Molecular mechanisms and intervention approaches of heart failure (Review)

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Abstract. Heart failure is a major health issue that threatens life and health. Previous studies have shown that heart failure is the terminal stage of arrhythmia, dilated cardiomyopathy, hypertension, hypertrophic cardiomyopathy and myocardial infarction. The pathological mechanisms through which cardiovascular diseases result in heart failure include myocardial fibrosis and hypertrophy, myocardial cell death, mitochondrial dysfunction, vascular remodeling and calcium dysregulation. However, the detailed molecular mechanisms of heart failure remain elusive because of its complexity, hindering the development of intervention approaches for heart failure. The present study reviewed recent research progress on heart failure and provided references and strategies for the prevention and treatment of heart failure.

Contents

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1. Introduction

There are >26 million individuals with heart failure worldwide (1). The incidence of heart failure increases with age and the prevalence of heart failure in patients >80 years of age is estimated to increase by 66% by 2030 (2,3). Heart failure is associated with high morbidity and >300,000 individuals die from heart failure each year worldwide, thus imposing a heavy medical burden on those affected (4-6). Heart failure is characterized by impaired ventricular filling or a decreased ejection fraction due to various pathological stimuli, such as high blood pressure, hyperglycemia, inflammatory factors and myocardial ischemia (7,8). In patients with heart failure, cardiac output cannot meet the metabolic needs of the body, which leads to insufficient blood perfusion of organs and tissues (9). Heart failure is the terminal stage of arrhythmia, dilated cardiomyopathy (DCM), hypertension, hypertrophic cardiomyopathy (HCM) and myocardial infarction (MI) (10). Therefore, studies on the molecular mechanisms through which the abovementioned cardiovascular diseases develop into heart failure will provide a solid basis for preventing heart failure.

The pathogenesis of heart failure is highly complex. The reported molecular mechanisms of heart failure mainly include the dysregulation of disease-related genes, noncoding RNAs, calcium ion homeostasis, mitochondrial homeostasis, cell apoptosis, extracellular matrix (ECM) remodeling, oxidative stress, the inflammatory response and the neuroendocrine system (11-22). Cardiac hypertrophy-related and fibrosis-related genes are associated with the occurrence and development of heart failure (23,24). The overexpression of cardiac hypertrophy-related genes, such as myosin binding protein C (*MYBPC3*) and myosin heavy chain 7 (*MYH7*), can lead to myocardial systolic and diastolic dysfunction (25,26). The expression of fibrosis-related genes such as transforming growth factor β1 (*TGFB1*) and actin α2 (*ACTA2*) can cause the activation and proliferation of myofibroblasts and the inflammatory response (27,28). The dysregulation of calcium ion homeostasis in myocardial cells also plays an important role in heart failure (17,18,29,30). The abnormal expression of microRNAs (miRNAs) is also associated with heart failure (14,15,31). miRNA-1 and miRNA-21 can regulate

the expression of myocardial function-related genes and their dysregulation can disrupt the metabolism, apoptosis and contraction of myocardial cells (31-33). Mitochondrial dysfunction can disrupt the energy supply to myocardial cells, leading to impaired myocardial function (18,34). In addition, increased myocardial cell apoptosis and necroptosis are important risk factors for heart failure (19,35,36). Cardiomyocyte necroptosis can lead to cell swelling, cell membrane rupture and intracellular contents overflow, which together triggers inflammatory responses and heart failure (36-38). Previous studies have shown that inflammatory factors such as interleukin-1 (IL-1), IL-6, tumor necrosis factor-α (TNF-α) and excessive reactive oxygen species (ROS) can activate the intracellular apoptotic signaling pathway, which promotes myocardial cell death and heart failure (28,39-42). Inflammatory responses are closely linked with the occurrence and development of heart failure (43). The release of inflammatory factors such as TNF-α and IL-6 can promote an inflammatory cascade, which results in myocardial cell damage and cardiac fibrosis (21,43). Oxidative stress induced by excessive ROS production can cause myocardial damage and dysfunction, which leads to heart failure (20,41). Neuroendocrine system overactivation can also lead to heart failure (22). The abnormal activation of the renin-angiotensin-aldosterone system (RAAS) can increase angiotensin II (Ang II) levels, thus promoting myocardial remodeling (22,44). However, there are few effective preventive targets and therapeutic methods for treating heart failure due to its complex molecular mechanisms. Further studies on the detailed mechanisms of heart failure are highly important for the diagnosis, treatment and prevention of heart failure.

The present study reviewed recent research progress on the pathogenesis of heart failure, providing more references for further studies on the molecular mechanisms of heart failure and contributing to the development of potential therapeutic targets for heart failure.

2. Arrhythmia

Arrhythmia has a high mortality rate of ~10-15%; it is characterized by abnormalities in the frequency, rhythm, origin, conduction velocity and sequence of cardiac impulses (45-47). Arrhythmia can lead to insufficient heart pumping, damage the blood supply to various tissues and organs and result in dizziness, fatigue, amaurosis and syncope (46,48). Furthermore, long-term or severe arrhythmia can promote myocardial oxygen consumption, which gradually leads to myocardial remodeling and heart failure (49,50). It is important to investigate and reveal the pathogenesis of arrhythmia to prevent heart failure (51). However, the mechanisms by which arrhythmia causes heart failure are complex and remain to be fully elucidated.

Arrhythmia can result in heart failure through TGF-β1/Smad signaling, Wnt/β-catenin signaling and IL-1β secretion (Fig. 1) (52-54). The activation of TGF-β1/Smad signaling can cause cardiac fibrosis in atrial fibrillation, which leads to structural and functional damage to the heart and to heart failure (52). Smad2 and Smad3 are receptor-regulated Smads (R-Smads) that can be phosphorylated and activated by type I receptors of TGF-β (55,56). In addition, Smad4 is a comodulator Smad and Smad7 is a type of inhibitory Smad that can compete with R-Smads for binding to type I receptors of TGF-β and inhibit the phosphorylation of R-Smads (56,57). TGF-β1 expression is upregulated in arrhythmias; this increase decreases Smad7, weakens the competitiveness of Smad7 and promotes the activation of Smad2 and Smad3 (58,59). Activated Smad2 and Smad3 can form a complex with Smad4, and the complex can be transferred to the nucleus, upregulate the transcription of fibrosis-related genes, including collagen type I α1 chain (*COL1A1*), *COL3A1*, fibronectin 1 and *ACTA2*, and ultimately result in cardiac fibrosis (58,60-62). Another pathway is the classical Wnt pathway (53,63). Without Wnt stimulation, the 'destruction complex', which is composed of Axin, adenomatous polyposis coli protein, glycogen synthase kinase 3β and casein kinase 1α, is active *in vivo* (64). β-catenin is phosphorylated by the 'destruction complex', and phosphorylated β-catenin is ubiquitinated and then degraded by proteasomes, resulting in a low protein level of β-catenin in the cytoplasm (63,64). Once Wnt ligands bind to the Frizzled receptor and low-density lipoprotein receptor-related protein 5/6, the 'destruction complex' can be disrupted and scattered (65), protecting β-catenin from being phosphorylated and degraded, and thus promoting β-catenin accumulation (53,64). The accumulated β-catenin then enters the cell nucleus, interacts with T-cell factor/lymphoid enhancer factor to form a transcription activation complex, and upregulates the transcription of Wnt signaling-related genes, including *ACTA2*, connective tissue growth factor, *COL1A1* and phosphoribosyl anthranilate isomerase 1, thus driving myocardial fibrosis (64,65). In the case of atrial fibrillation, the first and second pathways are abnormally activated, leading to myocardial fibrosis (66-69). Furthermore, as atrial fibrillation persists and atrial fibrosis progresses, the burden on the heart continues to increase, resulting in heart failure (69-71). In the third pathway, proinflammatory macrophages can induce atrial electrical remodeling by secreting IL-1β, which decreases the protein level of the atrial myocyte fibrillation protein Quaking (QKI) (54,72). Atrial fibrillation can induce proinflammatory macrophage polarization and IL-1β secretion from macrophages to downregulate QKI expression (72); it can reduce the binding of QKI and calcium voltage-gated channel subunit α1 C (CACNA1C) mRNA in atrial myocytes, which decreases the protein level of CACNA1C and L-type calcium currents (72,73). Ultimately, atrial fibrillation can induce electrical remodeling and affect cardiac function, which can cause heart failure in the long term (72-74).

There are numerous reported arrhythmia-targeted drugs, genes and surgical treatments for preventing heart failure (Table I) (75-81). In clinical practice, antiarrhythmic drugs include Class I, II, III and IV drugs (75,76). Class I sodium channel blockers can be divided into moderate sodium channel blockers (e.g., quinidine), mild blockers (e.g., lidocaine) and significant blockers (e.g., propafenone) (75,76); they can reduce the autonomy of myocardial cells to different degrees (75,76). Class II drugs, which are β-blockers (e.g., propranolol), can competitively block β adrenergic receptors to reduce myocardial autonomy; they are mainly used to treat sympathetic nervous system excitation-related arrhythmias (75,76). Class III drugs, which are potassium channel blockers (e.g., amiodarone), can prolong the action potential and refractory period of myocardial cells by blocking potassium

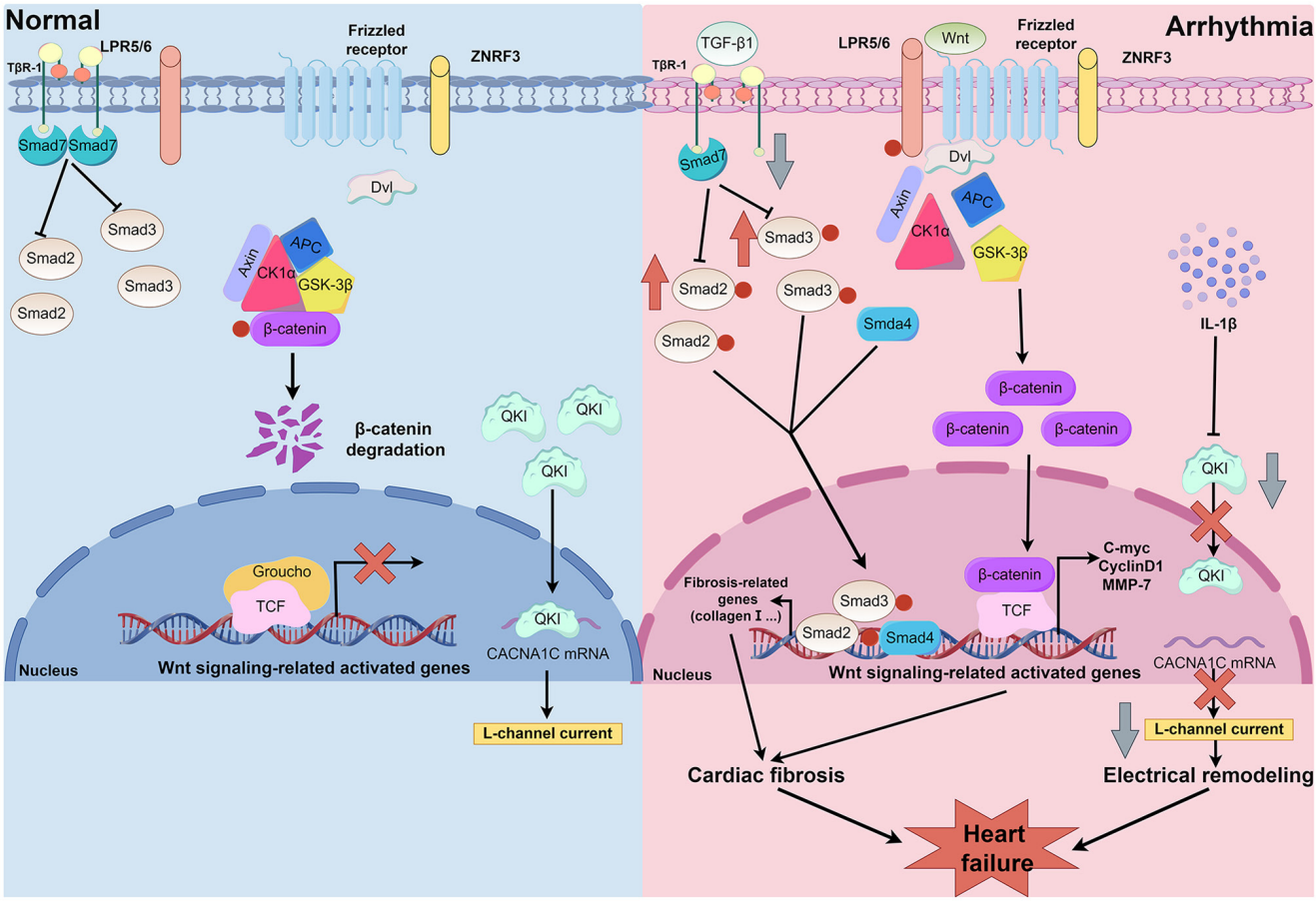

Figure 1. Molecular mechanisms through which arrhythmias lead to heart failure. The activation of the TGF-β1/Smad and Wnt/β-catenin signaling pathways can result in cardiac fibrosis and heart failure. In addition, the secretion of IL-1β can decrease the L-type calcium current and myocardial electrical remodeling and alleviate heart failure. Wnt, wingless-type MMTV integration site family; TβR-1, type I transforming growth factor β1 receptor; LPR5/6, lipoprotein receptor-associated protein 5/6; Dvl, disheveled; Axin, complex composed of axial proteins; APC, adenomatous polyposis coli protein; GSK-3β, glycogen synthase 3β; CK1α, casein kinase 1α; IL-1β, interleukin-1β; TCF, T cell factor; CACNA-1C, calcium voltage-gated channel subunit α1 C; QKI, quaking; ZNRF3, zinc and ring finger 3.

channels; they are commonly used to treat structural heart disease-related arrhythmias (75,76). Class IV drugs, which are calcium channel blockers (e.g., verapamil), can act mainly on L-type calcium channels in myocardial cells and vascular smooth muscle cells (VSMCs), inhibit calcium ion influx and reduce the autonomy of the sinoatrial node (75,76); these drugs can improve myocardial electrophysiological stability and inhibit the myocardial damage induced by arrhythmia, which ultimately prevents heart failure (75,76). It has been reported that the insulin-like hormone relaxin can reverse TGFβ-induced cardiac fibrosis and increase the conduction velocity of atrial action to suppress arrhythmias (77,78). In addition, numerous genes have been reported to play important roles in the development of arrhythmia and may be prospective targets for preventing heart failure (74,79-81). MicroRNA (miR)-210-3p, a miRNA within extracellular vesicles derived from atrial myocytes, promotes atrial fibrosis by targeting the glycerol-3-phosphate dehydrogenase 1-like protein/phosphatidylinositol 3-kinase/AKT pathway. Therefore, miR-210-3p inhibitors can prevent Ang II-induced AF occurrence and persistence in rats, alleviate atrial fibrosis and prevent the development of heart failure (79). QKI can act as a prospective target for inhibiting electrical remodeling and heart failure (75) Surgical treatments include catheter ablation and left-ventricular assisted devices (80,81). Catheter ablation involves the use of radiofrequency currents, cryogenic energy or other energy sources to generate high or low temperatures locally, causing coagulation necrosis or cryogenic damage to abnormal myocardial tissue that leads to arrhythmia, thereby disrupting the conduction pathway or origin point of abnormal electrical activity, restoring normal cardiac rhythm, improving cardiac rhythm and pumping function, and thus playing a certain therapeutic role in heart failure (80). Left ventricular assistance devices use mechanical assistance to help the left ventricle pump blood out, increase cardiac output and improve systemic blood circulation; they are effective for treating arrhythmia and heart failure (81).

3. DCM

The five-year mortality rate for patients with DCM is ~20% (82). DCM is a type of primary cardiomyopathy and characterized by an enlarged heart and weakened myocardial contractility (83); it can cause dyspnea, fatigue, edema and other heart failure-related clinical symptoms (83,84). Finally, DCM can lead to heart failure (84). It is important to investigate the detailed mechanisms of DCM to prevent heart failure.

Table I. Intervention and treatment approaches for heart failure.

Condition	Methods	Therapies	(Refs.)
Arrhythmia	Medication	Quinidine, lidocaine, propafenone, propranolol, amiodarone, verapamil and RLX	(75-78)
	Potential targets	QKI and miR-210-3p	(74,79)
	Surgical treatment	Catheter ablation and left-ventricular-assist device	(80,81)
Dilated cardiomyopathy	Medication	Prednisolone, azathioprine, intravenous immunoglobulin, immunoadsorption, AECI, β-blockers and MRA	(86,90-94)
	Potential targets	Gene therapy, gene editing technology to replace mutated sarcomeric-related genes (*TTN*, *TNNT2* and *TNNC1*)	(87,95)
	Surgical treatment	Intra-aortic balloon pump catheter and left-ventricular assist device	(97,98)
Hypertension	Medication	Lp-PLA2 inhibition, acetyltransferase p300 inhibitor, LCCBs (amlodipine, verapamil and diltiazem) NOX inhibitors (GKT137831 and GSK2795039), RAS, ACEIs and CCB	(115-120)
Hypertrophic cardiomyopathy	Medication	Sarcomere contractile inhibitors (aficamten)	(130-132)
	Surgical treatment	Alcohol septal ablation and surgical myectomy	(131)
	Potential targets	Gene-targeted therapy (repair *MYBPC3* gene)	(133)
Myocardial infarction	Medication	Ramipril, perindopril, clopidogrel, atorvastatin, simvastatin, rosuvastatin, stem cell therapy, anti-TNF-α antibody and SLC40A1 inhibition	(147-151)
	Surgical treatment	Coronary intervention combined with drugs to dissolve blood clots	(152,153)

RLX, relaxin; QKI, quaking homolog; ACEI, angiotensin-converting enzyme inhibitor; MRA, mineralocorticoid receptor antagonist; TTN, titin; TNNT2, cardiac troponin T2; LCCBs, L-type calcium channel blockers; NOX, nicotinamide adenine dinucleotide phosphate oxidase; RAS, renin-angiotensin system; CCB, calcium channel blocker; SLC40A1, solute carrier family 40 member; MYBPC3, myosin-binding protein C3.

DCM can lead to heart failure through the activation of the rho-associated coiled-coil containing protein kinase 1 (ROCK1)-vimentin (VIM) pathway, an inflammatory cascade initiated by immune cells and calcium-independent receptor for α-latrotoxin (CFIRL)-mediated cardiac remodeling (Fig. 2) (85-87). The first pathway involves cytoskeleton regulation and mitochondrial autophagy (85). In DCM, mitochondrial dysfunction can activate the ROCK1-VIM pathway, leading to mitophagy (86). VIM can interact directly with mitochondria (85). Abnormally activated ROCK1 can accelerate the transport speed of damaged mitochondria by phosphorylating S72 of VIM, leading to the substantial accumulation of damaged mitochondria and significantly enhancing mitophagy (85,88). These effects result in insufficient mitochondrial energy supply and severely impaired myocardial contractility, causing heart failure (85). The second pathway involves immune cells and the inflammatory cascade (86,89). In DCM, immune cell activation leads to the development of associated inflammation (86). Among cardiomyocytes are macrophages, monocytes, B cells, T cells, natural killer (NK) cells, dendritic cells and granulocytes, and these immune cells secrete a variety of fibrotic mediators, such as cytokines, growth factors and stromal cell proteins, which play important roles in the occurrence and progression of myocardial fibrosis (86). Monocytes and macrophages can be transformed into myofibroblasts under the stimulation of various cytokines, resulting in the secretion of inflammatory mediators and fibrotic growth factors. Myeloid differentiation protein-2 can induce the proinflammatory state of monocytes in patients with DCM through toll-like receptor 4/nuclear factor-κB signaling, resulting in the secretion of monocyte chemotactic protein-1 to recruit monocytes to the site of inflammation to promote DCM progression and, concurrently, induce the expression of adhesion factors and the secretion of IL-6 and IL-1β by monocytes (86,89). Elevated levels of IL-6 and IL-1β in patients with DCM may lead to cardiomyocyte apoptosis and impaired systolic function of the heart (89). Cardiac macrophages can be divided into two types, C-C motif chemokine receptor 2 (CCR)2^+ and $CCR2^-$, on the basis of the protein level of CCR2 (86). $CCR2^+$ macrophages are involved in cardiac fibrosis and inflammatory responses, whereas $CCR2^-$ macrophages mediate tissue repair (86). $CCR2^+$ macrophages in DCM can recruit monocytes and neutrophils to the inflammatory area by secreting inflammatory cytokines and chemokines, which promote the inflammatory response (86). B cells can secrete a variety of cytokines, including proinflammatory agents (e.g., TNF-α)

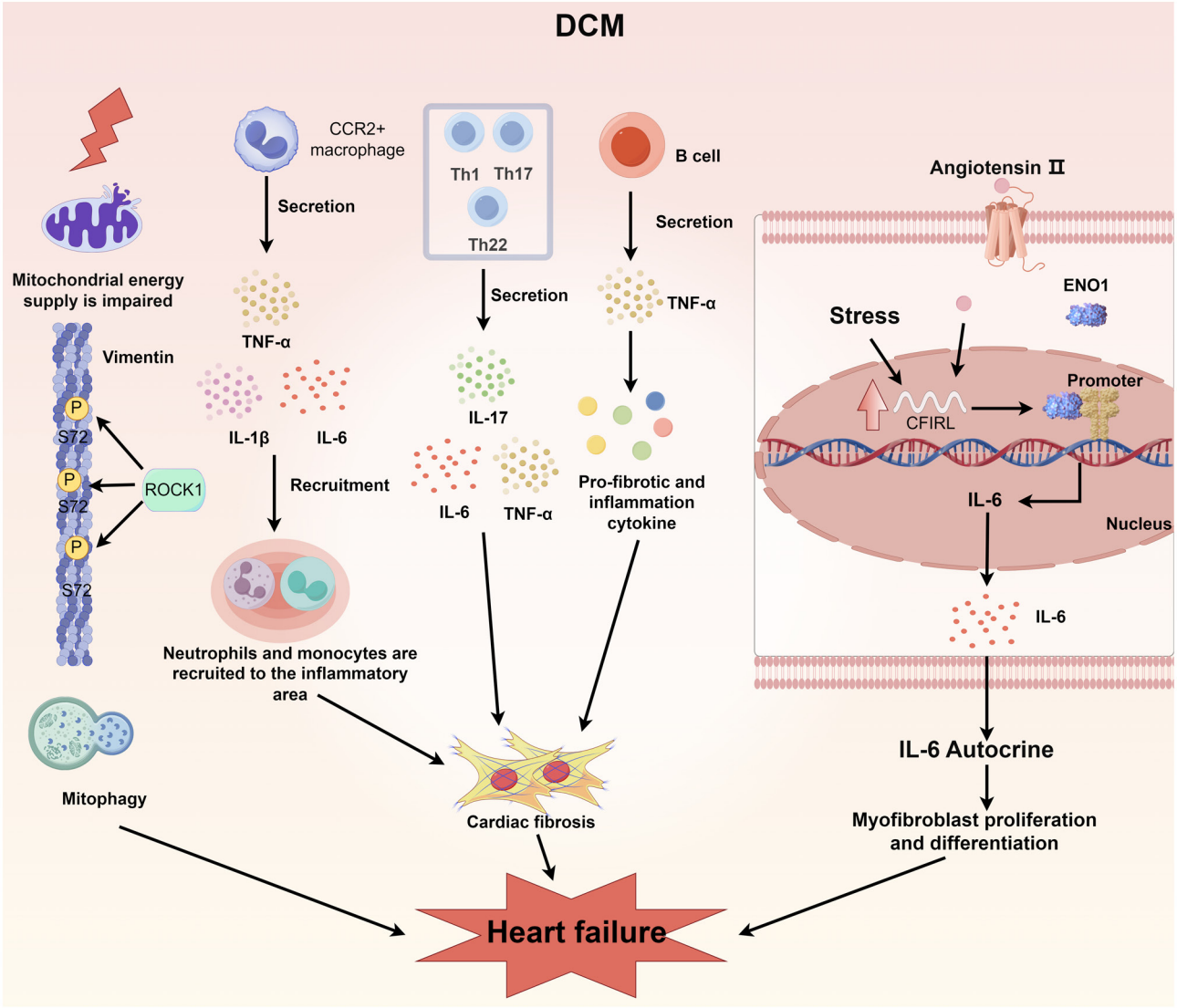

Figure 2. Molecular mechanisms through which DCM leads to heart failure. ROCK1-VIN pathway activation can lead to mitophagy and heart failure. Immune cells such as macrophages, T cells and B cells can secrete inflammatory and chemotactic factors, resulting in cardiac fibrosis and heart failure. The upregulation of CFIRL expression can cause IL-6 autocrine activity, myofibroblast proliferation and differentiation, and heart failure. ROCK1, rho-associated coiled-coil containing protein kinase 1; DCM, dilated cardiomyopathy; $CCR2^+$, C-C chemokine receptor 2 positive; TNF-α, tumor necrosis factor-α; Th1, T helper 1 cell; ENO1, enolase 1; CFIRL, calcium-independent receptor for α-latrotoxin.

and anti-inflammatory molecules (e.g., IL-1) (87). Patients with DCM have increased TNF-α and decreased IL-1 secreted by B cells, which impairs their anti-inflammatory ability (86). T cells can be divided into T helper 1 (Th1) cells, Th22 cells, Th17 cells, T follicular helper cells and regulatory T cells and are involved in cardiac inflammation and injury, which play crucial roles in the development of DCM (86). NK cells are important anti-inflammatory cells and their depletion can cause DCM and heart failure (86). The inflammatory cascade caused by various immune cells can eventually lead to cardiac fibrosis and heart failure (86). The third pathway is CFIRL-mediated cardiac remodeling (87). In DCM, significantly upregulated CFIRL expression stimulated by pressure overload or Ang II can recruit enolase 1 to the nucleus to form a transcription activation complex that promotes *IL6* gene transcription (87). The abnormal upregulation of IL-6 expression mediated by CFIRL has an autocrine effect, directly promoting the proliferation and differentiation of myofibroblasts and indirectly stimulating cardiac hypertrophy, which ultimately leads to heart failure (87).

Previous studies have reported numerous DCM-targeted drugs, genes and surgical treatments for preventing heart failure (Table I) (83,86,87,90-98). Immunotherapy is an important intervention approach for preventing DCM and heart failure (86,90). Immunotherapy can regulate the immune system and suppress the myocardial damage caused by autoimmune reactions (86); it includes immunosuppressive therapy, intravenous immunoglobulin and immunoadsorption (86). During the clinical trial stage, immunosuppressive therapy (e.g., prednisolone and azathioprine) can reduce the antibody immune response by inhibiting the activity of immune response-related cells such as T cells, B cells and macrophages (86). Intravenous immunoglobulin can recognize and bind to dysregulated antibodies in patients, which reduces the attack and damage caused by dysregulated antibodies on myocardial cells (86). In immune adsorption therapy,

extracorporeal circulation is used to selectively remove dysregulated antibodies, immune complexes and other related immune active substances from the blood using an immune adsorption column (86,90). Angiotensin-converting enzyme inhibitors (ACEIs) can effectively prevent cardiac fibrosis in DCM and the development of heart failure (91). β-blockers can reverse left ventricular dilation, which protects cardiac function and heart failure (92,93). Mineralocorticoid receptor antagonists, which can increase the ejection fraction in and reduce the mortality rate of patients with heart failure, are used to treat DCM (83,94). In addition, certain genes have been reported to play important roles in DCM and may be prospective targets for preventing heart failure (87,95). DCM is a typical hereditary cardiomyopathy and gene therapy can be used to replace diseased genes (95). The dysregulation of sarcomere-related genes [e.g., *titin*, troponin T2 (*TNNT2*) and *TNNC1*] is the main cause of DCM (95). By replacing these dysregulated genes, DCM can be used to intervene in the development of heart failure (95). A significant increase in CFIRL can mediate cardiac remodeling; therefore, CFIRL can serve as a potential therapeutic target (87). For surgical treatment, nonischemic DCM can be treated with a left ventricular assist device to reverse left ventricular remodeling and prevent progression to heart failure (96,97). Intra-aortic balloon pump catheters are used as a bridge to heart transplantation and a transitional therapy for patients with advanced heart failure (98).

4. Hypertension

Over the past 30 years, ~8.5 million individuals have died worldwide from hypertension (99). Hypertension is characterized by increased pressure overload of the heart and its long-term development can further enlarge the left ventricle, increase myocardial oxygen consumption, induce weakened myocardial contractility and reduce cardiac output, which eventually results in heart failure (100). It is essential to study the molecular mechanisms of hypertension and intervene in its development to prevent heart failure.

Vascular remodeling is an important pathway through which hypertension leads to heart failure (101). Vascular remodeling is a type of pathological change that is difficult to reverse (101). Key events in vascular remodeling include endothelial cell (EC) dysfunction, the migration and proliferation of VSMCs and changes in the collagen ECM (Fig. 3) (101,102). Hypertension is an important risk factor for EC dysfunction (102). EC dysfunction resulting from insufficient nitric oxide production and increased levels of ROS in blood vessels can lead to a decreased vasodilation capacity, which causes the blood vessels to narrow and blood pressure to continue to rise, eventually leading to vascular remodeling and heart failure (102,103). Hypertension is closely related to the contractile function of VSMCs (101). The phenotypic conversion of VSMCs from a contractile to a synthetic phenotype causes vascular calcification and the proliferation and migration of VSMCs due to the overproduction of Ang II in patients with hypertension, which leads to impaired vascular contraction function and heart failure (99,101,104). Alterations in the ECM are currently irreversible pathological changes in hypertension (101). The dysregulated synthesis of the ECM, such as increased collagen and decreased elastin synthesis, is caused by the activation of matrix metalloproteinases and the deposition of advanced glycation end products in hypertension, which can increase the hardness and weaken the elasticity of the vascular wall (101).

In addition, hypertension can cause heart failure through cardiac remodeling (105). Cardiac remodeling is a physiological adaptation to chronic pressure overload (106). Key events in cardiac remodeling include cardiomyocyte hypertrophy and myocardial fibrosis (Fig. 3) (107-109). Myocardial cell hypertrophy is an early adaptive change in the heart to hypertension (110). Myocardial cells are stimulated by mechanical traction and abnormalities in Ang II, norepinephrine and calcium regulation, which cause the compensatory hypertrophy of myocardial cells, promoting cardiac remodeling and heart failure (110,111). Long-term hypertension causes cardiac fibroblasts to transform into myofibroblasts, which secrete large amounts of type I and type III collagen, leading to excessive deposition of ECM and the gradual development of myocardial fibrosis (112,113). The infiltration of inflammatory cells, the release of inflammatory factors and the stimulation of Ang II promote myocardial fibrosis, leading to increased myocardial stiffness, limited cardiac diastolic function and ultimately heart failure (113,114).

Numerous hypertension-targeted drugs for preventing heart failure have been reported (Table I) (115-120). The acetyltransferase p300 inhibitor L002 can prevent the progression of heart failure by reversing hypertension-induced myocardial fibrosis and left ventricular hypertrophy (115). Lipoprotein-associated phospholipase A2 plays a key role in hypertensive cardiac fibrosis, and its inhibitor, darapladib, can prevent Ang II-induced cardiac remodeling and inflammation (116). Voltage-gated L-type Ca^{2+} channel blockersincluding dihydropyridines (e.g., amlodipine), phenylalkylamines (e.g., verapamil) and benzothiazepines (e.g., diltiazem), are mainly used to treat hypertension (117). The ROS produced by nicotinamide adenine dinucleotide phosphate oxidase (NOX) activation can induce the dysfunction of other oxidase systems, which leads to a vicious cycle and exacerbates cardiovascular tissue damage (118). Novel NOX inhibitors, such as GKT137831 and GSK2795039, have increased selectivity and specificity for alleviating oxidative stress (118). In a mouse model, NOX inhibitors have been shown to have inhibitory effects on ROS production, which implies that these inhibitors have the ability to suppress cardiac remodeling and heart failure (118). In addition, there are several clinically recommended antihypertensive drugs, including the RAAS blockers, ACEIs, angiotensin receptor blockers, calcium channel blockers and thiazides or thiazide diuretics (119,120).

5. HCM

The prevalence of HCM, which is influenced by genetic factors and sarcomere mutations, is 1:200 (121,122). HCM is characterized by myocardial hypertrophy, especially asymmetric thickening of the ventricular septum (123). This abnormal myocardial hypertrophy can reduce the size of the heart chambers and severely impair cardiac diastolic function, which leads to hemodynamic dysregulation (123). Long-term

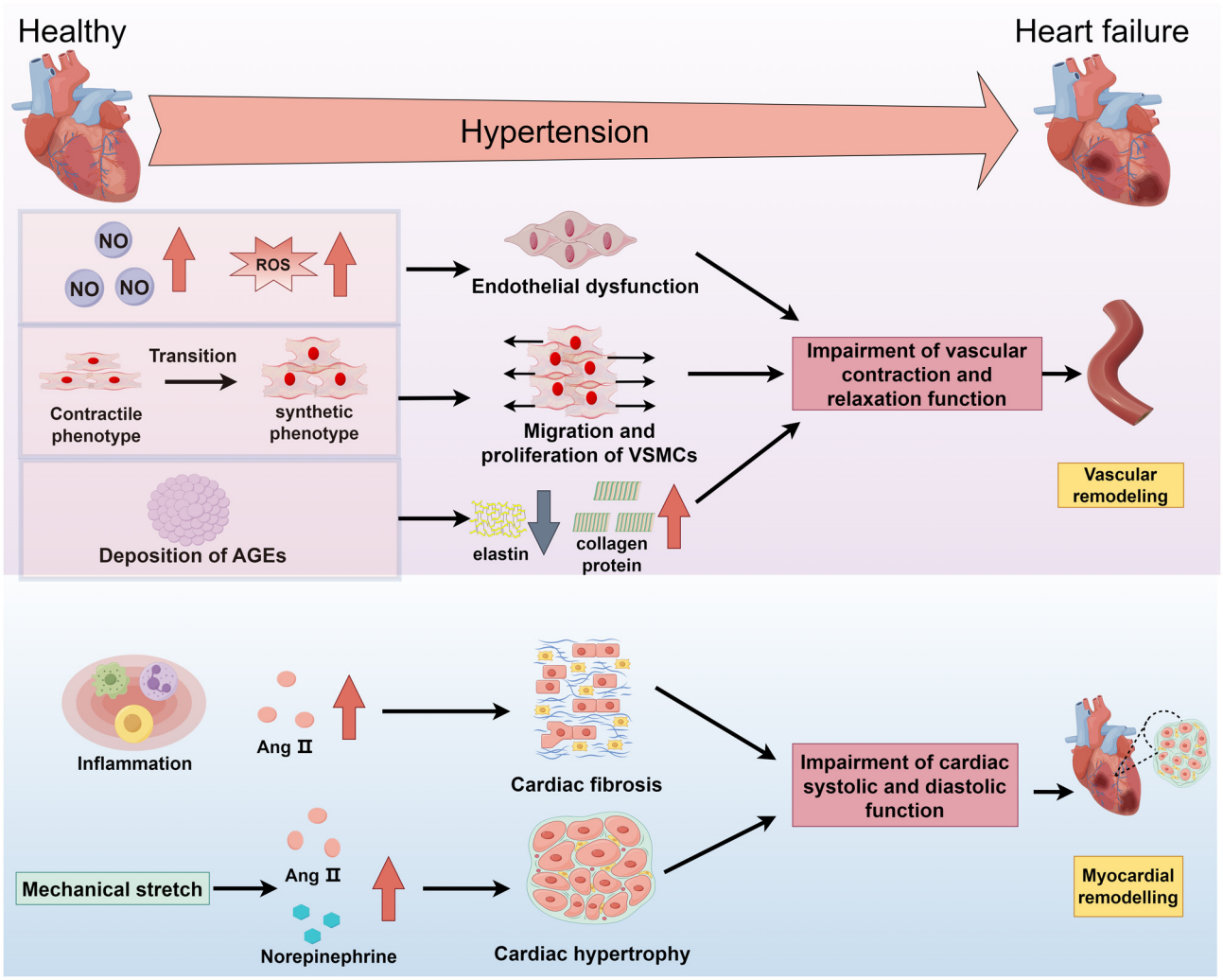

Figure 3. Molecular mechanisms through which hypertension leads to heart failure. Endothelial cell dysfunction, the migration and proliferation of VSMCs and the dysregulation of extracellular matrix components can cause vascular remodeling and heart failure. Cardiac fibrosis is induced by inflammation or Ang II and hypertrophy by Mechanical stretch, and Ang II or norepinephrine can result in myocardial remodeling and heart failure. NO, nitric oxide; ROS, reactive oxygen species; VSMCs, vascular smooth muscle cells; AGEs, advanced glycation end-products; Ang II, angiotensin II; RAAS, renin-angiotensin-aldosterone system.

hemodynamic dysregulations can gradually fatigue the heart and eventually contribute to heart failure (124). It is important to investigate the molecular mechanisms of HCM further, to identify more potential targets for developing therapeutic options for heart failure.

Mutations in sarcomere-related genes, including *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3* and tropomyosin 1 (*TPM1*), have been shown to lead to HCM and heart failure (Fig. 4) (123,124). These mutated sarcomere-related genes can impair the contraction, relaxation and energy metabolism of myocardial cells, potentially triggering the occurrence and development of HCM and heart failure (13). Mutations in *MYH7* may disrupt normal myosin head structure and function, thus damaging myocardial contractility (125). The cMyBPC truncation mutant of the *MYBPC3* gene increases the proportion of myosin in the more active DRX conformation through a haploinsufficiency mechanism, ultimately driving excessive contraction, impairing relaxation and increasing energy expenditure (25,126). Mutations in *TNNT2* can hinder the interaction of TNNT with calcium ions, thus disrupting calcium ion dynamics and the contraction and relaxation rhythm in myocardial cells (127). Mutations in *TNNI3* can weaken the inhibitory effect of TNNI3 on the actin-myosin interaction, which results in insufficient relaxation during diastole (128). Mutations in *TPM1* can induce the spiral structure of α-TPM to become distorted or destroyed, which destabilizes actin filaments and damages myocardial systolic and diastolic function (129).

There are numerous reported HCM-targeted drugs, genes and surgical treatments for preventing heart failure (Table I) (130-133). In clinical practice, the β-adrenergic antagonists verapamil and disopyramide are mainly used to treat HCM (130). Sarcomere contractile inhibitors can prevent heart failure by reducing myofilament sensitivity to calcium ions or directly inhibiting myosin to weaken myocardial contractile function (131). For instance, aficamten can decrease myosin ATPase activity and the interaction of myosin with actin, which reduces cardiac contractility (131); it has been reported to exhibit an inhibitory effect on cardiac contractility and good pharmacokinetic properties in healthy animals and HCM models (132). Currently, phase III clinical trials are

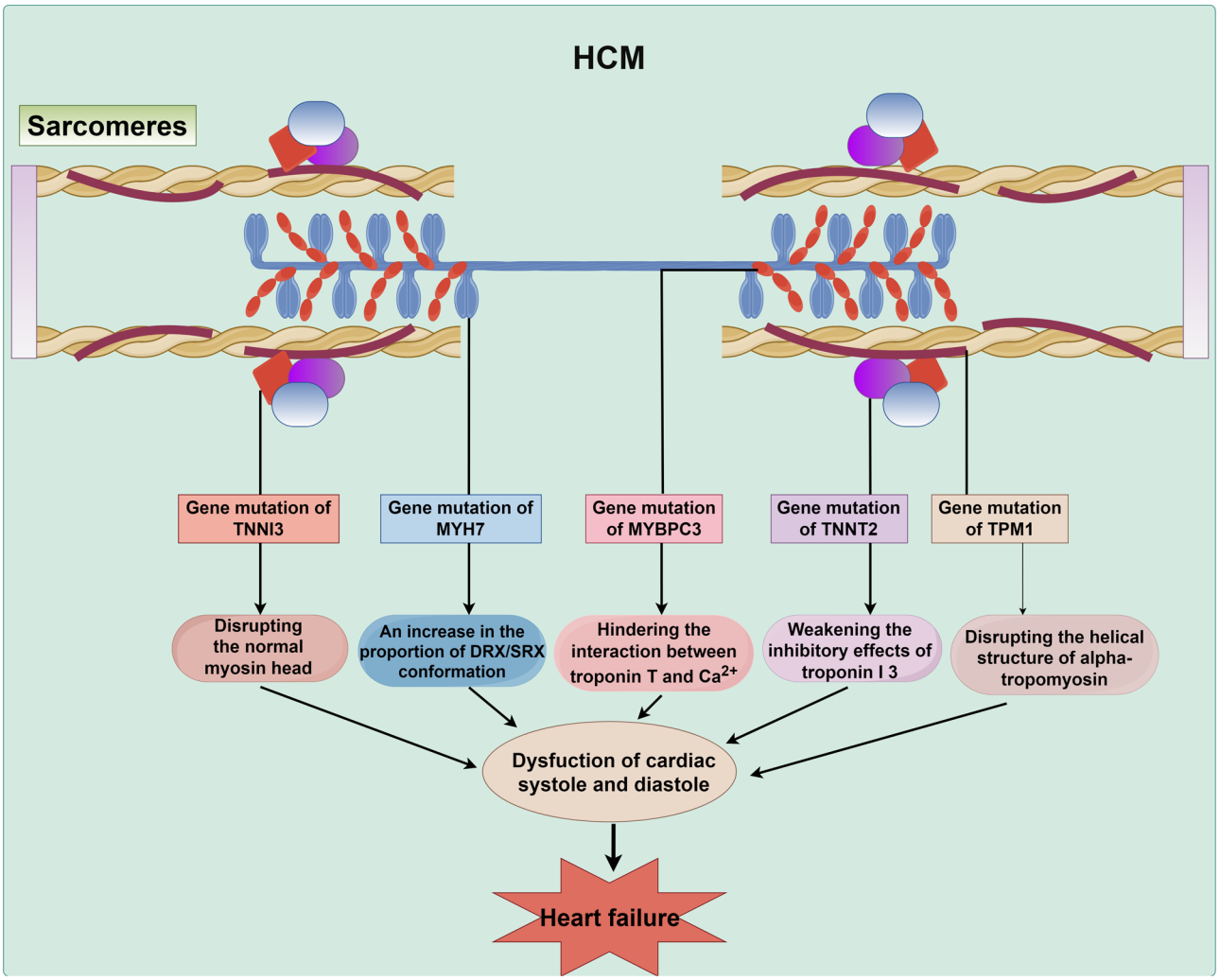

Figure 4. Molecular mechanisms through which HCM leads to heart failure. In hypertrophic cardiomyopathy, mutations in sarcomere-related genes, including *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3* and *TPM1*, can cause the dysregulation of cardiac systole and diastole function, which leads to heart failure. *MYH7*, myosin heavy chain7; *MYBPC3*, myosin-binding protein C3; *TNNT2*, cardiac-type troponin T2; *TPM1*, tropomyosin 1; DRX, disordered relaxation; SRX, super-relaxation; HCM, hypertrophic cardiomyopathy.

underway (132). Gene therapy is highly important for treating HCM (133). Exploring various genetic mutation sites to identify exon methylation and miRNA levels in HCM is beneficial for the development of gene-targeted therapy methods (133). For instance, in male patients with HCM with *MYBPC3* gene GAGT deletion, the successful repair of germline mutations was achieved, which improved homologous-directed repair efficiency without off-target events (133). Alcohol septal ablation and surgical myectomy are the primary surgical treatments used (131).

6. MI

Until 2019, MI accounted for 49.2% of deaths caused by CVD; additionally, MI has attracted widespread attention because of its high mortality rate (134). MI is characterized by myocardial ischemia due to atherosclerosis, which impairs cardiac contraction and relaxation and ultimately leads to heart failure (135,136). Studying the detailed mechanisms of MI will be beneficial for the development of potential treatment approaches for heart failure (137).

MI can result in heart failure through the regulation of cell death, including apoptosis, Ang II-induced necroptosis, mitochondrial homeostasis and Ca^{2+} transients (138-146). The first major pathway is cell death (Fig. 5). Previous studies have shown that solute carrier family 40 member 1 and steap family member 4 expression is upregulated in MI, which promotes iron efflux (138). More divalent iron ions are transported extracellularly, which causes iron deficiency in cells and myocardial mitochondrial dysfunction because electron transfer within mitochondria requires significant amounts of iron ions (138,139). Myocardial mitochondrial dysfunction leads to insufficient energy generation, disrupts the intracellular redox balance (e.g., NADPH/NADH levels), and promotes the production of ROS and oxidative stress, which ultimately stimulates myocardial cell apoptosis (Fig. 5) (138,140). In addition, Ang II-induced necroptosis plays an important role in the transition from MI to heart failure (Fig. 5) (141). In acute MI, Ang II levels are significantly elevated. Ang II is one of the main neurohumoral factors resulting in the development of heart failure (141). Ang II is involved in myocardial cell necroptosis by promoting the release of

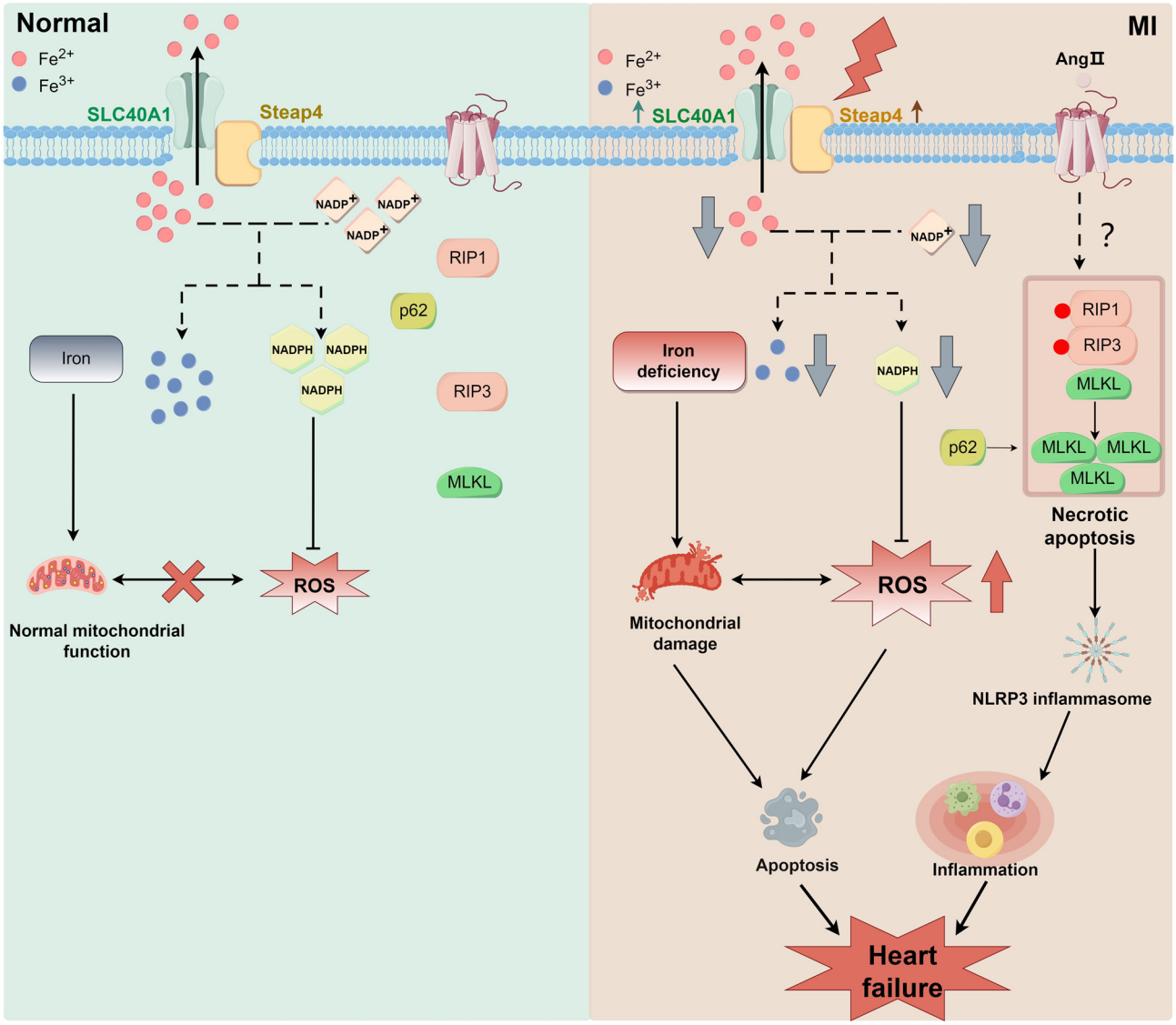

Figure 5. Molecular mechanisms through which MI leads to heart failure. The upregulation of SLC40A1 and Steap4 expression can result in mitochondrial impairment and increase ROS levels, which ultimately cause cell apoptosis and heart failure. Necrotic apoptosis mediated by Ang II can cause myocardial inflammation and heart failure. SLC40A1, solute carrier family 40 member 1; Steap4, steap family member 4; MI, myocardial infarction; NADPH, nicotinamide adenine dinucleotide phosphate-hydrogen; RIP1, receptor-interacting protein 1; ROS, reactive oxygen species; p62, sequestosome-1; MLKL, mixed-lineage kinase domain-like protein; Ang II, angiotensin II; NLRP3, NOD-like receptor protein 3.

humoral factors from cardiac fibroblasts (141). Necroptosis promotes cell rupture and the release of intracellular contents, such as damage-associated molecular patterns and lactate dehydrogenase, which stimulate an inflammatory response and ultimately trigger heart failure (141,142). In MI, mitochondrial dysfunction, mitochondrial morphological swelling and reduced cristae can lead to energy metabolism disorders and an insufficient cellular energy supply (143). Dysfunction of the mitochondrial electron transport chain in MI can result in the excessive production of ROS (143). Excessive ROS can attack mitochondrial membranes, proteins and DNA, which causes mitochondrial damage (143). The opening of the mitochondrial permeability transition pore in MI can result in abnormalities in the mitochondrial membrane potential, the cessation of ATP synthesis and the release of proinflammatory factors (e.g., cytochrome C) into the cytoplasm, which initiates cell apoptosis (143). Calcium transients are another important mechanism of MI (144). Changes in the calcium concentration significantly affect myocardial cells (144,145). A decrease in the amplitude of calcium transients can weaken the contractility of myocardial cells and affect the blood pumping function of the heart (145,146). A prolonged duration of calcium transients can hinder the reduction in the intracellular calcium concentration during diastole, which impairs diastolic function and limits cardiac filling (17,145).

There are numerous reported MI-targeted drugs and surgical treatments for preventing heart failure (Table I) (147-153). In clinical practice, MI-targeted drugs include ACEIs (e.g., ramipril and perindopril), P2Y12 receptor inhibitors (e.g., clopidogrel) and statins (e.g., atorvastatin, simvastatin and rosuvastatin) (147). ACEIs can improve endothelial function and reduce peripheral vascular resistance in the heart (147). They can reduce blood clots and the burden on the heart to intervene in heart failure (148). P2Y12 receptor antagonists can inhibit

platelet aggregation to reduce thrombosis and prevent myocardial ischemic necrosis and heart failure (149). Dual antiplatelet therapy comprises aspirin and a P2Y receptor antagonist, which has always been used to treat acute MI (149); it can protect patients with acute MI from developing heart failure by reducing the degree of systemic atherothrombosis (149,150). Statins can lower blood lipid levels, particularly the synthesis of low-density lipoprotein cholesterol, which reduces blood lipid levels and prevents plaque formation (151). In stem cell therapy, differentiated new cardiomyocytes can be used to replace cardiomyocytes damaged during MI, thus inhibiting cell apoptosis and heart failure (152). Coronary intervention can effectively clear up occluded coronary arteries, which increases myocardial blood supply and prevents heart failure (153).

7. Other CVDs

Other CVDs, including doxorubicin-induced cardiomyopathy, iron overload cardiomyopathy, sepsis cardiomyopathy, viral myocarditis and diabetic cardiomyopathy, can also develop into heart failure at the end stage (154-162). Doxorubicin-induced cardiomyopathy can result in heart failure through oxidative stress injury, apoptosis and mitochondrial damage (154,155). The development of inflammation, cardiac hypertrophy and fibrosis are the main pathways through which iron overload cardiomyopathy leads to heart failure (156,157). heart failure is caused primarily by inflammatory responses in sepsis cardiomyopathy (158). In viral myocarditis, heart failure mainly results from direct injury and immune-mediated injury pathways (159,160). Diabetic cardiomyopathy can result in heart failure through autonomic dysfunction, cardiac hypertrophy and fibrosis (161,162). However, the detailed mechanisms of the abovementioned CVDs remain to be elucidated.

8. Conclusion and perspective

The five-year mortality rate of patients with heart failure is estimated to be ~50% worldwide (163). The pathological mechanisms of heart failure include cardiac fibrosis, cardiac hypertrophy, cardiomyocyte death, cardiac sarcomere disorders, mitochondrial dysfunction and vascular remodeling (110,132,143,164-172). Intervention approaches for suppressing the progression of heart failure are available at both the experimental and clinical stages. However, these approaches have many challenges and limitations, including off-target effects, side effects and poor translation of basic research into clinical practice (173). Gene therapies, which mainly consist of gene editing technology and noncoding nucleotide acid methods, can be used to prevent and treat heart failure (174,175). Gene editing technology can be used to replace dysregulated sarcomere proteins by targeting related genes (174). CRISPR-Cas9 may be used as 'gene scissors' that can remove erroneous gene fragments and restore related normal genes. The RNA-guided adeno-associated virus 9 delivery of effective Cas9 nucleases can inactivate pathogenic mutant genes in HCM, thereby preventing the progression of heart failure (176). In addition, the discovery and application of regulatory RNA have attracted increasing attention in medical research. Ambrose and Rufkun were awarded the Nobel Prize in Physiology or Medicine in 2024 for their discovery of the miRNA-Lin-14 (177). miR-133, a type of noncoding nucleotide acid, can alleviate heart failure by downregulating the expression of proapoptotic proteins such as caspases-3 and Bax and reducing cardiomyocyte apoptosis (175). However, the main technical problem and challenge are off-target risks, which may cause other genetic abnormalities (174). Drug therapies for heart failure have side effects, including dry cough caused by ACEIs, slow movement and low blood pressure caused by β-blockers, and electrolyte imbalance caused by diuretics (178-180). In addition, it has been reported that human fibroblasts can be reprogrammed into induced cardiac-like myocytes to regenerate cardiomyocytes and prevent MI in the experimental stage; however, further studies are needed to promote their translation into clinical practice (152).

There are reported methods and strategies to address the abovementioned issues. Nanotechnology can improve the precise targeting and reduce off-target effects; it can be used to package and deliver drugs to the target site of related CVDs accurately, which thereby reduces off-target effects (181,182). The integration of traditional Chinese and Western medicine can diminish drug side effects (183-189). Previous studies have shown that *Platycodon grandiflorum* and Flos Farfarae can alleviate the dry cough caused by ACEIs, and that ginseng can ameliorate the bradycardia and hypotension caused by β-blockers (184-187). Specific traditional Chinese medicine active components, such as glycyrrhizic acid and ginsenoside, can protect patients from the adverse effects of Western medicine (188,189). In addition, clinical translation requires more in-depth clinical trials.

Current cutting-edge research technologies, such as super-resolution fluorescence microscopy, cryo-electron microscopy and photoelectric coupling technology, can promote research on heart failure and lay the foundation for drug development (190-192). In addition, nanotechnology and noncoding RNA technology can improve the precise targeting of disease treatments (176,182). The present review provides references for basic research on heart failure and lays a theoretical foundation for the development of therapeutic drugs.

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Authors' contributions

All of the authors contributed to the manuscript. SG, YH and ZR drafted the manuscript, and LL, ZY, LW, XY, ML and XG performed the literature search. SG, YH, LL, ZY, LW, XY, ML and XG edited the manuscript. ZR conceived the study and edited and finalized the manuscript. All authors have read and confirmed the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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