doi.org/10.36721/PJPS.2025.38.3.REG.13367.1

Mitophagy as a therapeutic target for myocardial fibrosis: Mechanistic insights and potential pharmacological interventions

Jie Wu[1], Tingjuan Mei[2], Yang Dong[1], Fen Zhang[1], Xingxing Li[1] and Lei Wang[3]*

[1]Department of Cardiology, Jinhua People's Hospital, Jinhua, China
[2]Department of General Medicine, Community Healthcare Center of Lanjiang Street, Lanxi, China
[3]Department of Laboratory Medicine, Jinhua Guangfu Oncology Hospital, Jinhua, China

Abstract: Myocardial fibrosis is a central pathological feature of various cardiovascular diseases, including heart failure and hypertension. It involves the activation of cardiac fibroblasts, transforming them into myofibroblasts that secrete pro-fibrotic factors, leading to excessive extracellular matrix deposition and progressive cardiac dysfunction. Mitochondrial dysfunction plays a critical role in the development of myocardial fibrosis, with mitophagy, a selective form of autophagy, essential for maintaining mitochondrial quality by removing damaged mitochondria. This process is vital in mitigating fibrosis progression. Recent studies suggest that pharmacological modulation of mitophagy may offer novel therapeutic strategies for cardiovascular diseases involving fibrosis. This review explores the mechanisms of mitophagy in myocardial fibrosis, highlighting key proteins and molecular pathways involved in fibroblast activation and mitochondrial dysfunction. Additionally, it discusses the therapeutic potential of targeting mitophagy to mitigate myocardial fibrosis, emphasizing the importance of balancing mitophagy modulation. Overall, targeting mitophagy pathways holds promise as a therapeutic approach for managing myocardial fibrosis and improving heart function.

Keywords: Cardiovascular diseases, mitophagy, myocardial fibrosis, fibroblasts.

Submitted on 09-09-2024 – Revised on 19-11-2024 – Accepted on 08-03-2025

INTRODUCTION

Myocardial Fibrosis (MF) can be caused by a variety of disease factors, such as infection and inflammation, hypertension, high serum cholesterol, and myocardial infarction. When myocardial tissue is damaged excessively or repeatedly, the normal repair process gradually evolves into an irreversible fibrotic response. Fibrosis is defined as the formation of excessive fibrous connective tissue in and around inflamed or damaged tissue, characterized by an aberrant buildup of extracellular matrix (ECM) components in the extracellular space. In a recent meta-analysis that includes 52 articles and involves 5921 individuals, it is reported that 32.7% of individuals with cardiometabolic conditions developed MF, with hypertension demonstrating the highest prevalence of 35.2%. Therefore, further understanding the potential pathogenesis of MF and search for novel targets are needed (Yeo *et al.,* 2025).

Activation of fibroblasts is thought to be a critical step leading to fibrosis. Cardiac fibroblasts (CFs) are activated following the initial cardiac tissue injury and later differentiate into myofibroblasts (myoFbs), which are the primary mediators of morbid remodeling. MyoFbs have multiplicative and secretory properties, and synthetic secreted collagen deposition leads to myocardial interstitial fibrosis. Excessive deposition of extracellular matrix proteins, primarily type I and type III collagen, in the myocardium adversely affects cardiac function. A growing body of studies has shown a close and complex relationship between MF and a variety of cardiovascular diseases, including viral myocarditis, hypertensive heart disease (HHD), diabetic cardiomyopathy (DCM), ischemic cardiomyopathy, and hypertrophic cardiomyopathy (HCM) (Chang *et al.,* 2023; Gonzalez *et al.,* 2024; Ho *et al.,* 2010; Schlittler *et al.,* 2023; Tuleta and Frangogiannis, 2021).

Mitochondria play a crucial character in maintaining the energy of cardiac metabolism. ATP is produced by oxidative phosphorylation on the inner mitochondrial membrane (IMM) to provide energy to cells. Mitochondria deplete oxygen sometimes produces reactive oxygen species (ROS), and the rate at which mitochondria produce reactive oxygen species is regulated by the transmembrane potential of the IMM. When mitochondria are exposed to external stimuli such as hypoxia and inflammation, the production of ROS increases significantly. Mitochondrial dysfunction leads to excessive production of ROS, which destroys lipids, DNA and cellular proteins, leading to oxidative injury to cardiomyocytes. Due to the imbalance between oxidants (ROS and RNS) and antioxidants, oxidative stress is caused. Oxidative stress and related mitochondrial dysfunction can lead to a variety of cardiovascular diseases such as cardiac dysfunction and heart failure (HF). In this case, timely removal of damaged mitochondria is very necessary (Zhou and Tian, 2018). In this case, timely removal of damaged mitochondria is very necessary.

**Corresponding author:* e-mail: wujie615@163.com

Sequestering cytotoxic protein aggregates, senescent organelles, and other cellular trash in autophagic vesicles and delivering them to lysosomes for clearance, autophagy is an evolutionarily conserved cellular recycling mechanism. Three primary routes in autophagy facilitate the lysosomal breakdown of intracellular payloads. They are chaperone-mediated autophagy, microautophagy, and macroautophagy, in that order. When it comes to macroautophagy, the endoplasmic reticulum (ER) produces a double-membrane structure called a phagosome, which grows into a globular structure. Macroautophagy is best for degrading protein aggregates and organelles such as mitochondria. Research has indicated that autophagy is a strictly regulated mechanism that targets particular organelles, such as the ER and mitochondria (Zhou and Tian, 2018; Hanna *et al.,* 2012; Mochida *et al.,* 2015). Because damaged mitochondria have a lower membrane potential and are surrounded by autophagosomes, they are identified and segregated, and passed on to breakdown to lysosomes, a process called mitophagy and an important mitochondrial quality control mechanism. Other mechanisms for quality control of mitochondria include proteases and chaperones unique to mitochondria that protect proteins from misfolding. In terms of molecules, as well as mitochondrial fission and fusion damage at the organelle level and separate and remove it.

Mechanism of mitophagy

Mammals typically use a route consisting of PTEN-induced putative kinase 1(PINK1, also recognized as PARK6) to clear damaged mitochondria and E3 ubiquitin ligase PARKIN (also recognized as PARK2) (Mochida *et al.,* 2015). There are two gene products linked to Parkinson's disease in families, because Parkinson's disease (PD) has been connected to dysregulated mitophagy. PINK1 and Parkin recognize and accumulate on damaged mitochondria, targeting these damaged mitochondria for mitophagic degradation, removing them from the mitochondrial network with discrimination. Mitophagy, the selective autophagic elimination of dysfunctional or superfluous mitochondria, constitutes a critical quality control mechanism essential for maintaining cellular homeostasis and energy metabolism. This evolutionarily conserved process exhibits two distinct molecular architectures: ubiquitination-dependent and non-ubiquitination-dependent pathways, each demonstrating context-specific activation patterns in physiological maintenance and pathological responses.

Ub-dependent mitophagy

PTEN-induced putative kinase 1(PINK1, also recognized as PARK6) is expressed at low levels in healthy, polarized mitochondria and is processed by matrix peptidase to remove its targeting signal after being introduced into the inner mitochondrial membrane via the translocase complexes TIM and TOM (Greene *et al.,* 2012). The hydrophobic domain of Protease associated with rhomboid-like mitochondrial presenilin cleaves PINK1 between amino acids Ala-103 and Phe-104 (PARL), and the exposed Phe-104 residue led to the rapid degradation of PINK1 by the proteasome system (Deas *et al.,* 2011; Meissner *et al.,* 2015; Yamano and Youle, 2013). However, the occurrence of basal mitophagy in mammals can also be independent of PINK1 (Yamano and Youle, 2013). The process of translocation of PINK1 to IMM is mitochondrial membrane potential (Mitochondrial membrane potential)-dependent (Jin *et al.,* 2010). When damaged mitochondria lose their ability to maintain mitochondrial membrane possible because of electron transport chain flaws, PINK1 is blocked from entering the inner membrane, interacting with the outer membrane's TOM complex and building up there, thus evading cleavage of PARL and proteolysis (Lazarou *et al.*, 2012).

The canonical ubiquitination-dependent pathway operates through the PINK1/Parkin signaling axis, a molecular surveillance system that orchestrates mitochondrial quality control (Ashrafi *et al.*, 2013). PINK1 and Parkin recognize and accumulate on damaged mitochondria to selectively target and remove them from the mitochondrial network (Narendra *et al.*, 2011). The control of post-translational modifications (PTMs) is crucial for the activity and function of PINK1 and PARKIN during mitophagy (Durcan and Fon, 2015). Upon mitochondrial membrane potential (Mitochondrial membrane potential) loss, PINK1 on the outer mitochondrial membrane undergoes autophosphorylation, recruits Parkin, and induces mitochondrial ubiquitination (Okatsu *et al.,* 2012). Parkin's Ser65 in the ubiquitin-like domain (Ubl) is phosphorylated in a PINK1-dependent manner, and this modification is essential for efficient Parkin translocation and subsequent protein degradation during mitophagy (Kondapalli *et al.,* 2012; Koyano *et al.,* 2014). Parkin has a high affinity for phosphorylated ubiquitin chain, and Ser65-phosphorylated ubiquitin is an essential Parkin activator (Okatsu *et al.,* 2015; Kane *et al.,* 2014). Through this feedforward mechanism, activated Parkin ubiquitinates various mitochondrial substrates (Shiba-Fukushima *et al.,* 2014).

In addition to mitochondrial membrane potential loss, PINK1 can detect the accumulation of misfolded proteins in the mitochondrial matrix, initiating Parkin-mediated mitophagy independently of membrane depolarization (Jin *et al.,* 2013). PARKIN mainly mediates the classical K48- and K63-linked ubiquitination chains of mitochondrial proteins, include the non-canonical K6- and K11-linked ubiquitination chains (Ordureau *et al.,* 2014). K48-linked ubiquitination promotes the separation of substrates from the outer mitochondrial membrane (OMM) and proteasomal degradation, while K63-linked ubiquitination is involved in autophagic clearance of misfolded proteins (Yoshii *et al.,* 2011). K63-linked

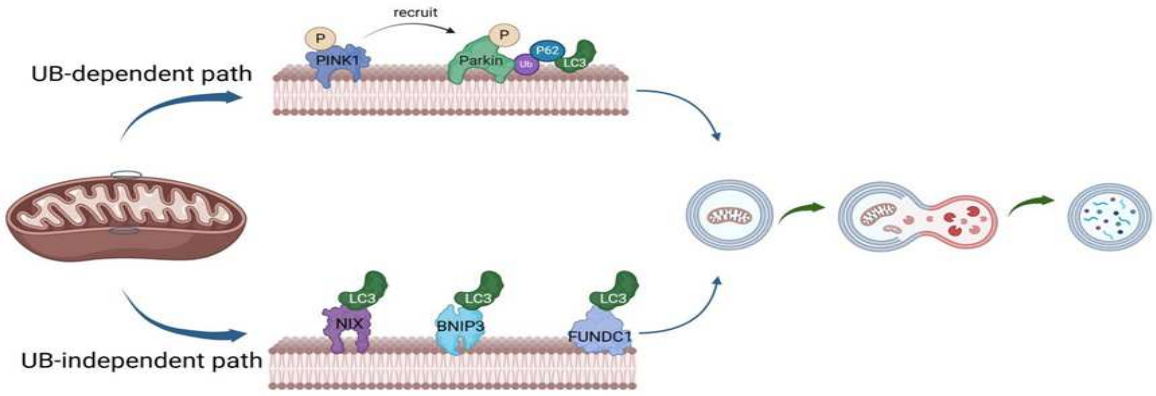

Fig. 1: The mechanisms of UB-dependent and UB-independent mitophagy.

ubiquitin chains act as molecular markers that recruit autophagy receptors, facilitating the efficient sequestration of damaged mitochondria into autophagosomes (Olzmann and Chin, 2008). Parkin, in collaboration with E2 ubiquitin ligases, facilitates K63-linked ubiquitination, driving the formation of aggresomes or their clearance via the autophagy-lysosome pathway (Chin *et al.,* 2010; Olzmann *et al.,* 2007. Mitofusins Mfn1 and Mfn2 are particularly susceptible to Parkin-mediated ubiquitination and degradation, preventing the fusion of damaged mitochondria with healthy ones (Tanaka *et al.,* 2010). PINK1 phosphorylates the mitochondrial transport protein Miro, and phosphorylation of Miro activates Miro's proteasomal breakdown in a Parkin-dependent way (Wang *et al.,* 2011). Thus, damaged mitochondria may be quarantined by the PINK1/Parkin pathway before being cleared (Fig. 1). Therefore, the regulation of ubiquitination modification of mitochondrial substrates has also become the target of many ubiquitination-related enzymes. These proteins constitute a ubiquitination and deubiquitination balance system that regulates mitochondrial homeostasis. Deubiquitination of mitochondrial proteins enables negative regulation of mitophagy. Parkin is selectively deprived of the non-canonical K6-linked ubiquitin chain by USP8, which facilitates parkin's recruitment to depolarized mitochondria and is necessary for the effective execution of mitophagy (Durcan *et al.,* 2014). Parkin is selectively deprived of the non-canonical K6-linked ubiquitin chain by USP8, which facilitates parkin's recruitment to depolarized mitochondria and is necessary for the effective execution of mitophagy (Cornelissen *et al.,* 2014). USP30 is a deubiquitinase (DUB) that specifically deubiquitinates the K6- and K11-linked atypical ubiquitination chains, regulates Lys6-polyubiquitinated TOM20 and counteracts Parkin-mediated ubiquitin chain formation, delays mitophagy by delaying PARK2 recruitment to the mitochondria (Cunningham *et al.,* 2015; Gersch *et al.,* 2017; Wang *et al.,* 2015). USP33 tends to deubiquitinate PRKN primarily at the Lys435 site and remove K6-, K11-, K48-, and K63-linked ubiquitin conjugates from PRKN, where mutations result in significantly lower K63-linked ubiquitin levels (Niu *et al.,* 2020). The above studies also support that mitophagy is tightly regulated (fig. 1).

Ub-independent mitophagy

In addition, the occurrence of basal mitophagy in mammals can also be independent of PINK1 (McWilliams *et al.,* 2018). The domain-containing 1 of FUN14 (FUNDC1), directly interacting with LC3 on autophagosomes via a LC3-interacting region (LIR) domain of microtubule-associated protein 1A/1B light chain 3B (LC3). Src phosphorylates FUNDC1 kinase at Tyr-18 and casein kinase 2α (CK2α) at Ser-13, inhibiting its relationship to LC3 and its inhibition of mitophagy. In reaction to low oxygen levels and mitochondrial oxidative phosphorylation uncoupler (FCCP) treatment, FUNDC1 is dephosphorylated by the mitochondrial phosphatase PGAM5, which initiates mitophagy (Zhou *et al.,* 2018). Similarly, ULK1 upregulates and translocates to fragmented mitochondria upon induction of mitophagy, engages in interaction with FUNDC1, and phosphorylates it at serine 17, thereby enhancing the binding of FUNDC1 to LC3 (Wu *et al.,* 2014). BNIP3-like protein 3 (BNIP3L/NIX) and BNIP3-interacting protein 3 (BNIP3) also contain LIR domains. Mitochondrial clearance can be mediated by the mitochondrial protein Nix, a specific autophagy receptor after mitochondrial injury and during erythrocyte differentiation by binding to the LC3/GABARAP protein (Novak *et al.,* 2010). Furthermore, mitophagy is activated by the entry of NDP52 and Optineurin (but not p62) into mitochondria, independent of parkin (Lazarou *et al.,* 2015). These mechanisms can likewise engage in mitophagy and autophagy and communicate with LC3, both of which have pro-apoptotic functions and may mediate crosstalk between autophagy and apoptosis (fig. 1) (Wilhelm *et al.,* 2022).

Upon mitochondrial damage and subsequent mitochondrial membrane potential loss, PINK1 accumulates on the outer membrane, evading proteasomal degradation. PINK1 can also sense misfolded proteins in the matrix and initiate Parkin (PARK2)-mediated autophagy without depolarization. PINK1 phosphorylates Parkin, recruiting it to damaged mitochondria to promote ubiquitination of mitochondrial proteins. Parkin's activation and translocation depend on PINK1 phosphorylation of Ser65 in the Ubl domain. The PINK1/Parkin pathway ubiquitinates and degrades Mfn1/Mfn2 and phosphorylates Miro, preventing fusion with healthy mitochondria and facilitating isolation. Independently of PINK1/Parkin, FUNDC1 interacts with LC3 for autophagosome formation, activated by dephosphorylation under hypoxic conditions or FCCP treatment. BNIP3L/NIX and BNIP3, containing LIR motifs, interact with LC3 to participate in autophagy and potentially link autophagy to apoptosis.

Autophagy receptors link ubiquitinated mitochondria to autophagosomes

Cellular autophagy executes lysosomal degradation through three evolutionarily conserved modalities: chaperone-mediated autophagy, microautophagy, and macroautophagy. Among these, macroautophagy demonstrates unique proficiency in eliminating bulky cytoplasmic components, particularly protein aggregates and organelles such as mitochondria. The process initiates with de novo formation of a cup-shaped phagophore membrane derived from endoplasmic reticulum (ER) exit sites, which progressively expands to encapsulate cargo within a double-membraned autophagosome. The molecular choreography of autophagosome biogenesis requires coordinated action of autophagy-related (ATG) proteins conserved from yeast to mammals.

An ubiquitin-like protein with two amino-terminal α helices and a ubiquitin-like core is encoded by the ATG8 gene family. Atg8's amino terminus protein varies in different subfamilies and performs a variety of regulatory tasks. GABARAP, GABAPAL1, GABARAPL2, and LC3 (LC3A, LC3B, LC3B2, LC3C) are the members of the human ATG8 protein family (Shpilka *et al.,* 2011). ATG proteins usually create multisubunit complexes that cooperate to aid in the development of autophagosomes and substrate phagocytosis. These include the transmembrane proteins ATG9 and ATG12, the autophagy-specific class III phosphatidylinositol 3-kinase complex I (PIK3C3-CI), and the Unc51-like kinase (ULK) complex in humans, and the Atg8 family proteolipidation complex (Melia *et al.,* 2020). Phosphatidylethanolamine on the autophagic membrane is bound by ATG8. These receptors engage with lipidated ATG8 proteins to attach their bound cargo to the autophagosomal membrane. p62/SQSTM1 is a key autophagy receptor that has a role in autophagy that is selective, and the C-terminal UBA domain interacts with mutated ubiquitin chains on the cargo. The LIR motif interacts with ATG8 proteins on the surface of the autophagic membrane (Johansen and Lamark, 2020). Self-interaction of the N-terminal PB1 domain results in a polymeric structure, and the cargo and autophagosomes can interact closely through P62. Modification of specific autophagy receptors post-translationally also plays a role in controlling these channels in reaction to stimuli (Lamark *et al.,* 2017; Xu and Wan, 2023). Selective autophagy receptors have been found to be involved during pathogen invasion, in innate immunity, including the eradication of microbiological pathogens, the start of antimicrobial defenses and the control of overly aggressive immune reactions such as NDP52, optineurin, and TAX1BP1 (Thurston *et al.,* 2009; White *et al.,* 2023; Wild *et al.,* 2011).

Mitophagy in Myocardial Fibrosis

Mitochondrial Quality Control in Cardiac Homeostasis

Most researches have demonstrated that mitophagy plays a crucial part in preserving cardiac homeostasis and regulating myocardial metabolism (Thomas and Gustafsson, 2013). The level in end-stage HF in humans of the PINK1 protein is significantly reduced. PINK1 activity plays a crucial role in preserving mitochondrial function and cardiomyocyte redox equilibrium, which is necessary for postnatal cardiac development (Billia *et al.,* 2011). Recent studies have found that Parkin-and PINK1/mediated mitophagy have a role in maintaining cardiomyocyte homeostasis (Wu *et al.,* 2022). Deletion of PINK1 leads to mitochondrial dysfunction of the mouse heart and increases vulnerability to ischemia-reperfusion injury (Siddall *et al.,* 2013). In addition, Parkin attenuates cardiac aging through encouraging TBK1's K63-linked ubiquitination to encourage mitophagy (Gao *et al.,* 2021).

A mitophagy receptor called FUNDC1 combines with LC3 to mediate platelet mitophagy as a reaction to hypoxia and reduce ischemia/reperfusion (I/R)-induced cardiac injury (Zhang *et al.,* 2017). One key mechanism mediating mitophagy in response to pressure overload (PO) is Ulk1-mediated alternative mitophagy, which has a significant function to protect the heart against cardiac dysfunction (Nah *et al.,* 2022). However, mitophagy facilitated by the route Ulk1/Rab9/Rip1/DRP1 is also involved in protecting the heart against ischemia (Siddall *et al.,* 2013). PCSK9 is increased in myocardial ischemia-reperfusion injured hearts and regulates mitophagy through the BNIP3 pathway, resulting in reperfusion injury following myocardial infarction, while inhibition of PCSK9 can reduce autophagy and enhance cardiac function (Huang *et al.,* 2022). Additionally, TBC1D15 plays a protective part in acute myocardial infarction-induced cordis abnormalities by modulating Fis1/Rab7-mediated mitochondria-lysosomal contact and activating subsequent lysosome-dependent mitophagy (Yu *et al.,* 2020). NDP52, as a mitochondrial autophagy receptor,

has been reported to promote autophagosome-lysosomal fusion by recruiting the RAB7 (the Ras-associated protein) and TBK1 (TANK-binding kinase 1) to protect against cardiac anomalies caused by myocardial infarction, including myocardial interstitial fibrosis (Sun *et al.,* 2022). Furthermore, the function of mitophagy in coronary heart disease has been researched, with a focus on targeting mitochondrial dysfunction and inflammation (Liu and Wu, 2022). These studies suggest that Mitochondrial Quality Control (MQC) is essential for maintaining optimal cardiac performance. Dysfunctional mitochondria can lead to myocardial damage and impaired heart function, as well as myocardial fibrosis and hypertrophy.

Mitochondrial dysfunction and signal pathways in fibroblast activation

One of the main events in cardiac fibrosis is the cytokine-dependent activation of fibroblasts to myofibroblasts, which is accompanied by phenotypic alterations and enhanced secretory and contractile capabilities, mitochondrial respiration and mitochondrial content increase in this process. The production of several pro-inflammatory cytokines and pro-fibrotic factors during acute myocardial damage in CFs is upregulated, resulting in increased proliferation of these cells and eventual transformation to the MF phenotype.

TGF-β plays a vital part in regulating fibroblast phenotype and gene expression, increasing the synthesis of collagen and fibronectin to promote the deposition of extracellular matrix in the infarct site, and causing protease inhibitors to be produced to decrease matrix breakdown (Bujak and Frangogiannis, 2007). By promoting the development of cardiomyocytes and causing interstitial fibrosis, TGF-β is also a crucial mediator in the pathophysiology of hypertrophic and dilated ventricular remodeling. The growth factor TGF-β is the most widespread mediator of fibroblast activation, strongly induces Mesenchymal-To-Epithelial Transition (EMT) and plays a leading part in the fibrotic course of many organs, and serum levels of TGF-β are used as a diagnostic tool (Gressner and Gao, 2014). Heart fibroblasts' TGF-β-Smad2/3 signaling is the primary mediator of the fibrotic response. The traditional TGF-β1 signaling pathway comprises phosphorylation of Smad2/3, which bind to Smad4 and translocate to the nucleus (Khalil *et al.,* 2017). The complex then functions as a transcription factor to induce the activation of many profibrotic genes. TGF-β1-induced activation contributes to cardiac fibrosis, and Tβ4 supplementation alleviates myocardial infarction and fibrosis by reducing inflammation, oxidative stress and promoting mitophagy (Wang *et al.,* 2022).

The silent information regulator sirtuin 1 (SIRT1) regulates mitophagy in heart failure by activating the SIRT-PINK1 and SIRT1-GPX4 signaling pathways, promoting mitochondrial health and inhibiting ferroptosis, thereby alleviating myocardial hypertrophy, fibrosis, and cardiac dysfunction. The SIRT1 protein also interacts with TGF-β signaling. It is reported that SIRT1 attenuates isoproterenol-induced cardiac fibrosis by regulating EMT via the TGF-β-Smad2/3 access (Liu *et al.,* 2019). Specifically, SIRT1 interacts with Smad2/3, downregulates TGFBR1 and P-Smad2/3 expressions and inhibits Smad2/3 nuclear translocation (Jiang *et al.,* 2021). This interaction between SIRT1 and TGF-β signaling further underscores its role in cardiac fibrosis, as it regulates mitophagy and reduces fibroblast activation, providing a potential therapeutic target for heart failure management.

Mitophagy machinery was reduced in response to angiotensin II, forkhead box protein O3 (FOXO3a) transcription activates PARKIN, promotes mitophagy by targeting Parkin and inhibits AngII-induced myocardial hypertrophy (Sun *et al.,* 2022). The latest study showed that the expression of FOXO3a was upregulated, the LC3 II/I rate and the expression of PINK1 and Parkin were increased in cardiac fibroblasts treated with AngII, showing increased proliferation, migration and collagen secretion, which can be significantly inhibited by FOXO3a knockdown, and this inhibition can be attenuated by mitochondrial autophagy inducers (Lin *et al.,* 2024). This evidence suggests that FOXO3a promotes the progression of myocardial fibrosis by triggering mitophagy and activation of cardiac fibroblasts.

Moreover, Mammalian STE20-like kinase 1 (Mst1) is substantially more expressed in hearts that have been reperfused. The activation of Mst1 inhibits the expression of FUNDC1, thereby inhibiting mitochondrial autophagy, which has a detrimental effect on cardiomyocytes and cardiac function (Yu *et al.,* 2019). Likewise, Matrix metalloproteinases (MMPs) produced by CFs can degrade the ECM and allow cells to migrate to the damaged area. A DAMTS16 belongs to the ADAMTS superfamily of extracellular proteases that are involved in the destruction and remodeling of the extracellular matrix (ECM), promotes cardiac fibrosis, hypertrophy, and heart failure by activating cardiac fibroblasts through the LAP-TGF-β signaling pathway (Yao *et al.,* 2020).

Genetic regulation in controlling mitophagy and cardiac fibrosis

Non-coding RNAs (miRNAs and lncRNAs) play a function in controlling mitophagy and cardiac fibrosis has been rarely reported. When Ang II was administered to cardiac fibroblasts (CFs) and transverse aortic constriction (TAC) animals, microRNA-24-3p expression was markedly down regulated (Zhang *et al.,* 2022). Mechanistically, by inhibiting the mitophagy of cardiac fibroblasts through the down regulation of PHB2, microRNA-24-3p reduces myocardial fibrosis. Prohibitin

2 (PHB2), an important mitochondrial autophagy acceptor, is engaged in the specific destruction of mitochondrial autophagy by binding to the autophagosomal membrane-associated protein LC3 through the LIR domain (Wei *et al.,* 2017). In addition, moreover, PHB2 can stimulate PARL-PGAM5-PINK1 axis-dependent PINK1-PRKN/Parkin-dependent mitophagy (Yan *et al.,* 2020). On the other hand, Parkin enhances the interaction between PHB2 and LC3B by directly binding to PHB2 through its RING1 domain and promoting K11- and K33-linked ubiquitination on PHB2's K142/K200 sites (Sun *et al.,* 2022). The 3'-untranslated region of the suppressor of high-mobility group box 1 protein (HMGB1) was directly impacted by MiR-410, which regulates the heat shock protein β-1 (HSPB1/HSP27) expression. HSPB1, a regulator of the cytoskeleton, is essential for dynamic intracellular trafficking in the processes of autophagy and mitophagy. Thereby, by modifying HSPB1, miR-410 may prevent mitophagy following cardiac I/R damage activity via directly targeting HMGB1 and PINK1/Parkin is required for HSPB1/HMGB1-mediated mitophagy (Kang *et al.,* 2011; Yang *et al.,* 2018). MiR-23a acts a deleterious part in the harm caused by myocardial ischemia/reperfusion (I/R) by blocking CX43 expression and enhancing mitophagy, while activation of CX43 signaling protects cardiomyocytes from myocardial I/R injury (Wang *et al.,* 2021). GJA1 rescues IRI by increasing the rate of synthesis of ATP and oxidative phosphorylation, while safeguarding the survival of cells, initiating mitophagy, and maintaining mitochondrial membrane potential (MMP). MiR-130a, on the other hand, targets GJA1 to prevent mitochondrial fusion and FUNDC1-mediated mitophagy, which hastens the development of myocardial IRI (Yan *et al.,* 2023).

Pharmacological Interventions

Regulation of mitophagy can ameliorate adverse effects on cardiac fibrosis. Given that myocardial fibrosis occurs in a variety of heart disease processes, we focus on those molecules engaged in the control of mitophagy in the mechanisms that lead to heart disease. Jinrun Zhou *et al.,* found that knockdown of MORN4 in myocardial infarction mice significantly rapid fibrosis and damage to the heart accompanied with worsening heart dysfunction (Zhou *et al.,* 2023). MORN4 binds to MFN2 and increases its phosphorylation at S442 via Rho-associated protein kinase 2 (ROCK2), resulting in advantageous mitophagy triggered by mitochondrial dynamics. Therefore, targeting mitophagy can be used as a strategy to prevent myocardial fibrosis and maintain myocardial homeostasis.

Streptozotocin (STZ)-induced diabetes causes cardio-myocyte apoptosis and mitochondrial damage, with inhibition of autophagy and mitophagy, and leads to cardiac interstitial fibrosis and dysfunction. SIRT3 exerts cardioprotective effects against diabetic cardiomyopathy via activate Parkin-mediated mitophagy to maintain mitochondrial homeostasis and suppress cardiomyocyte death, which is mainly achieved by deacetylating Foxo3a, which maintains Parkin expression (Yu *et al.,* 2017).

Aldehyde dehydrogenase 2 (ALDH2) protects hearts from I/R damage by inhibiting the PINK1/Parkin-dependent mitophagy process (Ji *et al.,* 2016). Interestingly, melatonin stimulates mitochondrial autophagy and cGAS-STING-TBK1 signaling via processes that rely on ALDH2, and improves APP/PS1-induced cardiac interstitial fibrosis and function (Wang *et al.,* 2020). A small GTPase, RhoA, promotes Parkin-mediated mitophagy and protects the aging heart, while RhoA knockout mice show fibrotic structural disorders of heart tissue and cardiac aging, and the mitochondrial structure of cardiomyocytes in elderly RhoA knockout mice is abnormal (Soh *et al.,* 2023). Active RhoA localizes to mitochondria and interacts with PINK1, stabilizing PINK1 protein by inhibiting PINK1 cleavage, inducing PINK1/Parkin-dependent mitophagy and protecting myocardium from ischemic stress (Tu and Miyamoto, 2023; Tu *et al.,* 2022).

Vaspin, a serine protease inhibitor derived from epicardial adipose tissue, has been reported to reduce inflammation, induce autophagy, and inhibit apoptosis, guards against atrial myocyte apoptosis brought on by Ang II, mitochondrial damage, as well as cardiac fibrosis by inducing mitophagy. Mechanistically, Vaspin stimulates unc-51 like autophagy activating kinase 1 (ULK1) to phosphorylate Fun14 domain-containing protein 1 (FUNDC1) on the Ser17 site, which induces mitophagy (Zhu *et al.,* 2022).

The calcium-dependent cysteine protease family includes calcains, which has been connected to inflammation, fibrosis, hypertrophy, and cardiac cell death. Researches have demonstrated that during ischemia, calpains target and harm mitochondria (ISC) and reperfusion (REP) (Chen *et al.,* 2019). Heart stress in pathological situations causes calpain, particularly cyto- and mito-calpain, to become overactive. Among these, cyto-calpain stimulates the route for mitofission and mitochondrial apoptosis and damages mitochondrial biogenesis and mitophagy. Additionally, mito-calpain promotes mitochondrial apoptosis and dampens mitofussion and mitochondrial energy metabolism (Zhang *et al.,* 2021).

In diabetic nephropathy, FGF21 negatively regulate TGF-β1-induced Smad2/3 nuclear translocation and reduce collagen precipitation and renal fibrosis (Lin *et al.,* 2020). Similarly, negative control of TGF-β-Smad2/3 communications might be applied as a treatment method to improve myocardial fibrosis. In vivo myocardial infarction mice's cardiac dysfunction and myocardial fibrosis are reduced by calycosin and inhibits Collagen

Table 1: Roles of proteins and noncoding RNAs on mitophagy regulation in cardiac disease and myocardial fibrosis.

Protein/mRNA	Role on mitophagy	Targets	Consequences	References
ADAM17	Inhibits PINK1/Parkin-dependent mitophagy	ATF6	Increases cardiac fibrosis	(Guan *et al.,* 2021)
ADAMTS16	Unknown	LAP-TGF-β pathway	Increases cardiac fibrosis	(Yao *et al.,* 2020)
ALDH2	Inhibits PINK1/Parkin-dependent mitophagy	PINK1/Parkin	Protects hearts against I/R injury (IRI)	(Ji *et al.,* 2016; Wang *et al.,* 2020)
Beclin-1	Induces Parkin-mediated mitophagy	Parkin	Reduces cardiac fibrosis	(Sun *et al.,* 2018)
Calpain	Inhibits mitophagy	Beclin-1	Increases myocardial IRI	(Chen *et al.,* 2019; Zhang *et al.,* 2021)
FOXO3a	Increases mitophagy	Parkin	Triggers activation of cardiac fibroblasts and increases myocardial fibrosis	(Lin *et al.,* 2024; Sun *et al.,* 2022)
FUNDC1	Induces mitophagy of platelet	LC3	Decreases myocardial IRI	(Zhang *et al.,* 2017)
MORN4	Increases mitophagy	MFN2	Decreases cardiac injury and fibrosis	(Zhou *et al.,* 2023)
Mst1	Inhibits the expression of FUNDC1 and mitophagy	FUNDC1	Increases cardiac cells apoptosis	(Yu *et al.,* 2019)
PCSK9	Increases mitophagy	Bcl-2/ BNIP3 pathway	Increases the size of myocardial infarcts	(Huang *et al.,* 2022)
RhoA	Induces PINK1/Parkin dependent mitophagy	PINK1	Protects myocardium from ischemic stress	(Soh *et al.,* 2023; Tu and Miyamoto, 2023; Tu *et al.,* 2022)
Sema3A	Increases mitophagy	SIRT1	Induced cardiomyocyte injury in VMC	(Lin *et al.,* 2023)
SIRT1	Induces PINK1/Parkin dependent mitophagy	Smad2/3 and PINK1	Reduces cardiac fibrosis	(Guan *et al.,* 2023)
SIRT3	Induces Parkin-mediated mitophagy	FOXO3a	Inhibits cardiomyocyte apoptosis	(Yu *et al.,* 2017)
TBC1D15	Increases mitophagy	Fis1/Rab7	Reduces myocardial interstitial fibrosis	(Yu *et al.,* 2020)
ULK1	Induces FUNDC1 dependent mitophagy	FUNDC1 and Rab9	Protects heart against ischemia	(Nah *et al.*, 2022; Wu *et al.,* 2014)
Vaspin	Enhances phosphorylation of FUNDC1 and induces ULK1/FUNDC1-mediated mitophagy	FUNDC1	Decreases atrial myocyte apoptosis	(Zhu *et al.,* 2022)
miR-130a-3p	Inhibits FUNDC1 dependent mitophagy	GJA1	Increases myocardial IRI	(Yan *et al.,* 2023)
miR-23a	Increases mitophagy	CX43	Increases myocardial IRI	(Wang *et al.,* 2021)
miR-24-3p	Inhibits mitophagy	PHB2	Reduces cardiac fibrosis	(Zhang *et al.,* 2022)
miR-410	Inhibits PINK1/Parkin dependent mitophagy	HMGB1	Inhibits cell viability	(Yang *et al.,* 2018)

deposition and the proliferation of CFs *in vitro* via suppressing the TGFBR1, or transforming growth factor-beta receptor signaling pathway (Chen *et al.,* 2022). Among which, ginsenoside Rg1 (GRg1) alleviates cordis reinventing by enhancing SIRT1/PINK1/Parkin-mediated mitophagy (Guan *et al.,* 2023). Sema3A increased cardiomyocyte mitophagy and reduced inflammasome activation via modulating SIRT1, thus attenuating macrophage infiltration-induced cardiomyocyte damage in viral myocarditis (VMC) (Lin *et al.,* 2023).

A disintegrin and metalloproteinase 17 (ADAM17), an enzyme that is membrane-bound that mediates the catalytic shedding of several growth factors and cytokines to control growth and development. Knockdown of ADAM17 activates the PINK1/Parkin pathway, reduces cardiac fibroblast activation, limits fibrosis and improves heart function in mice (Guan *et al.,* 2021). Cardiac-specific overexpression of Beclin-1 decreased the release of molecular patterns linked to mitochondrial risk (DAMPs) in LPS-induced sepsis mice and promoted mitophagy through Parkin, thereby alleviating following an LPS exposure, fibrosis and inflammation and improving cardiac function (Sun *et al.,* 2018). Overall, the effective regulation of mitophagy is a key process for maintaining heart health and preventing myocardial fibrosis.

DISCUSSION

Mitophagy is a significant method of mitochondrial quality control in cardiovascular diseases, and plays a role in maintaining myocardial homeostasis and cardiac function. Hypoxia and inflammation trigger myocardial injury and fibroblast activation, leading to ECM buildup. Regulated mitophagy is a potential therapeutic target in myocardial fibrosis. However, the presence or absence of specific markers of myocardial fibrosis is controversial. While the therapeutic potential of modulating mitophagy in myocardial fibrosis is promising, it is imperative to critically evaluate the potential adverse effects associated with either overactivation or suppression of this pathway. Excessive mitophagy may lead to the unintended removal of functional mitochondria, compromising cellular energy production and exacerbating cardiomyocyte dysfunction. For instance, sustained activation of PINK1/Parkin signaling could destabilize mitochondrial networks, impairing cardiac contractility and accelerating heart failure. Conversely, inadequate mitophagy may fail to eliminate damaged mitochondria, perpetuating oxidative stress, inflammation, and fibroblast activation, thereby worsening fibrosis. Therefore, there is an urgent need to understand the mitophagy signaling associated with myocardial fibrosis and elucidate its potential link to crosstalk. This article discusses the mechanisms by which mitophagy occurs, as well as those molecules that have an impact on myocardial fibrosis by regulating mitophagy (table 1).

CONCLUSION

In conclusion, mitophagy plays a crucial role in maintaining mitochondrial homeostasis and preventing myocardial fibrosis by regulating mitochondrial dysfunction, oxidative stress and fibroblast activation. Targeting key mitophagy pathways, such as PINK1/Parkin and FUNDC1, offers promising therapeutic strategies to mitigate myocardial fibrosis and improve cardiac function. However, further research is needed to address the challenges of safe and effective clinical application, including balancing mitophagy modulation to avoid potential adverse effects.

Conflict of interest

There is no conflict of interest.

REFERENCES

Billia F, Hauck L, Konecny F, Rao V, Shen J and Mak TW (2021). PTEN-inducible kinase 1 (PINK1)/Park6 is indispensable for normal heart function. *Proc. Natl. Acad. Sci. USA.*, **108**(23): 9572–9577.

Bujak M and Frangogiannis NG (2007). The role of TGF-beta signaling in myocardial infarction and cardiac remodeling. *Cardiovasc Res.*, **74**(2): 184-195.

Chang X, Liu R, Li R, Peng Y, Zhu P and Zhou H (2023). Molecular mechanisms of mitochondrial quality control in ischemic cardiomyopathy. *Int. J. Biol. Sci.*, **19**(2): 426-448.

Chen G, Xu H, Xu T, Ding W, Zhang G and Hua Y (2022). Calycosin reduces myocardial fibrosis and improves cardiac function in post-myocardial infarction mice by suppressing TGFBR1 signaling pathways. *Phytomedicine*, **104**: 154277.

Chen Q, Thompson J, Hu Y, Dean J and Lesnefsky EJ (2019). Inhibition of the ubiquitous calpains protects complex I activity and enables improved mitophagy in the heart following ischemia-reperfusion. *Am. J. Physiol. Cell. Physiol.*, **317**(5): C910-C921.

Chin LS, Olzmann JA and Li L (2010). Parkin-mediated ubiquitin signalling in aggresome formation and autophagy. *Biochem. Soc. Trans.*, **38**(1): 144-149.

Cornelissen T, Haddad D, Wauters F, Van Humbeeck C, Mandemakers W and Koentjoro B (2014). The deubiquitinase USP15 antagonizes Parkin-mediated mitochondrial ubiquitination and mitophagy. *Hum. Mol. Genet.*, **23**(19): 5227–5242.

Cunningham CN, Baughman JM, Phu L, Tea JS, Yu C and Coons M (2015). USP30 and parkin homeostatically regulate atypical ubiquitin chains on mitochondria. *Nat. Cell. Biol.*, **17**(2): 160-169.

Deas E, Plun-Favreau H, Gandhi S, Desmond H, Kjaer S and Loh SH (2011). PINK1 cleavage at position A103 by the mitochondrial protease PARL. *Hum. Mol. Genet.*, **20**(5): 867-879.

Durcan TM and Fon EA (2015). The three 'P's of mitophagy: PARKIN, PINK1, and post-translational modifications. *Genes Dev.*, **29**(10): 989-999.

Durcan TM, Tang MY, Perusse JR, Dashti EA, Aguileta MA and McLelland GL (2014). USP8 regulates mitophagy by removing K6-linked ubiquitin conjugates from parkin. *EMBO J.*, **33**(21): 2473-2491.

Gao B, Yu W, Lv P, Liang X, Sun S and Zhang Y (2021). Parkin overexpression alleviates cardiac aging through facilitating K63-polyubiquitination of TBK1 to

facilitate mitophagy. *Biochim. Biophys. Acta Mol. Basis Dis.*, **1867**(1): 165997.

Gersch M, Gladkova C, Schubert AF, Michel MA, Maslen S and Komander D (2017). Mechanism and regulation of the Lys6-selective deubiquitinase USP30. *Nat. Struct. Mol. Biol.*, **24**(11): 920-930.

Gonzalez A, Lopez B, Ravassa S, San Jose G, Latasa I and Butler J (2023). Myocardial interstitial fibrosis in hypertensive heart disease: From mechanisms to clinical management. *Hypertension*, **81**(2): 218-228.

Greene AW, Grenier K, Aguileta MA, Muise S, Farazifard R and Haque ME (2012). Mitochondrial processing peptidase regulates PINK1 processing, import and Parkin recruitment. *EMBO Rep.*, **13**(4): 378-385.

Gressner OA and Gao C (2014). Monitoring fibrogenic progression in the liver. *Clin. Chim. Acta*, **433**: 111-122.

Guan C, Zhang HF, Wang YJ, Chen ZT, Deng BQ and Qiu Q (2021). The downregulation of ADAM17 exerts protective effects against cardiac fibrosis by regulating endoplasmic reticulum stress and mitophagy. *Oxid. Med. Cell Longev.*, **2021**: 5572088.

Guan S, Xin Y, Ding Y, Zhang Q and Han W (2023). Ginsenoside Rg1 protects against cardiac remodeling in heart failure via SIRT1/PINK1/Parkin-mediated mitophagy. *Chem. Biodivers.*, **20**(2): e202200730.

Hanna RA, Quinsay MN, Orogo AM, Giang K, Rikka S and Gustafsson AB (2012). Microtubule-associated protein 1 light chain 3 (LC3) interacts with Bnip3 protein to selectively remove endoplasmic reticulum and mitochondria via autophagy. *J. Biol. Chem.*, **287**(23): 19094-19104.

Ho CY, López B, Coelho-Filho OR, Lakdawala NK, Cirino AL and Jarolim P (2010). Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy. *N. Engl. J. Med.*, **363**(6): 552-563.

Huang G, Lu X, Zhou H, Li R, Huang Q and Xiong X (2022). PCSK9 inhibition protects against myocardial ischemia-reperfusion injury via suppressing autophagy. *Microvasc. Res.*, **142**: 104371.

Ji W, Wei S, Hao P, Xing J, Yuan Q and Wang J (2016). Aldehyde dehydrogenase 2 has cardioprotective effects on myocardial ischaemia/reperfusion injury via suppressing mitophagy. *Front. Pharmacol.*, **7**: 101.

Jiang T, Liu T, Deng X, Ding W, Yue Z and Yang W (2021). Adiponectin ameliorates lung ischemia-reperfusion injury through SIRT1-PINK1 signaling-mediated mitophagy in type 2 diabetic rats. *Respir. Res.*, **22**(1): 258.

Jin SM and Youle RJ (2013). The accumulation of misfolded proteins in the mitochondrial matrix is sensed by PINK1 to induce PARK2/Parkin-mediated mitophagy of polarized mitochondria. *Autophagy*, **9**(11): 1750-1757.

Jin SM, Lazarou M, Wang C, Kane LA, Narendra DP and Youle RJ (2010). Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL. *J. Cell Biol.*, **191**(5): 933-942.

Johansen T and Lamark T (2020). Selective autophagy: ATG8 family proteins, LIR motifs and cargo receptors. *J. Mol. Biol.*, **432**(1): 80-103.

Kane LA, Lazarou M, Fogel AI, Li Y, Yamano K and Sarraf SA (2014). PINK1 phosphorylates ubiquitin to activate Parkin E3 ubiquitin ligase activity. *J. Cell Biol.*, **205**(2): 143-153.

Kang R, Livesey KM, Zeh III HJ, Lotze MT and Tang D (2011). Metabolic regulation by HMGB1-mediated autophagy and mitophagy. *Autophagy*, **7**(10): 1256-1258.

Khalil H, Kanisicak O, Prasad V, Correll RN, Fu X and Schips T (2017). Fibroblast-specific TGF-beta-Smad2/3 signaling underlies cardiac fibrosis. *J. Clin. Invest.*, **127**(10): 3770-3783.

Kondapalli C, Kazlauskaite A, Zhang N, Woodroof HI, Campbell DG and Gourlay R (2012). PINK1 is activated by mitochondrial membrane potential depolarization and stimulates Parkin E3 ligase activity by phosphorylating serine 65. *Open Biol.*, **2**(5): 120080.

Koyano F, Okatsu K, Kosako H, Tamura Y, Go E and Kimura M (2014). Ubiquitin is phosphorylated by PINK1 to activate parkin. *Nature*, **510**(7503): 162-166.

Lamark T, Svenning S and Johansen T (2017). Regulation of selective autophagy: the p62/SQSTM1 paradigm. *Essays Biochem.*, **61**(6): 609-624.

Lazarou M, Sliter DA, Kane LA, Sarraf SA, Wang C and Burman JL (2015). The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. *Nature*, **524**(7565): 309-314.

Lazarou M, Jin SM, Kane LA and Youle RJ (2012). Role of PINK1 binding to the TOM complex and alternate intracellular membranes in recruitment and activation of the E3 ligase Parkin. *Dev. Cell*, **22**(2): 320-333.

Lin D, Luo H, Dong B, He Z, Ma L and Wang Z (2024). FOXO3a induces myocardial fibrosis by upregulating mitophagy. *Front Biosci (Landmark Ed)*, **29**(2): 56.

Lin L, Wei J, Zhu C, Hao G, Xu J and Zhu Y (2023). Sema3A alleviates viral myocarditis by modulating SIRT1 to regulate cardiomyocyte mitophagy. *Environ. Toxicol.*, **38**(6): 1305-1317.

Lin S, Yu L, Ni Y, He L, Weng X and Lu X (2020). Fibroblast growth factor 21 attenuates diabetes-induced renal fibrosis by negatively regulating TGF-beta-p53-Smad2/3-mediatedepithelial-to-mesenchymal transition via activation of AKT. *Diabetes Metab. J.*, **44**(1): 158-172.

Liu M and Wu Y (2022). Role of mitophagy in coronary heart disease: Targeting the mitochondrial dysfunction and inflammatory regulation. *Front. Cardiovasc. Med.*, **9**: 819454.

Liu ZH, Zhang Y, Wang X, Fan XF, Zhang Y and Li X (2019). SIRT1 activation attenuates cardiac fibrosis by endothelial-to-mesenchymal transition. *Biomed. Pharmacother.*, **118**: 109227.

McWilliams TG, Prescott AR, Montava-Garriga L, Ball G, Singh F and Barini E (2018). Basal mitophagy occurs

independently of PINK1 in mouse tissues of high metabolic demand. *Cell Metab.*, **27**(2): 439-449.e5.

Meissner C, Lorenz H, Hehn B and Lemberg MK (2015). Intramembrane protease PARL defines a negative regulator of PINK1- and PARK2/Parkin-dependent mitophagy. *Autophagy*, **11**(9): 1484-1498.

Melia TJ, Lystad AH and Simonsen A (2020). Autophagosome biogenesis: From membrane growth to closure. *J. Cell Biol.*, **219**(6).

Mochida K, Oikawa Y, Kimura Y, Kirisako H, Hirano H and Ohsumi Y (2015). Receptor-mediated selective autophagy degrades the endoplasmic reticulum and the nucleus. *Nature*, **522**(7556): 359-362.

Nah J, Shirakabe A, Mukai R, Zhai P, Sung EA and Ivessa A (2022). Ulk1-dependent alternative mitophagy plays a protective role during pressure overload in the heart. *Cardiovasc. Res.*, **118**(12): 2638-2651.

Narendra DP and Youle RJ (2011). Targeting mitochondrial dysfunction: Role for PINK1 and Parkin in mitochondrial quality control. *Antioxid. Redox Signal*, **14**(10): 1929-1938.

Niu K, Fang H, Chen Z, Zhu Y, Tan Q, Wei D and Wang L (2019). USP33 deubiquitinates PRKN/parkin and antagonizes its role in mitophagy. *Autophagy*, **16**(4): 724-734.

Novak I, Kirkin V, McEwan DG, Zhang J, Wild P, Rozenknop A and Orozco I (2009). Nix is a selective autophagy receptor for mitochondrial clearance. *EMBO Rep.*, **11**(1): 45-51.

Okatsu K, Koyano FM, Kimura Kosako HY, Saeki Tanaka K and Koyama T (2015). Phosphorylated ubiquitin chain is the genuine Parkin receptor. *J. Cell Biol.*, **209**(1): 111-128.

Okatsu K, Oka T, Iguchi M, Imamura KH, Kosako N, Tani and Tazaki Y (2012). PINK1 autophosphorylation upon membrane potential dissipation is essential for Parkin recruitment to damaged mitochondria. *Nat. Commun.*, **3**: 1016.

Olzmann JA and Chin LS (2008). Parkin-mediated K63-linked polyubiquitination: A signal for targeting misfolded proteins to the aggresome-autophagy pathway. *Autophagy*, **4**(1): 85-87.

Olzmann JA, Li L, Chudaev MV, Chen J, Perez FA, Palmiter RD and Allen K (2007). Parkin-mediated K63-linked polyubiquitination targets misfolded DJ-1 to aggresomes via binding to HDAC6. *J. Cell Biol.*, **178**(6): 1025-1038.

Ordureau A, Sarraf SA, Duda DM, Heo JM, Jedrychowski MP, Sviderskiy VO and Shaw SE (2014). Quantitative proteomics reveal a feedforward mechanism for mitochondrial PARKIN translocation and ubiquitin chain synthesis. *Mol. Cell*, **56**(3): 360-375.

Saito T, Nah J, Oka SI, Mukai R, Monden Y, Maejima Y and Nishida N (2019). An alternative mitophagy pathway mediated by Rab9 protects the heart against ischemia. *J. Clin. Invest.*, **129**(2): 802–819.

Schlittler M, Pramstaller PP, Rossini A and De Bortoli M (2023). Myocardial fibrosis in hypertrophic cardiomyopathy: A perspective from fibroblasts. *Int. J. Mol. Sci.*, **24**(19): 14845.

Shiba-Fukushima K, Arano T, Matsumoto G, Inoshita T, Yoshida S and Ishihama Y (2014). Phosphorylation of mitochondrial polyubiquitin by PINK1 promotes Parkin mitochondrial tethering. *PLoS Genet.*, **10**(12): e1004861.

Shpilka T, Weidberg H, Pietrokovski S and Elazar Z (2011). Atg8: An autophagy-related ubiquitin-like protein family. *Genome Biol.*, **12**(7): 226.

Siddall HK, Yellon DM, Ong SB, Mukherjee UA, Burke N and Hall AR (2013). Loss of PINK1 increases the heart's vulnerability to ischemia-reperfusion injury. *PLoS One*, **8**(4): e62400.

Soh JEC, Shimizu A, Molla MR, Zankov DP, Nguyen LKC and Khan MR (2023). RhoA rescues cardiac senescence by regulating Parkin-mediated mitophagy. *J. Biol. Chem.*, **299**(3): 102993.

Sun M, Zhang W, Bi Y, Xu H, Abudureyimu M and Peng H (2022). NDP52 protects against myocardial infarction-provoked cardiac anomalies through promoting autophagosome-lysosome fusion via recruiting TBK1 and RAB7. *Antioxid. Redox Signal.*, **36**(16-18): 1119-1135.

Sun S, Hou H, Ma G, Ma Q, Li N and Zhang L (2023). The interaction between E3 ubiquitin ligase Parkin and mitophagy receptor PHB2 links inner mitochondrial membrane ubiquitination to efficient mitophagy. *J. Biol. Chem.*, **298**(12): 102704.

Sun T, Han Y, Li JL, Jiao XY, Zuo L and Wang J (2023). FOXO3a-dependent PARKIN negatively regulates cardiac hypertrophy by restoring mitophagy. *Cell Biosci.*, **12**(1): 204.

Sun Y, Yao X, Zhang QJ, Zhu M, Liu ZP and Ci B (2018). Beclin-1-dependent autophagy protects the heart during sepsis. *Circulation*, **138**(20): 2247-2262.

Tanaka A, Cleland MM, Xu S, Narendra DP, Suen DF and Karbowski M (2010). Proteasome and p97 mediate mitophagy and degradation of mitofusins induced by Parkin. *J. Cell Biol.*, **191**(7): 1367-1380.

Thomas RL and Gustafsson AB (2013). Mitochondrial autophagy — An essential quality control mechanism for myocardial homeostasis. *Circ. J.*, **77**(10): 2449-2454.

Thurston TL, Ryzhakov G, Bloor S, von Muhlinen N and Randow F (2009). The TBK1 adaptor and autophagy receptor NDP52 restricts the proliferation of ubiquitin-coated bacteria. *Nat. Immunol.*, **10**(11): 1215-1221.

Tu M and Miyamoto S (2023). RHOA, a small G-protein, signals to mitophagy through regulation of PINK1 protein stability and protects cardiomyocytes against ischemia. *Autophagy*, **19**(6): 1865-1866.

Tu M, Tan VP, Yu JD, Tripathi R, Bigham Z and Barlow M (2023). RhoA signaling increases mitophagy and protects cardiomyocytes against ischemia by stabilizing

PINK1 protein and recruiting Parkin to mitochondria. *Cell Death Differ.*, **29**(12): 2472-2486.

Tuleta I and Frangogiannis NG (2021). Fibrosis of the diabetic heart: Clinical significance, molecular mechanisms, and therapeutic opportunities. *Adv. Drug Deliv. Rev.*, **176**: 113904.

Wang F, He Y, Yao N, Ruan L and Tian Z (2022). Thymosin beta4 protects against cardiac damage and subsequent cardiac fibrosis in mice with myocardial infarction. *Cardiovasc Ther.*, 1308651.

Wang L, Li Q, Diao J, Lin L and Wei J (2021). MiR-23a is involved in myocardial ischemia-reperfusion injury by directly targeting CX43 and regulating mitophagy. *Inflammation*, **44**(4): 1581-1591.

Wang S, Wang L, Qin X, Turdi S, Sun D and Culver B (2020). ALDH2 contributes to melatonin-induced protection against APP/PS1 mutation-prompted cardiac anomalies through cGAS-STING-TBK1-mediated regulation of mitophagy. *Signal Transduct. Target Ther.*, **5**(1): 119.

Wang X, Winter D, Ashrafi G, Schlehe J, Wong YL and Selkoe D (2011). PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility. *Cell*, **147**(4): 893-906.

Wang Y, Serricchio M, Jauregui M, Shanbhag R, Stoltz T and Di Paolo CT (2015). Deubiquitinating enzymes regulate PARK2-mediated mitophagy. *Autophagy*, **11**(4): 595-606.

Wei Y, Chiang WC, Sumpter R Jr, Mishra P and Levine B (2017). Prohibitin 2 is an inner mitochondrial membrane mitophagy receptor. *Cell*, **168**(1-2): 224-238 e10.

White J, Suklabaidya S, Vo MT, Choi YB and Harhaj EW (2023). Multifaceted roles of TAX1BP1 in autophagy. *Autophagy*, **19**(1): 44-53.

Wild P, Farhan H, McEwan DG, Wagner S, Rogov VV and Brady NR (2011). Phosphorylation of the autophagy receptor optineurin restricts Salmonella growth. *Science*, **333**(6039): 228-233.

Wilhelm LP, Zapata-Munoz J, Villarejo-Zori B, Pellegrin S, Freire CM and Toye AM (2022). BNIP3L/NIX regulates both mitophagy and pexophagy. *EMBO J.*, **41**(24): e111115.

Wu W, Tian W, Hu Z, Chen G, Huang L and Li W (2014). ULK1 translocates to mitochondria and phosphorylates FUNDC1 to regulate mitophagy. *EMBO Rep.*, **15**(5): 566-575.

Wu Y, Jiang T, Hua J, Xiong Z, Dai K and Chen H (2022). PINK1/Parkin-mediated mitophagy in cardiovascular disease: From pathogenesis to novel therapy. *Int. J. Cardiol.*, **361**: 61-69.

Xu Y and Wan W (2023). Acetylation in the regulation of autophagy. *Autophagy*, **19**(2): 379–387.

Yamano K and Youle RJ (2013). PINK1 is degraded through the N-end rule pathway. *Autophagy*, **9**(11): 1758-1769.

Yan C, Gong L, Chen L, Xu M, Abou-Hamdan H and Tang M (2020). PHB2 (prohibitin 2) promotes PINK1-PRKN/Parkin-dependent mitophagy by the PARL-PGAM5-PINK1 axis. *Autophagy*, **16**(3): 419-434.

Yan Y, Tian LY, Jia Q, Han Y, Tian Y and Chen HN (2023). MiR-130a-3p regulates FUNDC1-mediated mitophagy by targeting GJA1 in myocardial ischemia-reperfusion injury. *Cell Death Discov.*, **9**(1): 77.

Yang F, Li T, Dong Z and Mi R (2018). MicroRNA-410 is involved in mitophagy after cardiac ischemia-reperfusion injury by targeting high-mobility group box 1 protein. *J. Cell Biochem.*, **119**(2): 2427-2439.

Yao Y, Hu C, Song Q, Li Y, Da X and Yu Y (2020). ADAMTS16 activates latent TGF-beta, accentuating fibrosis and dysfunction of the pressure-overloaded heart. *Cardiovasc. Res.*, **116**(5): 956-969.

Yeo TM, Chin WLC, Seah CWA, Cheng LJ, Lin W and Dalakoti M (2025). Global prevalence of myocardial fibrosis among individuals with cardiometabolic conditions: A systematic review and meta-analysis. *Eur J. Prev. Cardiol.*, Online ahead of print. Available from: https://pubmed.ncbi.nlm.nih.gov/39968765.

Yoshii SR, Kishi C, Ishihara N and Mizushima N (2011). Parkin mediates proteasome-dependent protein degradation and rupture of the outer mitochondrial membrane. *J. Biol. Chem.*, **286**(22): 19630-19640.

Yu W, Gao B, Li N, Wang J, Qiu C and Zhang G (2017). Sirt3 deficiency exacerbates diabetic cardiac dysfunction: Role of Foxo3A-Parkin-mediated mitophagy. *Biochim. Biophys. Acta Mol. Basis Dis.*, **1863**(8): 1973-1983.

Yu W, Xu M, Zhang T, Zhang Q and Zou C (2019). Mst1 promotes cardiac ischemia-reperfusion injury by inhibiting the ERK-CREB pathway and repressing FUNDC1-mediated mitophagy. *J. Physiol. Sci.*, **69**(1): 113–127.

Yu W, Sun S, Xu H, Li C, Ren J and Zhang Y (2020). TBC1D15/RAB7-regulated mitochondria-lysosome interaction confers cardioprotection against acute myocardial infarction-induced cardiac injury. *Theranostics*, **10**(24): 11244-11263.

Zhang M, Wang G and Peng T (2021). Calpain-mediated mitochondrial damage: An emerging mechanism contributing to cardiac disease. *Cells*, **10**(8): doi.org/10.3390/cells10082024

Zhang W, Siraj S, Zhang R and Chen Q (2017). Mitophagy receptor FUNDC1 regulates mitochondrial homeostasis and protects the heart from I/R injury. *Autophagy*, **13**(6): 1080-1081.

Zhang Y, Wang Z, Lan D, Zhao J, Wang L and Shao X (2022). MicroRNA-24-3p alleviates cardiac fibrosis by suppressing cardiac fibroblasts mitophagy via downregulating PHB2. *Pharmacol. Res.*, **177**: 106124.

Zhou B and Tian R (2018). Mitochondrial dysfunction in pathophysiology of heart failure. *J. Clin. Invest.*,

128(9): 3716-3726.

Zhou H, Zhu P, Wang J, Zhu H, Ren J and Chen Y (2018). Pathogenesis of cardiac ischemia-reperfusion injury is associated with CK2alpha-disturbed mitochondrial homeostasis via suppression of FUNDC1-related mitophagy. *Cell Death Differ.*, **25**(6): 1080-1093.

Zhou J, Liu H, Zhang T, Wang Z, Zhang J and Lu Y (2023). MORN4 protects cardiomyocytes against ischemic injury via MFN2-mediated mitochondrial dynamics and mitophagy. *Free Radic. Biol. Med.*, **196**: 156–170.

Zhu Y, Gu Z, Shi J, Chen CH, Xu and Lu Q (2022). Vaspin attenuates atrial abnormalities by promoting ULK1/FUNDC1-mediated mitophagy. *Oxid. Med. Cell Longev.*, **2022**: 3187463.