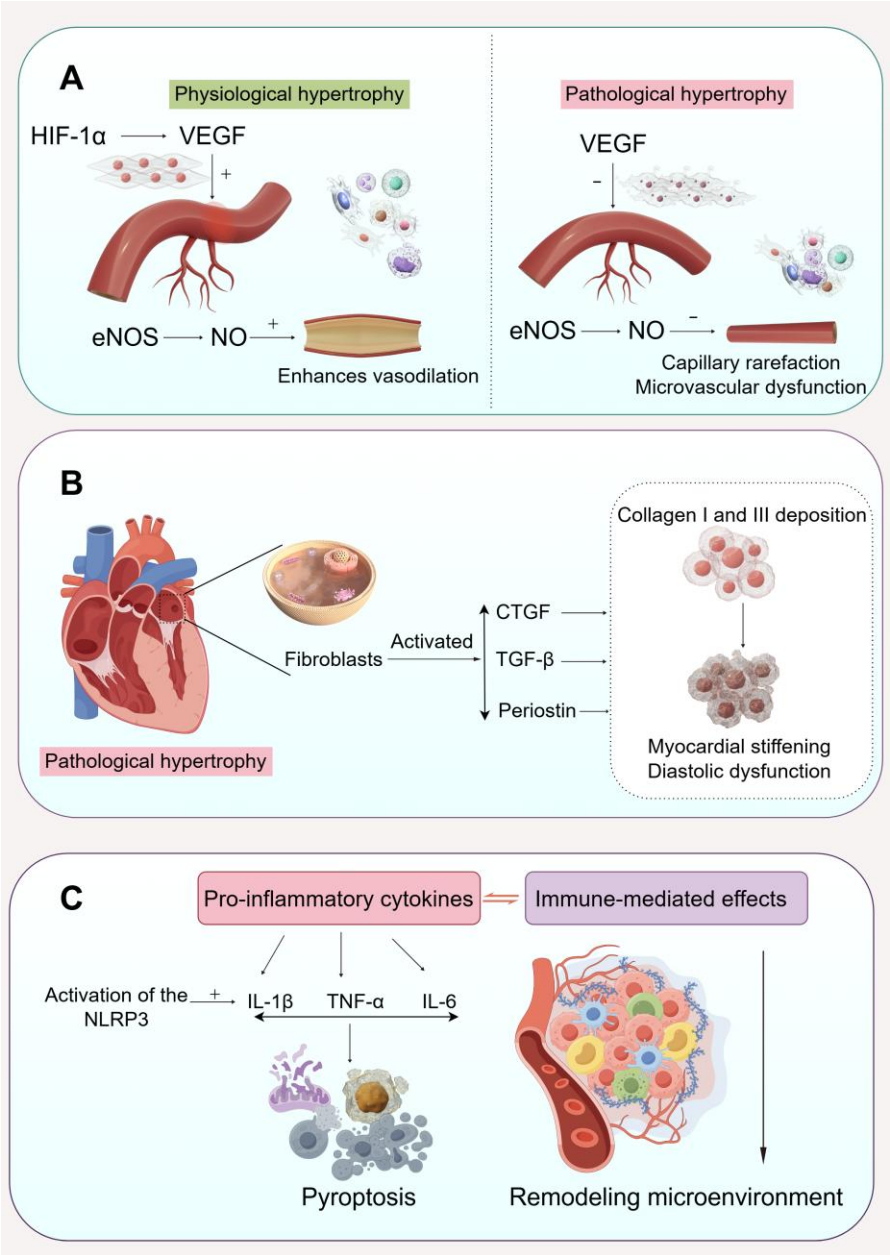

Figure 6. Intercellular interactions and microenvironmental factors. (A) Endothelial and angiogenic signals; **(B)** Fibroblasts and extracellular matrix remodeling; **(C)** Immune cells and inflammatory mediators.

5.2 Emerging Mechanisms

While canonical pathways have been extensively studied in cardiac hypertrophy, emerging evidence highlights several unconventional regulators and mechanisms that refine our understanding of disease progression and offer new therapeutic perspectives.

5.2.1 Mechanosensors and Integrin Pathways

Mechanical stress, a central trigger of hypertrophy, is sensed by a network of mechanoreceptors and integrin-associated proteins. Among these, melusin—a muscle-specific integrin-binding protein—activates ERK1/2 and AKT signaling in response to stretch, promoting adaptive hypertrophic responses and cardioprotection [120]. Similarly, talin connects integrins to the actin cytoskeleton, facilitating force transmission and mechanotransduction. Importantly, YAP1, a downstream effector of the Hippo pathway, also serves as a mechanosensory [121]. Under mechanical strain, YAP1 translocates to the nucleus and modulates genes related to proliferation and growth. While transient YAP1 activation may be protective, chronic activation has been linked to pathological hypertrophy and fibrosis. Thus, mechano-transduction involves both protective and maladaptive elements depending on the temporal context and signal integration.

5.2.2 Protein Quality Control and Autophagy

Cardiomyocytes rely on robust protein quality control systems to maintain proteostasis during stress. The ubiquitin–proteasome system (UPS) degrades misfolded proteins and prevents toxic aggregate accumulation. In hypertrophic hearts, however, UPS function is often impaired, leading to proteotoxic stress. The unfolded protein response (UPR) and endoplasmic reticulum (ER) stress pathways are also activated, contributing to maladaptive remodeling. Autophagy—particularly selective autophagy—acts as a compensatory mechanism to clear damaged organelles and protein aggregates. Insufficient autophagic flux has been observed in models of pressure overload and human heart failure, exacerbating cellular injury. Conversely, stimulation of autophagy (e.g., via AMPK activation) improves cardiac function and limits hypertrophy progression. Understanding the interplay between UPS, ER stress, and autophagy is critical for targeting proteotoxicity in cardiac disease.

5.2.3 Sex-Specific Molecular Features

Sex-based differences in cardiac hypertrophy are increasingly recognized, both in clinical presentation and molecular pathways [21]. Estrogen signaling confers cardioprotective effects via ERα/ERβ-dependent regulation of calcium homeostasis, mitochondrial function, and anti-inflammatory responses. Post-menopausal decline in estrogen correlates with increased hypertrophic risk in women. Fibroblast growth factor 21 (FGF21), a metabolic hormone, also displays sex-specific effects. It enhances fatty acid oxidation and mitochondrial protection and has been shown to suppress hypertrophy more efficiently in females. Additionally, differences in substrate metabolism and epigenetic regulation between sexes may modulate disease susceptibility. These findings support the development of personalized, sex-aware therapies for cardiac hypertrophy.

5.3 Translational Therapeutics

Advances in molecular cardiology have identified numerous therapeutic targets across signaling, metabolic, and epigenetic pathways. Translating these insights into effective clinical strategies remains both promising and challenging.

5.3.1 Therapeutic Targeting of Kinases

Protein kinases represent attractive intervention points due to their central roles in signal transduction. mTOR inhibitors, such as rapamycin, have shown efficacy in reversing pathological remodeling by restoring autophagy and reducing protein synthesis [122]. On the contrary, controlled activation of AKT has been explored to promote physiological hypertrophy and preserve cardiac output. GPCR modulators, including angiotensin receptor blockers (ARBs) and endothelin receptor antagonists, remain cornerstone therapies in clinical practice, although next-generation agents aim for more selective pathway modulation with fewer side effects.

5.3.2 Metabolic Therapeutics

Targeting cardiac metabolism offers a novel avenue to combat energy deficiency in hypertrophied hearts. Ketone esters, which serve as efficient alternative fuels, improve mitochondrial energetics and have demonstrated cardioprotective effects in heart failure [123]. Peroxisome proliferator-activated receptor (PPAR) agonists enhance fatty acid oxidation and reduce lipid accumulation, while AMPK activators restore energy balance and autophagy [124]. These metabolic therapies not only address ATP deficits but also modulate inflammatory and fibrotic responses.

5.3.3 Non-Coding RNA and Epigenetic Therapies

Manipulating non-coding RNAs offers high specificity in modulating gene networks. AntagomiRs targeting miR-21 or miR-208a have been used to inhibit pro-hypertrophic pathways and attenuate fibrosis [125]. Small interfering RNAs (siRNAs) can silence pathological transcripts, and nanoparticle-based delivery systems are under investigation to improve cardiac targeting. Epigenetic drugs, such as HDAC inhibitors, reverse aberrant gene expression and have shown promise in preclinical hypertrophy models [126]. However, broad epigenetic modulation must be carefully balanced to avoid off-target effects.

5.3.4 Cell-specific or Paracrine Factor Therapy

Emerging approaches focus on modulating intercellular communication and enhancing endogenous repair mechanisms. Neuregulin-1, a paracrine factor from endothelial cells, promotes cardiomyocyte proliferation and improves myocardial function in heart failure models. VEGF therapy aims to restore capillary density and prevent ischemia in hypertrophic hearts [127]. Exosome-based delivery systems, carrying therapeutic RNAs or proteins, represent a cutting-edge strategy for targeting specific cardiac cell types while minimizing immune activation.

5.4 Translational Barriers and Opportunities

Although preclinical models have provided key insights into the molecular basis of cardiac hypertrophy, several obstacles hinder successful clinical translation. Current rodent and cellular models fail to capture the chronic metabolic and inflammatory complexity observed in human hypertrophic cardiomyopathy. Drug delivery remains a major challenge, as gene- and RNA-based therapies face issues of off-target activity, immunogenicity, and delivery efficiency. Targeting post-translational modifications or microbial metabolites is particularly difficult because of enzyme redundancy, systemic cross-reactivity, and tissue-specific variability.

From a translational perspective, early-phase clinical trials evaluating AMPK activators, such as metformin and AICAR derivatives, and microbiota-modulating agents have shown encouraging yet preliminary results [128]. However, regulatory requirements, safety profiles, and biomarker validation remain critical barriers to clinical adoption. Addressing these challenges will be essential for bridging the gap between mechanistic discoveries and precision-based cardiovascular therapies. Collectively, these translational insights underscore not only the technical and regulatory challenges facing clinical implementation but also the persistent scientific gaps that demand further investigation, as discussed in the following section.

5.5 Clinical Phenotype Correlation

Clinical manifestations of cardiac hypertrophy vary substantially across patient populations. Elderly individuals typically exhibit concentric remodeling with preserved ejection fraction, reflecting age-associated metabolic decline, impaired mitochondrial quality control, and increased oxidative stress. In contrast, hypertensive patients show pressure-overload–driven hypertrophy characterized by enhanced fibrosis, extracellular matrix deposition, and TGF-β/Smad pathway activation. Diabetic cardiomyopathy, on the other hand, displays prominent lipid accumulation, chronic inflammation, and reduced AMPK activity, reflecting metabolic inflexibility and mitochondrial dysfunction.

Sex-specific patterns have also been reported, with premenopausal women demonstrating relative protection against pathological remodeling, attributed to estrogen-mediated mitochondrial and epigenetic regulation. Estrogen receptor α signaling promotes mitochondrial biogenesis through PGC-1α activation, enhances oxidative phosphorylation efficiency, and mitigates reactive oxygen species generation, thereby preserving cardiomyocyte energy homeostasis and reducing apoptosis. Beyond metabolic regulation, estrogen exerts epigenetic control by modulating histone acetylation, DNA methylation, and noncoding RNA expression, influencing cardiac gene transcription and antifibrotic pathways. Recent studies have also revealed sex-dependent variations in the cardiac acylome and chromatin accessibility, suggesting that hormonal status influences epigenetic landscape remodeling and transcriptional responses to cardiac stress.

Recent human biopsy and transcriptomic studies further support molecular divergence among phenotypes. For instance, acylation profiling of left ventricular tissue from patients with hypertrophic cardiomyopathy reveals altered lysine crotonylation and acetylation patterns associated with metabolic stress [129]. Likewise, microbiome analyses of hypertensive and diabetic cohorts demonstrate distinct gut microbial signatures and metabolite profiles, correlating with left ventricular mass and diastolic function [130].

Together, these findings underscore that cardiac hypertrophy is not a uniform pathological process but rather a syndrome shaped by age, sex, metabolic state, and gut microbial composition. Understanding these phenotype-specific molecular pathways is essential for

developing precision and sex-tailored therapeutic strategies in hypertrophic heart disease (Fig. 7).

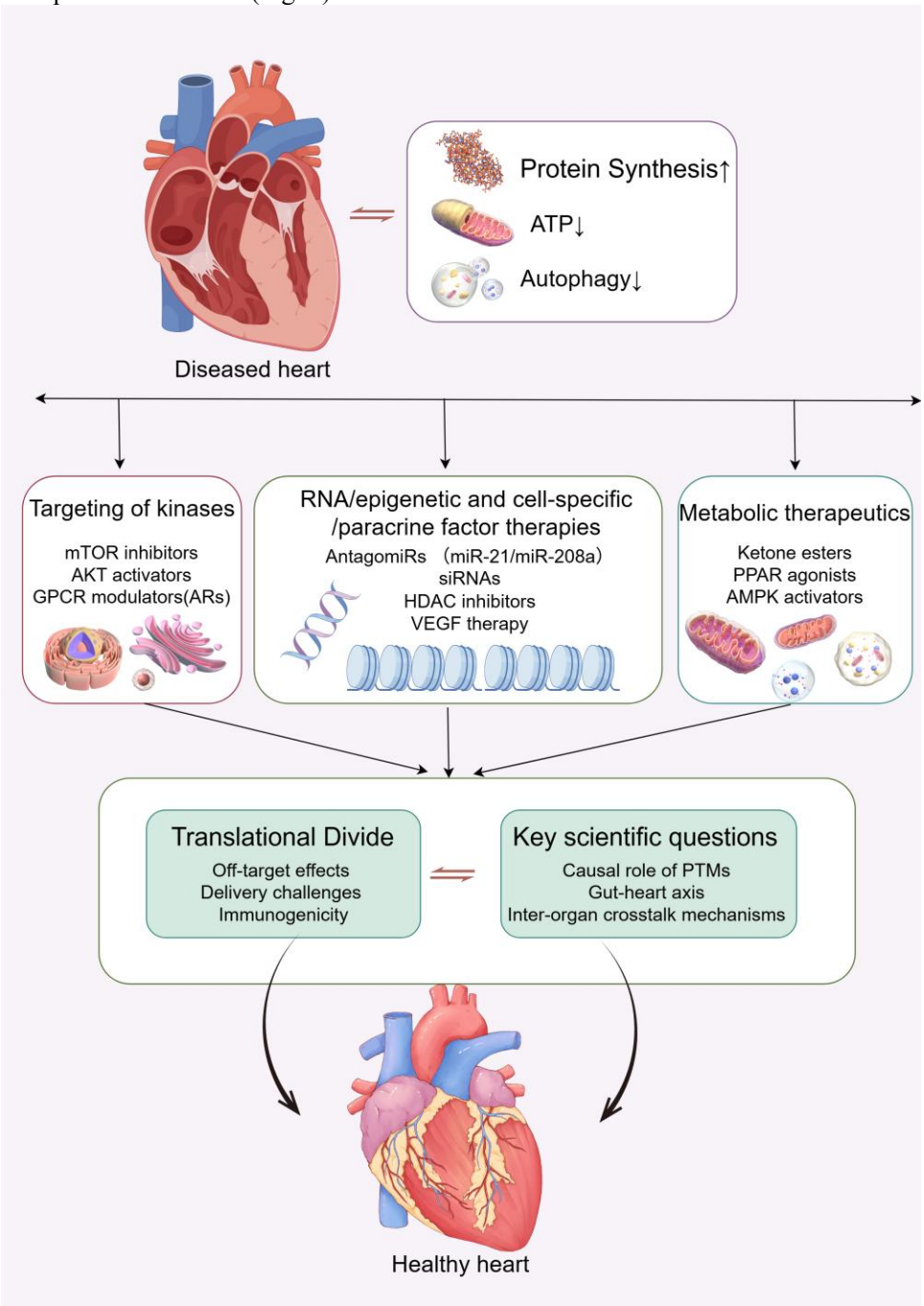

Figure 7. Translational therapeutics and clinical challenges. (All figures by Figdraw 2.0)

6. Limitations and Future Directions

Building upon these translational considerations, it is equally important to recognize the broader scientific limitations that continue to constrain our understanding of cardiac hypertrophy mechanisms. Most mechanistic insights have been obtained from animal or *in vitro* models, which only partially reproduce the heterogeneity, comorbidities, and sex-specific characteristics observed in human disease. In addition, many studies remain primarily correlative and lack the temporal and mechanistic resolution needed to establish causality—particularly in relation to PTMs and microbiota-derived metabolites.

Translational progress is further impeded by several practical obstacles. Off-target effects, immunogenicity,

and delivery inefficiency remain major barriers for gene- and RNA-based therapeutic approaches. The intrinsic molecular complexity of cardiac hypertrophy also challenges the effectiveness of single-target interventions, highlighting the necessity for combination therapies and context-dependent strategies. Addressing these challenges requires the development of clinically relevant disease models, refinement of trial designs to incorporate sex-specific variables and long-term safety considerations, and greater emphasis on precision-medicine frameworks that can more accurately predict therapeutic outcomes.

Future investigations should also focus on microbiota-targeted therapeutic strategies that may modulate cardiac remodeling through metabolic and inflammatory pathways. Emerging evidence suggests that probiotics and prebiotics can restore gut microbial balance, reduce systemic inflammation, and improve myocardial energy metabolism in hypertrophic and cardiometabolic models. In parallel, FMT has shown potential to reshape gut microbial composition and metabolite signaling, thereby influencing cardiac structure and function. However, key challenges remain, including donor variability, procedural safety, and durability of therapeutic effects. Addressing these issues through standardized protocols and well-controlled clinical trials will be essential to determine whether microbiota modulation can serve as a viable precision-medicine approach in preventing or reversing pathological cardiac hypertrophy.

Bridging these gaps between scientific and clinical translation will demand comprehensive integration of multi-omics, spatial transcriptomics, and longitudinal human datasets to connect preclinical observations with patient-centered outcomes. Within this framework, several key research questions remain unresolved: (1) the causal role of PTMs in cardiac hypertrophy requires clarification, particularly in distinguishing whether they act as primary drivers or secondary markers of disease progression; (2) the therapeutic potential of specific gut microbial strains or their metabolites in reversing established myocardial remodeling remains an emerging and promising direction; (3) the spatiotemporal dynamics and tissue-specific regulation of protein acylation events during hypertrophy progression are still insufficiently characterized; (4) multi-omics and spatial transcriptomic technologies provide powerful tools to decipher inter-organ communication networks in cardiac remodeling; and (5) bridging the translational gap between murine models and human cardiovascular pathophysiology remains a critical prerequisite for advancing gut–heart axis research.

Collectively, overcoming these limitations and addressing the outstanding questions outlined above will be essential for transforming mechanistic discoveries into durable, targeted, and personalized therapeutic strategies for pathological conditions.

7. Conclusions

Cardiac hypertrophy represents a critical turning point between adaptive compensation and maladaptive remodeling. This review summarizes the key molecular pathways involved in both physiological and pathological hypertrophy, including signaling cascades (PI3K–Akt, MAPK, GPCR, AMPK, Hippo–YAP and Wnt/β-Catenin), metabolic remodeling, epigenetic reprogramming, and novel contributors such as the gut microbiome and immune-fibrotic crosstalk. Despite significant advances, translating preclinical insights into clinical success remains challenging. Many existing models lack the complexity to reflect human pathophysiological diversity, including sex-specific responses and comorbid states. Additionally, the integration of spatial omics and systems biology is expected to overcome current limitations in biomarker discovery and therapeutic targeting. Rather than isolated mechanisms, future research must address cardiac hypertrophy as a multi-organ, multi-dimensional syndrome—requiring cross-disciplinary and precision-based strategies.

In addition, the gut–heart axis reveals the gut microbiota as a pivotal extrinsic factor in hypertrophic progression. Dysbiosis-induced inflammation, metabolite signaling such as TMAO and *SCFAs*, and impaired intestinal barrier integrity collectively reprogram cardiac metabolism, immune responses, and gene expression. Experimental and clinical evidence strongly supports a causal role for gut-derived signals in promoting or mitigating hypertrophy.

Future therapeutic strategies should prioritize microbiota-targeted interventions—including dietary modulation, microbial metabolite control, and engineered probiotics—alongside approaches restoring PTMs homeostasis. Together, these avenues may enable personalized, multi-dimensional therapies that address both intracellular dysregulation and inter-organ crosstalk in pathological cardiac remodeling.

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Declaration of competing interest

The authors declare that they do not have any conflict of interest.

Author contributions

Wen Cao and Guo-Wei He researched data for the article, discussed its content and wrote the manuscript. All the authors reviewed/edited the manuscript before submission.

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