Cardiac Remodeling: Novel Pathophysiological Mechanisms and Therapeutic Strategies

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Abstract

Morphological and structural remodeling of the heart, including cardiac hypertrophy and fibrosis, has been considered a therapeutic target for heart failure for approximately three decades. Groundbreaking heart failure medications demonstrating reverse remodeling effects have contributed significantly to medical advancements. However, nearly 50% of heart failure patients still exhibit drug resistance, posing a challenge to the healthcare system. Recently, characteristics of heart failure resistant to ARBs and β-blockers have been defined, highlighting preserved systolic function despite impaired diastolic function, leading to the classification of heart failure with preserved ejection fraction (HFpEF). The pathogenesis and etiology of HFpEF may be related to metabolic abnormalities, as evidenced by its mimicry through endothelial dysfunction and excessive intake of high-fat diets. Our recent findings indicate a significant involvement of mitochondrial hyper-fission in the progression of heart failure. This mitochondrial pathological remodeling is associated with redox imbalance, especially hydrogen sulfide accumulation due to abnormal electron leak in myocardium. In this review, we also introduce a novel therapeutic strategy for heart failure from the current perspective of mitochondrial redox-metabolic remodeling.

Running title: New therapeutic strategies for reverse cardiac remodeling

Key words: cardiac remodeling, redox/energy metabolism, transient receptor potential, mitochondria, supersulfide
1. Introduction

The myocardial cells that govern the pumping function of the heart are robust cells that continue the rhythmic contraction-relaxation tirelessly from birth to death, with minimal turnover. For adapting to various environmental stresses, the heart flexibly alters its structure and morphology, a process known as cardiac remodeling. Although various types of cardiac remodeling exist (Figure 1), the clinical importance is whether the response is reversible or irreversible. For instance, hearts exposed to chronic stressors such as hypertension, myocardial infarction, or angina undergo tissue remodeling involving pathological myocardial hypertrophy, interstitial fibrosis, and inflammation mediated by the infiltration of macrophages and neutrophils. Such pathological cardiac remodeling does not easily recover even with the administration of anti-hypertensive drugs or anti-angina drugs, and the therapeutic effects on heart failure are not promising. In the case of patients with cancer cachexia, the heart undergoes atrophy due to decreased blood volume resulting from reduced food and water intakes, and long-time bed rest, leading to mechanical unloading of the myocardium. There is also no breakthrough treatment for myocardial atrophy. On the other hand, hard exercises or pregnancy sometimes cause physiological hypertrophy, which can be reversed by releasing from mechanical loading to the heart. Since the physiological hypertrophy is reportedly unassociated with fibrosis and inflammation, the interstitial fibrosis and inflammation have been focused as new therapeutic targets for pathological cardiac remodeling. Approximately 30% of all cells comprising the heart are cardiomyocytes, occupying a significant portion of the body surface area. The remaining approximately 60% are cardiac fibroblasts, which regulate the phenotype of cardiac remodeling. While regulatory roles by resident immune cells such as
macrophages and neutrophils have been widely reported, this review focuses on cardiomyocytes and cardiac fibroblasts as the responsible cells for cardiac remodeling. We also describe a novel strategy for controlling the reversibility of myocardial remodeling, focusing on mitochondrial quality and redox/energy metabolism.

2. Ca\(^{2+}\)-dependent excitation-transcription coupling in cardiac hypertrophy

The typical phenotype of cardiomyocyte hypertrophy includes structural rearrangement of actin cytoskeleton and increased hypertrophy-related gene expression levels (Figure 2). Actin rearrangement is predominantly regulated by Rho small GTPase-dependent signaling pathways. Stimulation of the heterotrimeric G\(_{12}\) family protein-coupled receptors, such as α1 adrenergic receptor (α\(_1\)AR), angiotensin type 1 receptor (AT\(_1\)R), endothelin-1 type A receptor (ET\(_A\)R), and purinergic P2Y\(_6\) receptor (P2Y\(_6\)R), reportedly causes actin rearrangement of cultured cardiomyocytes through G\(_{12/13}\)-Rho-dependent signaling pathway. The monomeric G-actin binds with myocardin-related transcription factor A (MTRF-A), and actin polymerization induces dissociation of MRTF-A from F-actin, leading to nuclear translocation of MRTF-A followed by induction of pro-fibrotic genes. These G\(_{12/13}\) protein-coupled receptors are fundamentally coupled with G\(_q\) family proteins, which also leads to activation of Ca\(^{2+}\)-dependent and extracellular signal-regulated kinase (ERK)-dependent hypertrophy-related gene transcription.

Research on the pathophysiology and etiology of cardiac remodeling has evolved in conjunction with the development of therapeutic drugs and changes in medical strategies. Given that the decline in cardiac pump function is directly linked to mortality, initial efforts focused on the discovery and development of positive
Inotropic agents to enhance pump function, along with research on their mechanisms of action. The pump function of the heart relies on the contraction and relaxation functions of working cardiomyocytes and is primarily controlled by intracellular calcium (Ca\textsuperscript{2+}) concentration. Specifically, depolarization of excitatory cardiomyocytes activates voltage-dependent L-type Ca\textsuperscript{2+} channels, allowing a minimal influx of Ca\textsuperscript{2+} from the extracellular space through the channels. The ryanodine receptors on the sarcoplasmic reticulum membrane, serving as Ca\textsuperscript{2+} stores, sense this influx and trigger a massive release of Ca\textsuperscript{2+} from the stores. This transiently increases cytoplasmic Ca\textsuperscript{2+} concentration, leading to the contraction of muscles through the actin-myosin sliding, mediated by Ca\textsuperscript{2+}-dependent troponin C. Subsequently, energy-dependent processes such as Ca\textsuperscript{2+} reuptake into the sarcoplasmic reticulum and extracellular expulsion through Ca\textsuperscript{2+} ATPase induce the return of intracellular Ca\textsuperscript{2+} concentration to baseline, causing muscle relaxation. Positive inotropic agents like digoxin inhibit Na\textsuperscript{+}/K\textsuperscript{+} ATPase, promoting an increase in intracellular Ca\textsuperscript{2+} concentration via the Na\textsuperscript{+}/Ca\textsuperscript{2+} exchange system, thereby enhancing myocardial contractility. β-adrenergic receptor agonists enhance heart function by mimicking the release of norepinephrine from sympathetic nervous endings. Pimobendan exerts positive inotropic effects by increasing the Ca\textsuperscript{2+} sensitivity of troponin C \textsuperscript{11}. Thus, Ca\textsuperscript{2+} plays a crucial role as a mediator in regulating the excitation-contraction coupling of the heart. Familial hypertrophic cardiomyopathy and dilated cardiomyopathy arise from nearly 1,500 distinct mutations in the genes that encode for proteins of the sarcomere \textsuperscript{12}. These mutations typically alter calcium-dependent tension generation within the sarcomeres. Davis J et al. suggested a myocardial tension-based model that can distinguish hypertrophic versus dilated cardiomyopathy \textsuperscript{13}. According to this model, abnormal Ca\textsuperscript{2+} handling is involved in both
cardiomyopathies, while additional ERK activation is positively associated with hypertrophic cardiomyopathy.

The impairment of ATP-dependent Ca\(^{2+}\) elimination after muscle contraction can activate the Ca\(^{2+}\)-dependent signaling pathway, leading to an increase in the expression of hypertrophy-related genes in myocardial cells. The hypertrophied myocardium increases the protein expression levels of α-skeletal muscle actin (α-SKA), fetal-type β-myosin heavy chain (MHC), atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and other proteins. Additionally, this condition stimulates the reconstruction of the actin cytoskeleton. In mouse experiments, FK506, an immunosuppressive agent, suppressed cardiac hypertrophy, highlighting the significance of the Ca\(^{2+}\)-dependent phosphatase, calcineurin, in this context. Calcineurin dephosphorylates the transcription factor nuclear factor of activated T cells (NFAT) in the cytoplasm in a Ca\(^{2+}\)-dependent manner, facilitating its translocation to the nucleus. Considering concerns about the overall immune function suppression with immunosuppressive agents and the inhibition of cardiac contractility with voltage-dependent Ca\(^{2+}\) channel blockers, many research groups including ours, have explored the activation of calcineurin by searching for substantial Ca\(^{2+}\) mobilization sources, identifying transient receptor potential canonical (TRPC) channels as novel drug targets. TRP channels, identified as receptor-operated and diacylglycerol-activated channels in Drosophila melanogaster photoreceptor mutants, consist of 28 homologs in animals. In cardiovascular tissues regulated by various neurohormonal factors, there is accumulating evidence that the localized and sustained cation influx through receptor-operated TRPC channels is crucial for NFAT activation, particularly of the NFAT3 and NFAT4 isoforms. Results from studies using
genetically modified mice reveal that among the seven TRPC isoforms, the diacylglycerol-activated TRPC3 and TRPC6 isoforms are implicated in pathological hypertrophy of the myocardium \(^{21-24}\). However, our recent studies using systemic TRPC3-knockout (KO) and TRPC6-KO mice revealed that TRPC3 participates in the development of cardiac fibrosis rather than hypertrophy \(^{25, 26}\) in vivo. Additionally, TRPC6 physiologically contributes to baroreflex-dependent increase in cardiac contractility (i.e., positive inotropic effect) through Zn\(^{2+}\) influx \(^{27}\), suggesting an importance of understanding TRPC isoform-specific (patho) physiological functions and drug discovery strategies.

Interestingly, transcriptional reprogramming of gene expression has also reportedly participated in the induction of cardiac hypertrophy and failure \(^{28}\). Normal adult cardiomyocytes primarily express \(\alpha\)-MHC, whereas pathologic hypertrophied cardiomyocytes express fetal \(\beta\)-MHC. Hang et al. reported that Brg1, a chromatin remodeling protein that is basically turned off in adult cardiomyocytes, is reactivated by physico-chemical stresses to form a complex with its embryonic partners, histone deacetylase and poly ADP ribose polymerase, resulting in pathological shift of \(\alpha\)-MHC to \(\beta\)-MHC, suggesting a new strategy for reversing pathological hypertrophy.

### 3. Rho-dependent cardiomyocyte-fibroblast interaction in cardiac fibrosis

The connective tissue of the myocardium contains elastin (elastic fibers) which control elasticity and collagen (collagen fibers) which control strength. Increased collagen deposition in the interstitium leads to myocardial stiffening and decreased myocardial flexibility \(^{29}\). Recent reports have also discussed effective biomarkers for predicting the progression of human myocardial remodeling \(^{30}\). Procollagen type III
amino-terminal (PIIINP) and procollagen type 1 carboxy-terminal peptide (PICP) are propeptides released during collagen synthesis, while carboxyl-terminal telopeptide of collagen type I (CITP) is produced during collagen degradation, and matrix metalloproteinases (MMPs) are involved in cytoskeletal and extracellular myocardial matrix remodeling. These enzymes are inhibited by specific tissue inhibitors (TIMPs). PICP and PIIINP can be examined using magnetic resonance imaging (MRI) of the heart and have been shown to strongly correlate with the severity of heart failure. Growth factors released from myocardial cells, such as transforming growth factor (TGF)-β and connective tissue growth factor (CTGF), stimulate fibroblasts in the interstitial tissue and perivascular tissue via receptor activation, inducing their differentiation into muscle fibroblasts with high collagen-producing capacity. The gene expression of TGF-β and CTGF from myocardial cells is believed to be regulated by the Rho-actin-MTRF signaling pathway, with the hypertrophy of myocardial cells involving actin remodeling believed to lead to the production of fibrosis-inducing factors. Actin remodeling is primarily induced by mechanical stress, with G protein-coupled receptors (GPCRs) such as AT1R and P2Y6R reported to sense and activate mechanical stress. From experiments using TRPC3KO mice and a TRPC3-selective inhibitor, we reported that TRPC3 channels in myocardial cells activate Ca2+-dependent Rho guanine nucleotide exchange factor (GEF-H1) downstream, strongly influencing interstitial fibrosis rather than myocardial hypertrophy. Thus, the interaction between myocardial cells and fibroblasts mediated by fibrosis-promoting factors derived from myocardial cells is considered to play an important role in the fibrotic response of the myocardium.

In addition, fibroblasts themselves have mechanisms to induce fibrosis. Muscle
differentiation induction by TGF-β receptor stimulation is known, with increased expression of α-smooth muscle actin (SMA) being a primary indicator of muscle fibroblasts. Serine protease 3, Htra3, is reportedly a critical regulator of cardiac fibrosis by maintaining the identity of quiescent cardiac fibroblasts through degrading TGF-β. TRPC3 channels are also expressed in cardiac fibroblasts, and mechanical stretching stimulation activates GEF-H1 in a Ca^{2+}-dependent manner, promoting differentiation of cardiac fibroblasts into muscle fibroblasts. In primary culture experiments using cardiac fibroblasts derived from rats and mice, TGF-β stimulation-induced α-SMA expression induction is reversible, but oxidative stress, inflammation, and energy metabolism changes observed during aging make it irreversible. Moderate exercise has been reported in mice as a method to recover myocardial remodeling, with coiled-coil domain-containing protein 80 (CCDC80), which increases in the bloodstream during exercise, shown to directly bind to JAK and inhibit the JAK/STAT3 pathway. Moderate exercise also restores mitochondrial energy metabolism function, making it a promising therapeutic strategy to promote recovery of myocardial tissue remodeling through multifaceted effects.

4. Mitochondrial remodeling as new determinants of pathological remodeling

Sodium/glucose cotransporter (SGLT) 2 inhibitors, particularly prominent among anti-diabetic agents, have attracted attention as a beneficial treatment for HFrEF. When blood glucose levels rise, the heart actively takes up glucose and undergoes glucose metabolism through glycolysis to maintain energy production. However, sustained hyperglycemia induces a metabolic shift from β-fatty acid oxidation to aerobic glycolysis, observed in hypertrophied hearts. Therefore, it is considered important to
maintain the quality and function of mitochondria for the prevention and treatment of HFpEF. Factors regulating the metabolic switch from glucose oxidation to aerobic glycolysis include pyruvate and coenzymes such as nicotinamide adenine dinucleotide (NAD\(^+\)) and flavin adenine dinucleotide (FAD\(^+\)), which are substrates necessary for ATP production via the TCA cycle. For instance, studies have reported that decreased expression of the mitochondrial pyruvate carrier (MPC) protein on the mitochondrial membrane in mice exacerbates pathological cardiac hypertrophy, inhibition of lactate exporter monocarboxylate transporter 4 (MCT4) on the cell membrane promotes reuse of lactate, thereby suppressing pathological cardiac hypertrophy, and administration of nicotinamide, a stable precursor of NAD\(^+\), improves HFpEF-like heart failure. These strategies primarily focus on maintaining oxidative phosphorylation of cardiac mitochondria, suggesting reduced levels of oxidative phosphorylation in HFpEF myocardium. However, the precise mechanisms underlying mitochondrial metabolic shifts remain unclear.

We are conducting research focusing on the mechanism of cardiac mitochondrial quality control. Mitochondria continually adapt to environmental changes by altering their morphology and structure. Risk factors for heart failure include aging, hypertension, smoking, ischemia, hyperglycemia, and hyperlipidemia. We have observed significant mitochondrial fission in the mouse heart in response to ischemia, exposure to cigarette smoke, high blood pressure, and high glucose loads (Figure 3). Mitochondrial fission is induced by dynamin-related GTP binding protein 1 (Drp1) translocating to the mitochondrial outer membrane in a GTP-dependent manner, where it binds to fission proteins such as fission protein-1 (Fis1), mitochondrial fission factor (Mff), and mitochondrial dynamics proteins of 49 and 51 kDa (MiD49 and MiD51).
Mitochondrial fusion, on the other hand, is regulated by fusion-promoting GTP-binding proteins such as mitofusin-1 (Mfn1), mitofusin-2 (Mfn2), and optic atrophy-1 (Opa1). Dysfunctional mitochondria are degraded via mitophagy, while healthy mitochondria fuse and recycle through Mfn1, Mfn2, and Opa1. The roles of mitochondrial dynamics control in the heart have been elucidated through phenotypic analysis using Drp1 or Mfn1/Mfn2 KO mice. Drp1-KO mice exhibit a phenotype resembling dilated cardiomyopathy, characterized by prominent mitochondrial fusion and elongation, increased mitophagy and mitochondrial loss, and myocardial necrosis. In contrast, hearts of Mfn1/Mfn2 double KO mice display a phenotype resembling concentric hypertrophy, characterized by increased mitochondrial fission, mitochondrial accumulation accompanied by reduced mitophagy, and cardiomyocyte hypertrophy. Hearts of Drp1/Mfn1/Mfn2 triple KO mice exhibit a phenotype resembling eccentric hypertrophy, with heterogeneous mitochondrial populations, accumulation of giant mitochondria with impaired mitophagy, and distortion of sarcomere structure. These findings suggest that quality control mechanisms through mitochondrial fission/fusion play a crucial role in maintaining myocardial homeostasis. It has been reported that cytoskeletal proteins such as myosin II and actin fibers promote Drp1 aggregation at mitochondrial constriction sites. However, activation of Drp1 solely by actin or myosin II is insufficient, and the mechanism by which the cytoskeleton activates Drp1 and promotes mitochondrial fission has remained unclear.

We identified cilnidipine as an approved drug that strongly suppresses myocardial mitochondrial fission and myocardial early senescence caused by ischemic stress. Cilnidipine is one of voltage-dependent L-type calcium channel blockers with a dihydropyridine chemical structure used for the treatment of hypertension, but we

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revealed that only cilnidipine has an ability to prevent the pathological interactions between Drp1 and actin-binding protein filamin-A, a GTP/GDP exchange factor for Drp1. Treatment of mice with cilnidipine 1 week after myocardial infarction significantly improved chronic heart failure 49.

Another cause of mitochondrial over-fission induced by stress is the relationship between the processing of Opa1 and heart failure, as reported in mice 52. In mice lacking YME1L, one of the two mitochondrial proteases involved in Opa1 processing and degradation, Oma1-dependent Opa1 processing is enhanced, resulting in severe dilated cardiomyopathy. In these mouse myocardia, a metabolic switch (from fatty acids to glucose) occurs in mitochondria, and although mitochondrial fragmentation is not suppressed by feeding a high-fat diet, myocardial metabolic abnormalities and dysfunction can be alleviated. Future studies focusing on Opa1-dependent mitochondrial quality control will understand the systemic control of mitochondrial quality during the progression of heart failure, to develop a breakthrough therapeutic strategy.

5. Redox-energy metabolism as a key player in the reversibility of cardiac remodeling

The redox-dependent Drp1 activation is also implicated as a cause for bad prognosis of heart failure 48. Specifically, improvements in heart function in diabetic cardiomyopathy and chronic heart failure model mice have been observed with Drp1 inhibition 53, and a genetic mutation (Cys452) in Drp1 has been reported to lead to python cardiomyopathy 54, post-translational modifications, including phosphorylation, SUMOylation, ubiquitination, S-nitrosylation, and glycation, are involved in the
regulation of Drp1 activity. Among these, the cysteine at the C-terminal (Cys644) exhibits high redox activity, sensing environmental stress changes through oxidation modifications (S-nitrosylation (SNO) or sulfonylation (SOH)), leading to its activation. Conversely, it has been shown that Cys644 is polysulfidated by increased expression of mitochondrial-localized cysteinyll-tRNA synthetase (CARS2) and cystathionine-γ-lyase (CSE), which have intracellular cysteine persulfide (Cys-SSH) synthesis activity, resulting in negative control of Drp1 activity. Conversely, no formation of polysulfide chains was observed in the mitochondrial fusion-promoting G proteins Mfn1, Mfn2, and Opa1. Substituting Cys644 in Drp1 with serine, a smaller molecular weight amino acid, increased Drp1-dependent mitochondrial fission activity; while substitution with tryptophan, a larger molecular weight amino acid, decreased Drp1-dependent mitochondrial fission activity. Therefore, Cys644 of Drp1 is shown to become bulky by Cys polysulfidation, negatively regulating Drp1 activity.

Systemically, regulating nucleophilic sulfur molecules is increasingly implicated in the control of myocardial robustness. The metabolism and generation of intracellular persulfides and/or polysulfides (we generally term them ‘supersulfide’) can be visualized through live imaging by combining selective fluorescent indicators for reduced supersulfide (QS10, SSip1, SSP) and H₂S/HS⁻ selective fluorescent indicators. We found that catabolism of supersulfides to H₂S/HS⁻ is enhanced in myocardial tissues exposed to ischemia (hypoxia). This may be due to electron accumulation under low O₂ conditions, supersulfide acts as electron acceptor. As a medical application, echinochrome-A (EchA), a naphthoquinone derivative marine drug, is known for its antioxidant and anti-inflammatory properties. We found that EchA administration suppressed the accumulation of H₂S/HS⁻ in ischemic myocardial tissues.
and maintained high levels of supersulfides, leading to recovery of cardiac function\textsuperscript{57}. Although the mechanism by which EchA inhibits sulfur metabolism is still largely unknown, the demonstration that maintenance of persulfide molecule activity within cardiac cells contributes to the maintenance of myocardial robustness is intriguing. Especially considering that compounds showing ischemic myocardial protection effects such as EchA and oxidized supersulfides commonly possess electrophilic properties, it may be effective to improve chronic heart failure after ischemia using compounds with both electrophilic and nucleophilic properties rather than existing antioxidant therapies (Figure 4).

6. Conclusion

Based on morphological and structural analyses using animal models of cardiac diseases, the pathogenesis and etiology of cardiac remodeling have been successively elucidated. Conducting multi-level research, from individual organisms to molecules and cells, has also shown the potential for controlling the reversibility of cardiac remodeling through transfigurations in cardiac energy metabolism. This approach offers insights into new therapeutic strategies for diabetic heart failure and HFpEF, where effective treatments have not been established. Particularly, the advancement of redox studies focusing on supersulfide metabolism and dynamics and associated mitochondrial quality control may lead to the development of groundbreaking therapeutic agents that promote myocardial repair.
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Figure 1. Various phenotypes of cardiac remodeling.

Figure 2. Intracellular signaling pathways involved in hypertrophic growth of cardiomyocytes and fibrotic response (myofibroblast differentiation) of cardiac fibroblasts, and their intercellular interactions.

Figure 3. Mitochondrial hyperfission as a risk factor of bad prognosis of heart failure after myocardial infarction. Environmental electrophiles, such as aldehyde, heavy metals, and PM2.5 may cause mitochondrial fragmentation in myocardium through Drp1 activation.

Figure 4. Intracellular supersulfide catabolism caused by ischemic stress and environmental electrophiles promotes cardiac vulnerability by promoting myocardial early senescence. A naphthoquinone-structure marine drug, echinochrome-A (Ech-A), has potency to oxidize hydrogen sulfide, preventing myocardial supersulfide catabolism and heart failure after myocardial infarction.
Figure 1
cardiomyocytes

AT1R, P2Y1R, α-AR

G12

Gαs

Gαs

DAG

Zn2+

Ca2+

Gs

cAMP/PKA

Ca2+

NFAT

hypertrophic genes ↑

F-actin

G-actin

MRTF

TRPC3/6

fibrotic factor (TGF-β, CTGF)

Rho

TRPC3

Ca2+

Smad

p-Smad

MRTF

Collagen I, III

Figure 2
Figure 3
Figure 4
Graphical Abstract

Ech-A → GSH → Cys SH

Drp1 ↑
Cilnidipine

Cardiomyocyte cell size ↑
Fibrosis ↑
Inflammation ↑

Heart failure → Cell death

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