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Review Article

Mitophagy: A Potential Target for Pressure Overload-Induced Cardiac Remodelling

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The pathological mechanisms underlying cardiac remodelling and cardiac dysfunction caused by pressure overload are poorly understood. Mitochondrial damage and functional dysfunction, including mitochondrial bioenergetic disorder, oxidative stress, and mtDNA damage, contribute to heart injury caused by pressure overload. Mitophagy, an important regulator of mitochondrial homeostasis and function, is triggered by mitochondrial damage and participates in the pathological process of cardiovascular diseases. Recent studies indicate that mitophagy plays a critical role in the pressure overload model, but evidence on the causal relationship between mitophagy abnormality and pressure overload-induced heart injury is inconclusive. This review summarises the mechanism, role, and regulation of mitophagy in the pressure overload model. It also pays special attention to active compounds that may regulate mitophagy in pressure overload, which provide clues for possible clinical applications.

1. Introduction

Pressure overload-induced cardiac dysfunction is a common pathological basis in numerous heart disease, including aortic stenosis and chronic hypertension. Pressure overload induced by TAC has become a classical animal model in rodents to simulate cardiac damage caused by pressure overload in humans [1]. Continuous exposure to increased pressure gradually transforms the initially compensatory response into pathological cardiac remodelling, manifested as increased cardiomyocyte mass, sarcomere rearrangement, extracellular matrix deposition, and immune cell activation, which eventually lead to terminal-stage heart failure [2, 3]. The heart mainly relies on mitochondria to manufacture the energy used for its contractile function; these account for over 30% of the volume of myocardial cells and provide 90% of cellular ATP energy via oxidative phosphorylation and fatty acid oxidation [4]. Mitochondria are also involved in various key cellular processes, such as the regulation of cell proliferation and apoptosis, maintenance of calcium homeostasis, and communication and functional coordination with lysosomes, the endoplasmic reticulum, the nucleus, and other organelles [5, 6]. Therefore, the abnormality of the structure and function of mitochondria in the pressure overload model has been frequently investigated. In vivo and in vitro experiments have confirmed that mitochondria swell and cristae become fragmented and disordered in cardiomyocytes under pressure overload [7, 8]. Mitophagy is a selective autophagy pathway that mediates mitochondrial quality control by scavenging damaged mitochondria and coordinating the dynamic balance between mitochondrial and cellular energy requirements [9] (Figure 1). Although mitophagy has been widely studied in the pressure overload model, the role, regulation, and potential clinical interventions of mitophagy have not been systematically summarised. This review addresses this gap and generalises the problems that remain to be explored.

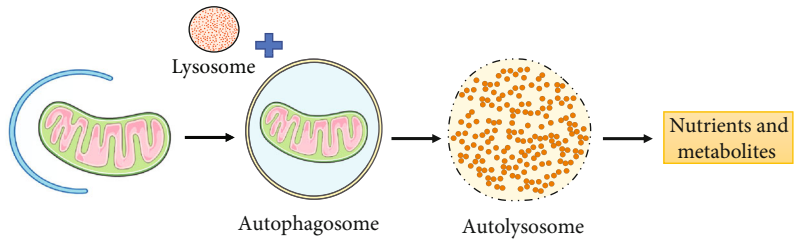

Figure 1: Overview of mitophagy. Mitophagy is a selective autophagy that maintains physiological functions by selectively degradation of damaged or dysfunctional mitochondria. During mitophagy, the damaged mitochondria are labeled and surrounded by vesicles which stretch to form autophagosome. Lastly, autophagosomes fuse with lysosomes to form autophagolysosomes, where hydrolases degrade the sequestered materials and released the degraded products into cytoplasm.

2. Mitochondrial-Related Damage in Pressure Overload Model

2.1. Mitochondrial Bioenergetic Disorder. Heart failure caused by pressure overload is accompanied by a decline in mitochondrial respiratory capacity [10]. Morphologically, mitochondrial cristae disorders, decreased cristae density, and mitochondrial swelling occur after pressure overload [11, 12]. Bugger et al. [11] identified that oxidative phosphorylation and fatty acid oxidation proteins are generally downregulated. Griffiths et al. [13] found that the activities of ETC complexes I and II are significantly impaired after TAC, which may be a reasonable explanation for the reduction of ATP production in the hypertrophic myocardium. One mitochondrial proteomic study revealed that metabolism-related ETC proteins account for over half of the mitochondrial proteins that change significantly after TAC and that the subunits of complex I, III, IV, and V are abnormal [14]. Some interventions on the cardiac phenotype of pressure overload can be attributed to improving mitochondrial respiratory function. MitoQ is a mitochondrial antioxidant that restores the potential of interfibrillar mitochondria for ATP production and mitochondrial respiratory function. MitoQ treatment has been shown to reduce cardiac hypertrophy caused by pressure overload through this mechanism [15]. AMS alleviates myocardial hypertrophy and fibrosis after TAC. At the same time, AMS has been reported to increase the expression and activity of complex I, II, III, IV, V, and oxidative phosphorylation-related proteins and to increase mitochondrial membrane potential and mitochondrial oxygen consumption rate [16].

2.2. Oxidative Stress. Previous studies have fully proved the role of oxidative stress in cardiac hypertrophy and cardiac dysfunction induced by pressure overload. Oxidative stress occurs when the rate of metabolism or inactivation of ROS and RNS do not match their production rate [17]. Mitochondrial-derived ROS were reported to mediate heart failure induced by volume overload [18]. Subsequently, many experiments have confirmed its negative role in the pressure overload model. ROS can activate various hypertrophy signal pathways, mediate extracellular matrix remodelling by activating matrix metalloproteinase, mediate cardiomyocyte apoptosis, and modify excitation-contraction coupling to induce cardiac hypertrophy due to pressure overload [19, 20]. Intracellular ROS mainly comes from the mitochondrial respiratory chain [21, 22]. Outside mitochondria, NOXs produce $O_2^{\bullet-}$ by transferring electrons from NADPH to molecular oxygen [23]. In the TAC model, the absence of NOX4 attenuate the production of $O_2^{\bullet-}$ and alleviates cardiac hypertrophy and cardiac remodelling caused by pressure overload [24]. Shimizu et al. [25] found in the rat heart pressure overload model, mitochondrial BH4 decreased, which mediated the decoupling of NOS3 into monomer to generate $O_2^{\bullet-}$, and no longer produced the protective NO in the form of a dimer. Superoxide dismutase performs a protective mechanism against oxygen free radicals and converts $O_2^{\bullet-}$ into H_2O_2, which also causes damage to bioactive molecules [26]. $O_2^{\bullet-}$ can also undergo the Haber-Weiss reaction with existing H_2O_2 to produce hydroxyl radicals with more vital oxidation [27]. $O_2^{\bullet-}$ can also reduce NO to $ONOO^-$, thus inhibiting mitochondrial respiratory complex through tyrosine nitration and resulting in both reduced ATP synthesis and cell dysfunction [28]. In human cardiomyocytes, $ONOO^-$ induces the nitration of alpha-actinin, resulting in systolic dysfunction [29]. Exposure to $ONOO^-$ releases Zn^{2+} from the zinc-thiolate cluster of NOS and destroys the NOS dimer [30]. Targeting oxidative stress has become a hot spot in cardiac remodelling and cardiac dysfunction intervention under pressure overload. Exogenous BH4 supplementation recouples NOS, inhibits ROS, and saves cardiac remodelling after TAC [31, 32]. Murphy et al. [33] suggested that Ffar4 reduces oxidative stress and potentially protects the heart after TAC. Zang et al. [34] revealed that the overexpression of JMJD1A promotes the production of catalase, reduces mitochondrial ROS and total cellular ROS, and inhibits cardiomyocyte hypertrophy.

2.3. mtDNA Homeostasis. Human mtDNA is a small amount of closed-loop double-stranded DNA in the mitochondrial matrix. It is responsible for coding 37 genes, including 2 ribosomal subunits, 13 subunits of ETC, and transfer RNA [35]. mtDNA plays an unparalleled role in maintaining mitochondrial function and is associated with various pathological changes of the human myocardium. Ischaemia–reperfusion leads to oxidative damage of mtDNA and reduces its content and transcription levels. Lycopene protects cardiomyocytes from ischaemia–reperfusion injury through its antioxidant properties and the function of preventing the reduction of mitochondrial transcription factor

A, which maintains mtDNA stability [36]. mtDNA damage includes (but is not limited to) point mutation and the removal of mtDNA copy number, due to its proximity to ROS production sites, lack of histone protection, and repair dysfunction in specific cases [37]. mtDNA replication is performed by Pol γ. Under oxidative stress, Pol γ reduces its exonuclease activity, increases mutation, and decreases mtDNA copy number [38]. ROS also induces strand breaks and abasic sites, leading to mtDNA double-strand breaks and degradation [39]. In rat cardiomyocytes, mtDNA damage leads to mitochondrial dysfunction, which further worsens the imbalance of electron transfer and produces ROS, forming a series of vicious cycles [36]. Consistent with these theories, multitudinous studies have detected mtDNA depletion and oxidative damage under pressure overload. Zou et al. [40] found that knockdown of NDUFS1 increases ROS production, downregulates mtDNA content, and develops cardiac hypertrophy under pressure overload. Kuroda et al. [24] observed an increase in mitochondrial DNA content after knockout of NOX4 in mice, with significantly alleviated cardiac hypertrophy and interstitial fibrosis exhibited in response to pressure overload. Twinkle is an integral part of the minimal replication complex of mtDNA and acts as a part of annealing and helicase. It plays a role in mtDNA replication initiation and damage repair [41]. In the pressure overload model, the overexpression of Twinkle increases the copy number of mtDNA and alleviates the deterioration of cardiac function caused by cardiac fibrosis after TAC [42]. In vitro experiments have confirmed that Twinkle can inhibit the TGF-β1 signalling pathway [42]. Silymarin is a widely used natural bioactive substance that can increase the concentration of mitochondrial DNA; it prevented cardiac hypertrophy in a rat model of partial abdominal aortic coarctation [43].

3. Potential Role of Mitophagy in Pathological Cardiac Remodelling under Pressure Overload

When cells are under the pressure of ROS, mitophagy is activated in a variety of ways. On the one hand, ROS activates mitophagy at the transcriptional level. ROS can activate TIGAR, BINP3/NIX, LC3, P62, and Atg4 to induce autophagy through P53, HIF-1, FOXO3, and Nrf2 pathways [44]. On the other hand, ROS interact with ubiquitin-dependent mitophagy [45]. However, the effect of RNS on Pink1/Parkin remains controversial. NO·free radical-induced S-nitrosylation at Cys568 of Pink1 inhibits its ability to phosphorylate Parkin and reduces Parkin recruitment to mitochondria [46]. S-Nitrosylation of Parkin in Cys323 enhances its E3 ligase activity [47]. The initiation of mitophagy can inhibit the production of ROS in mitochondria to avoid oxidative damage and then inhibit pressure overload-induced myocardial hypertrophy and fibrosis and improve cardiac systolic dysfunction [48]. Mitophagy is also capable of mediating the elimination of damaged mtDNA. In adult drosophila cells, the activation of Pink1/Parkin promotes mitophagy and clears mtDNA, with multiple genes removed or destroyed [49]. ATAD3B was recently identified as a novel mitophagy receptor. ATAD3B is a mitochondrial outer membrane protein that binds to LC3 through its LIR-3 (LC3 interaction region) motif and connects to mtDNA through the ATAD3B–ATAD3BA–mtDNA axis. Under oxidative stress, the heterooligomer of ATAD3B-ATAD3BA decreases, resulting in the exposure of its LIR motif in the cytoplasm, activating mitophagy and eliminating mtDNA mutations that induce oxidative stress [50]. Numerous studies have shown that mitophagy plays an important role in mitochondrial ecology, but mitophagy does not always play a protective role in disease models under unrestricted conditions. Zhang et al. [51] showed that melatonin alleviates cardiac ischaemia–reperfusion injury by activating OPA1-related mitophagy. The deletion of DUSP1 promotes BNIP3-mediated mitophagy and aggravates cardiac dysfunction caused by ischaemia–reperfusion injury [52]. The double-edged sword effect of mitophagy in numerous organs and systems reveals that the regulation and effect of mitophagy are generally related and coordinated. Although there are certain clues, the specific phenotypes caused by mitophagy in different scenarios still need to be examined holistically and dialectically. Fully mobilising active mitophagy while avoiding uncontrolled or maladaptive mitophagy is the key to alleviating cardiac remodelling and cardiac dysfunction caused by pressure overload (Figure 2).

4. Regulation of Mitophagy during Cardiac Pressure Overload

4.1. Mitochondrial Dynamics

4.1.1. Mitochondrial Division and Fusion. Mitochondrial division and fusion promote the circulation of matrix components between mitochondria, which is of great significance for maintaining their function [53]. Mitochondrial fusion can dynamically repair reversible damage to parts of mitochondria to form functional elongated organelles. Mitochondrial fission occurs when the mitochondria are irreversibly damaged [54]. MFN1, MFN2, and OPA1 mainly mediate mitochondrial fusion [55]. The C-terminal and redox sensitive cysteine residue residence of MFN1 and MFN2 are located in the IMS of mitochondria, and redox-mediated disulfide modifications within the IMS domain regulate the oligomerization of MFNs [56]. MFNs can form MFN1 isooligomers, MFN2 isooligomers, and MFN1-MFN2 heterooligomers. These three types of complexes cooperate to bind the outer mitochondrial membrane of adjacent mitochondria and mediate outer membrane fusion [57, 58]. Mitochondrial intimal fusion depends on OPA1, which is a member of the GTPase family. It is located on the mitochondrial ridge and is of great significance in maintaining mitochondrial morphology. After OPA1-specific knockout, mitochondrial inner membrane fusion is blocked; mitochondrial cristae disappear and multiple matrix components appear inside, but mitochondrial outer membrane fusion is not affected [59]. Membrane-anchored long-form OPA1 (L-OPA1) is hydrolysed at site S1 or S2 by a group of proteases located in the mitochondrial membrane space, resulting in the loss of OPA1 transmembrane domain and the

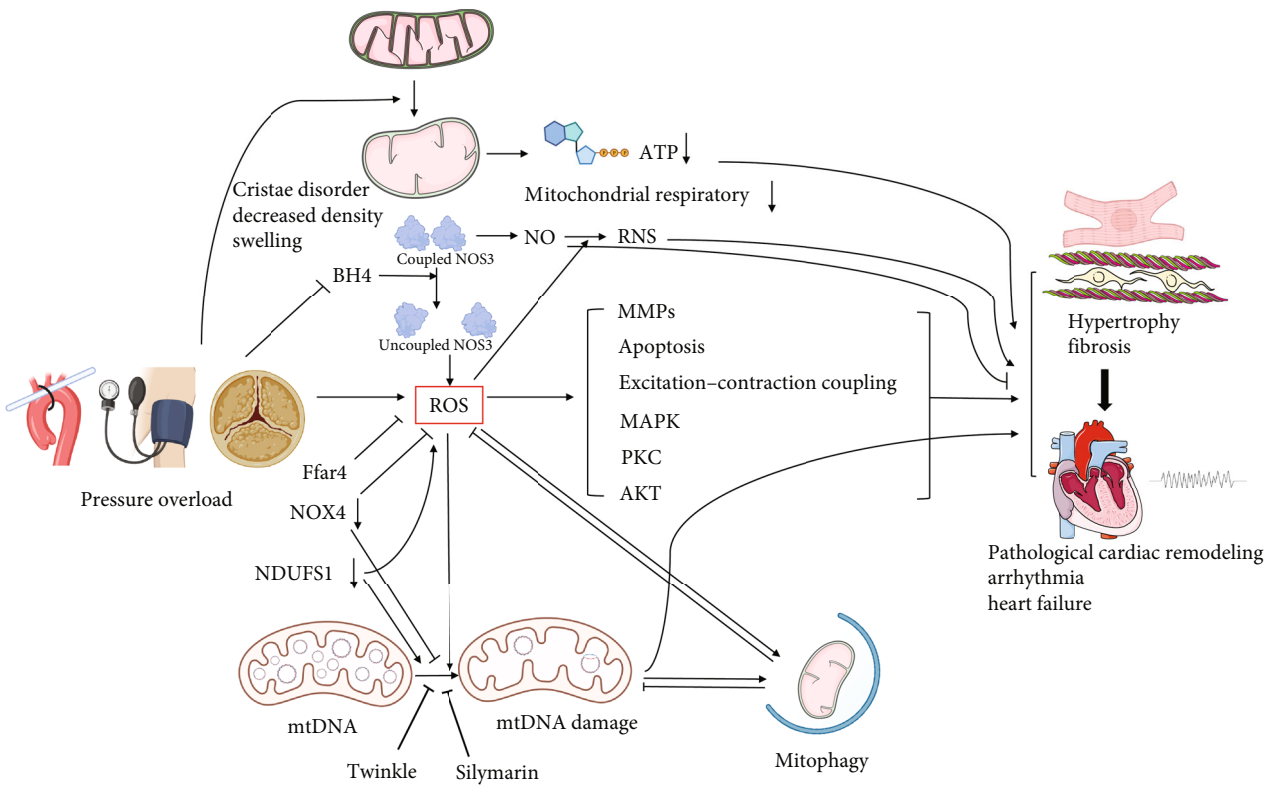

Figure 2: Mitochondria-related damage and potential role of mitophagy in pressure overload model. More mitochondrial cristae disorders, decreased cristae density, and mitochondrial swelling appear after pressure overloaded. Mitochondrial respiration is impaired. Oxidative stress is an important mediator in the mechanism of pathological cardiac remodelling. Under pressure overload, a variety of mechanisms regulate the increase of ROS and RNS. Under pressure overload, ROS and a variety of upstream signals also lead to mtDNA damage, resulting in pathological cardiac remodelling. mtDNA damage and ROS activate mitophagy through a variety of mechanisms. Mitophagy inhibits the adverse effects of ROS and mtDNA.

production of soluble short form OPA1 (S-OPA1) [60]. Using the helical three-dimensional reconstruction technology of freeze electron microscope, Zhang et al. [61] found that s-OPA1 can be divided into three parts: GTPase domain for GTP hydrolysis, STALK region mediating the formation of high polymer assembly state, and EMB domain related to membrane binding. S-OPA1, after GTPγS-binding, makes its arrangement on liposome tubes looser by adjusting its own conformation and assembly mode, which is closely related to the function of OPA1 in inducing mitochondrial intimal fusion [61]. S-OPA1 cooperates with L-OPA1 to catalyse fast and efficient fusion. Equimolar L-OPA1 and S-OPA1 mediate the best pore opening efficiency and pore opening kinetics [62].

Mitochondrial fission is mainly regulated by DRP1 [63]. DRP1 has an N-terminal GTPase domain thought to provide mechanical force, a dynamin-like middle domain, and a GTPase effector domain located in the C-terminal region [64]. DRP1 is recruited to the outer mitochondrial membrane by a variety of resident protein receptors, including FIS1, MFF, MID49, and MID51 [23], and cleaves mitochondria when GTPase decomposes GTP for energy [65]. MFF plays a recruiting role for DRP1 through its 50 residues containing short amino acid repeats [65]. The actual function of some protein receptors remains controversial. According to Oliver et al. [66], FIS1, MID49, and MID51 can recruit DRP1 and promote mitochondrial fission. However, some studies have indicated that overexpression of MID49 and MID51 recruits DRP1 to mitochondria and causes mitochondrial fusion [67, 68]. Knocking down FIS1 in HCT116 cells does not reduce the level of DRP1 localised to mitochondria [69]. In a nutshell, the regulation of DRP1 recruitment and subsequent fission induction is subject to complex regulation.

4.1.2. Interaction between Mitochondrial Dynamics and Mitophagy. There is increasing evidence that mitochondrial dynamics coordinate mitophagy as a coherent mechanism. Gilad et al. [70] found the asymmetric division of mildly damaged mitochondria resulted in a healthy hyperpolarised mitochondrion, while another depolarised mitochondrion was cleared by mitophagy. In MEFs, mitochondrial fusion disorder caused by the knockout of MFN1 and MFN2 inhibits mitophagy during mitochondrial damage and leads to the accumulation of dysfunctional mitochondria [71]. MFN2 can mediate mitophagy as a mitochondrial receptor of Parkin. Pink1-mediated phosphorylation of MFN2 at Thr111 and Ser442 results in Parkin binding activity of MFN2. Functional ablation of these phosphorylation sites by their mutational substitution with Ala abrogates MFN2-Parkin binding, whereas mimicking MFN2 phosphorylation by mutational substitution with Glu confers constitutive

Parkin binding [72]. MFN2 knockdown can also lead to impaired autophagy degradation and reduce autophagy flux to inhibit mitophagy. In the heart, MFN2 mediates autophagosome-lysosome fusion by attracting and binding RAB7 to the autophagosome membrane. MFN2-deficient mice were reported to have a large accumulation of autophagosomes in the heart [73]. MFN2 can also connect the endoplasmic reticulum and mitochondria by forming homo- and heterocomplexes with MFN1 or MFN2 on mitochondria through MFN2 at the endoplasmic reticulum [74]. This may indicate that the ER–mitochondrial contact site plays a role in mitophagy and may act as a bridge between mitochondrial dynamics and mitophagy. In the dominantly inherited optic atrophy model, OPA1 has shown negative regulation of mitophagy [75]. However, there is evidence that OPA1 plays a role in promoting mitophagy in the heart. Zhang et al. [51] found that melatonin-mediated mitophagy was inhibited after the knockout of OPA1. According to Xin et al. [76], OPA1 overexpression protects cardiomyocytes against hypoxia-induced damage and enhanced cell viability by inducing mitophagy. DRP1 and its receptors are also involved in mitophagy. BNIP3 is an effective inducer of mitophagy. It induces mitochondrial translocation of DRP1, and the inhibition of DRP1 reduces BNIP3-mediated mitophagy [77]. In the myocardium, DRP1 downregulation induces mitochondrial elongation and the accumulation of damaged mitochondria and inhibits mitophagy [78]. Six amino acid domains between Dnm1 (Drp1, Dnm1 in yeast) 24△ and Dnm1 30△ at the C-terminal of Dnm1 GTPase domain in yeast can bind to ATG11 and mediate mitochondrial degradation through the interaction between ATG32 and ATG11 [79]. By contrast, Song et al. [71] proposed that inhibition of DRP1, thereby inhibiting mitochondrial division, enhances mitochondrial autophagy. Yamashita and Kanki [80] proposed a new Dnm1-independent model of simultaneous mitophagy and mitochondrial division, where the budded portion of the mitochondria is divided simultaneously with phagophore closure. Burman et al. [81] had a similar view that DRP1-mediated mitochondrial division does not affect mitophagy. Instead, it protects healthy mitochondrial domains against elimination by the unchecked Pink1-Parkin activity [81]. After 2 hours of CCCP treatment, the loss of MFF significantly reduced the translocation of Parkin from the cytoplasm to damaged mitochondria and prevented mitochondrial clearance; Parkin ubiquitinated MFF at lysine 251, and the K251r mutant of MFF lost its P62 binding activity [82]. Knockdown of MID49 initiates Parkin translocation after CCCP short-term stimulation, further accelerates the degradation of MFN2 and FIS1 through the UPS pathway, and positively regulates mitophagy [83]. Overexpression of exogenous FIS1 enhances autophagosome production of mitophagy in MEF cells [84]. TBC1D15, a mitochondrial Rab GTPase-activating protein, and its amino acid residues 200–300 directly interact with FIS1 and further promote proper autophagic encapsulation of mitochondria [85]. STX17 is localised to the endoplasmic reticulum and mitochondria and regulates mitochondrial division by determining the localisation and fissionable activity of DRP1 [86]. However, the TPR2 structure of FIS1 can bind to STX17 and negatively regulate STX17-induced mitophagy [87]. In conclusion, various mitochondrial dynamic proteins play important roles in balancing mitophagy. These contradictory data support the complex regulation of mitochondria shaping proteins in mitophagy. The regulation of mitophagy by mitochondrial dynamics is not a simple dichotomous relationship, and different regulatory modes dominate in different cells and models, mediating a variety of effects.

4.1.3. Mitochondrial Dynamics in Pressure Overload Models. Abnormal mitochondrial fission and fusion are the main causes of multiple human diseases [88, 89]. Numerous studies have revealed that mitochondrial dynamics and dynamic-related proteins including MFN2, OPA1, and DRP1 play critical role in pressure overload myocardial hypertrophy. MFN2 was found to be downregulated in both spontaneous hypertension and TAC-induced pressure overload models [90]. In vitro, a decrease of MFN2 was also observed in Ang II-induced cardiomyocyte injury [91]. The binding domain of Mir-17-5p significantly increases after TAC. It complements the 3′-UTR of MFN2 and negatively regulates MFN2 expression. Restoring the MFN2 level can reduce cardiomyocyte hypertrophy caused by Mir-17-5p [92]. Another study on the TAC model found that Mir-106a is able to promote cardiac hypertrophy. In the associated in vitro experiments, MFN2 was proved to be a downstream target inhibited by Mir-106a to play a role in promoting hypertrophy [93]. A recent study confirmed that TAC resulted in more significant ventricular dilation and ventricular dysfunction in $OPA1^{+/-}$ mice [94]. Guo et al. [95] found that fatty acids inhibited L-OPA1 to S-OPA1 transformation by upregulation of YME1L and improved mitochondrial and cardiac function in TAC mice. In mice cardiomyocytes, TNFR2 activation-mediated acetylation of K370 and K383 residues at STAT3 increased STAT3/RelA interaction to activate OPA1 expression and played a protective role in TAC-induced mouse cardiac remodelling [96].

Not only fusion proteins of mitochondria but also fission proteins are reported to participate TAC-induced cardiac dysfunction. Myocardial sections obtained from human heart failure patients showed significantly lower DRP1 phosphorylation at S616 than in normal controls [97]. In mice, the phosphorylation of DRP1 at S616 increased significantly soon after TAC, reflecting the enhancement of mitochondrial fission mediated by DRP1. At the same time, the lysosomal localisation of Mito-Keima increased, reflecting the enhancement of mitophagy. However, TAC suppresses mitophagy after 7 days with the downregulation of phosphorylation of DRP1 at S616, followed by mitochondrial dysfunction [97]. Cardiac-specific heterozygotic knockout of DRP1 was reported to exacerbate pressure overload-induced mitochondrial dysfunction, cardiac hypertrophy, and cardiac dysfunction [97]. However, Ma et al. [98] concluded that excessive mitochondrial division and mitophagy are the causes of mitochondrial structure and function damage after TAC, aerobic exercise, and choline intervention balances mitochondrial fusion and fission, reduces mitophagy, and improves cardiac hypertrophy after TAC.

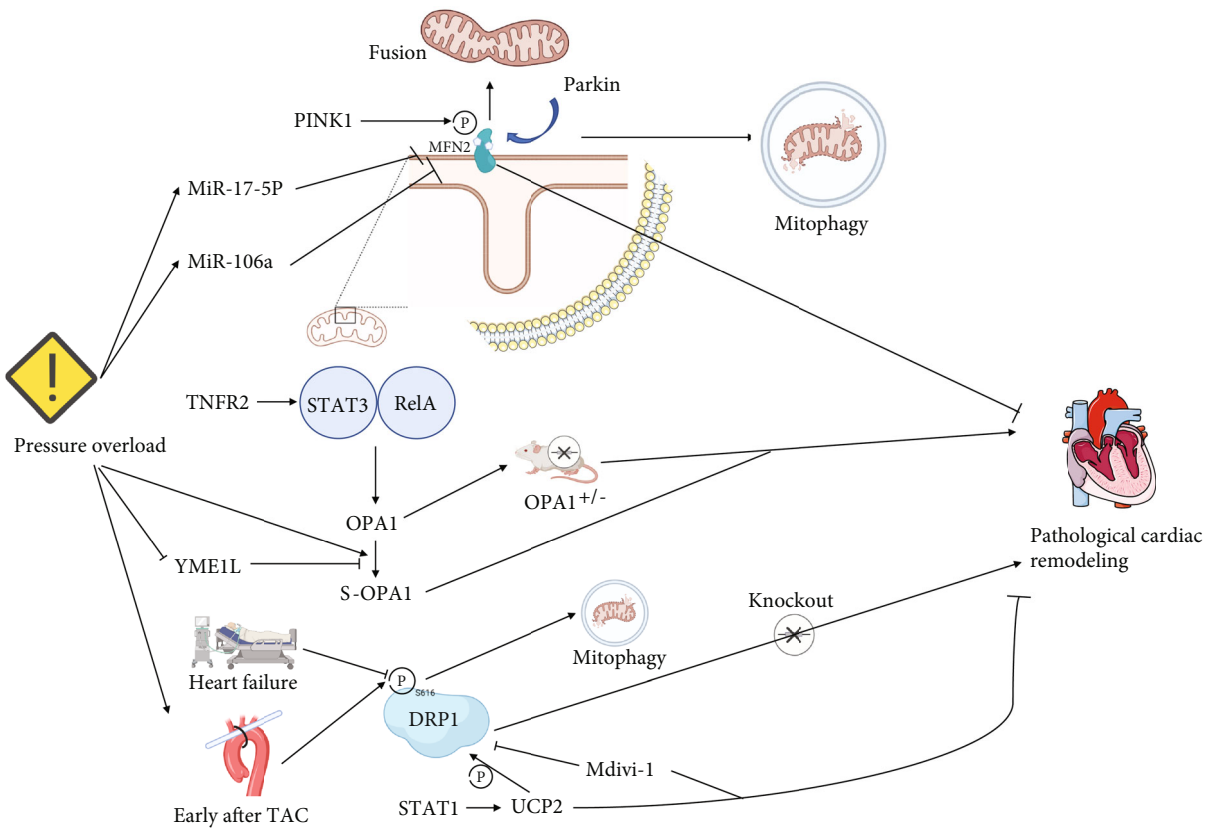

Figure 3: Mitochondrial dynamics in pressure overload model. In the pressure overload model, MFN2 was downregulated. After TAC, Mir-17-5p and Mir-106a inhibit MFN2 and cause cardiac hypertrophy. In OPA1+/- mice, TAC results in more severe cardiac remodelling and cardiac dysfunction. Increased expression of OPA1 by upregulating YME1L or TNFR2 protects hearts from pressure overload. The decreased level phosphorylation at s616 of DRP1 accompanies a decrease in mitophagy. Knockout of DRP1 aggravates mitochondrial dysfunction, cardiac hypertrophy, and cardiac dysfunction caused by pressure overload. STAT1 promotes mitochondrial division through UCP2/P-DRP1 pathway to resist TAC-induced myocardial hypertrophy. However, the use of DRP1 inhibitor Mdivi-1 improves cardiac dysfunction and cardiac remodelling after TAC.

Givvimani et al. [99] improved cardiac dysfunction and ventricular remodelling after TAC, I/R, or LPS treatment using the DRP1 inhibitor Mdivi-1, Dynasore or P110. However, the evidence provided by small molecule inhibitors and gene knockout was not completely consistent. These studies show that although existing research cannot provide irrefutable conclusions, it is undeniable that mitochondrial dynamics are a potentially promising intervention target to provide protection when the heart is exposed to pressure overload injury (Figure 3).

4.2. Ubiquitin Pathways (Pink1/Parkin). According to the available data, Pink1/Parkin-mediated mitophagy has been relatively fully characterised. Pink1 is a Ser/Thr kinase that takes possession of an N-terminal mitochondrial targeting sequence (MTS), α-helical transmembrane domain, and conserved Ser/Thr domain, along with the C-terminal regulatory domain [100]. The MTS of Pink1 is recognised by Tom20 and Tom22 and passes through the Tom40 channel [101]. Then, it enters the interior of mitochondria through TIM23 driven by mitochondrial inner membrane potential [101]. Under physiological conditions, mitochondrial processing peptidase cuts the MTS sequence of Pink1 [102], and presenilin-associated rhomboid-like protein cuts the amino acid between Ala-103 and Phe-104 of the transmembrane domain of Pink1 [103], which promotes the translocation of Pink1 precursors into the cytoplasm. Parkin is an E3 ubiquitin ligase composed of a ubiquitin-like domain, a 60-amino acid linker, and zinc finger domains (RING) [104]. Parkin is originally in a state of automatic inhibition. The RING0 domain blocks the Cys431 site in the RING2 domain, and the α helix bound to RING1 (reporter element of Parkin) blocks the E2 binding site in the RING1 region [104]. When Parkin is activated by injury, the Parkin conformation changes and exposes its C431 site [105]. Parkin collaborates with E1 activating enzyme together with E2 binding enzyme to promote substrate protein ubiquitination [106]. Pink1 accumulates on the outer mitochondrial membrane when the mitochondrial membrane potential is lost [107], which leads to autophosphorylation at the Ser228 and Ser402 sites of Pink1 and summons Parkin to mitochondria [108]. Parkin ubiquitination is not limited to substrate MOM proteins such as VDAC1, MFN1, and MFN2 [109]. Pink1 phosphorylates the Ser65 residue of Parkin and amplifies its E3 ligase activity under excitation by potential depolarisation of the mitochondrial membrane [110].

Subsequently, they are recognised by a variety of autophagy receptors, such as NDP52, OPTN, and P62, and then expand autophagosomes through the LC3 interaction region [111]. On the other hand, Pink1-mediated mitophagy may not depend on Parkin. In cells lacking Parkin, Pink1 can phosphorylate ubiquitin protein and mobilise OPTN and NDP52 to mitochondria, and then ULK1, DFCP1, and WIPI1 are recruited to initiate autophagy [112]. The preponderance of evidence suggests that pathways targeting Pink1/Parkin exert influences on pressure overload, although the current results show divergences to some extent. There is evidence that the upregulation of Pink/Parkin under pressure overload plays a protective role [113]. Cao et al.'s research provides another perspective: Miro2 mediates mitochondrial communication through mitochondrial nanotube formation, which maintains mitochondrial function and heart function under stress overload [114]. After TAC, increased Parkin degrades Miro2 through the ubiquitination pathway [114]. To sum up, the role of the Pink–Parkin pathway in mediating mitophagy in heart failure induced by pressure overload needs the support of additional research.

4.3. Mitophagy Receptor Pathways

4.3.1. BNIP3/NIX. BNIP3 and NIX are proteins with homology to BCL2 in the BH3 domain [115]. BNIP3 and NIX have multiple effects of inducing cell death and mitophagy [115]. BNIP3 acts as an effective inducer of autophagy in a variety of cells, including cardiomyocytes [116]. Six residues in BNIP3 are important for dimerisation. They jointly mediate the formation of BNIP3 dimer by forming inter monomer hydrogen bonds, tandem GXXG motif, and Van der Waals contacts [117]. LC3 binds to the LIR motif in the BNIP3 homodimer to induce mitophagy and endoplasmic reticulum autophagy [118]. Phosphorylation of serine residues 17 and 24 on both sides of BNIP3 LIR promotes its binding to LC3B and GATE-16 [119]. The role of NIX in mitophagy was first found in the process of erythrocyte differentiation and maturation [120]. Subsequently, Sandoval et al. [121] found that NIX induces mitophagy by mediating the reduction of mitochondrial membrane potential. Yang et al. [122] demonstrated that NIX deficiency does not interfere with Parkin's recruitment of mitochondria and recognised that NIX mediates mitophagy independently of Parkin and plays a compensatory role at a low level of Parkin. At present, NIX is defined as a selective mitophagy receiver because its terminal amino acids 3–38 form an LIR sequence and bind to LC3a [123]. NIX-mediated mitophagy requires phosphorylation of NIX Ser81, and NIX S81a mutation cannot bind to LC3a or LC3b [122]. NIX usually appears as a homologous dimer [124] through the important role of glycine 204 and glycine 208 in the transmembrane domain. The dimerised NIX significantly increases the binding percentage of LC3a compared with the NIX monomer [124]. Other studies have confirmed the interaction between Nix and the Pink–Parkin pathway. The C-terminal transmembrane domain of BNIP3 binds to Pink1 and inhibits the cleavage of Pink1, promoting the recruitment of Parkin to mitochondria and mitophagy [125]. The current evidence tends to suggest that BNIP3-mediated mitophagy aggravates the negative effects of pressure. BNIP3/NIX is significantly increased after receiving TAC [126]. Knockout of the RAGE prevented the upregulation of BNIP3 in TAC mice and improved TAC-induced cardiac dysfunction [127]. Another study showed that raloxifene is a novel IL-6 inhibitor that can inhibit IL-6-induced BNIP3 elevation as well as cardiac dysfunction and remodelling caused by pressure overload [128]. In vitro, the stress-related hormone norepinephrine induces the upregulation of NIX in 3T3 cells and promotes the expression of collagen and fibronectin [129]. After being transfected with BNIP3, H9C2 cells show both hypertrophic growth (accompanied by the activation of many upstream pathways related to myocardial hypertrophy) and increases in ANP and BNP [130].

4.3.2. FUNDC1. In terms of receiver mediated mitophagy pathway, MOM-anchored protein FUNDC1 participates in mitophagy but does not affect autophagy. FUNDC1 is anchored to the mitochondrial outer membrane through its C-terminal domain. The N-terminal cytoplasmic region of FUNDC1 contains a Y (18) xxL (21) motif, which is a typical LIR [131]. Phosphorylation of FUNDC1 at Ser17 binds to LC3b Lys49 to activate mitophagy through additional hydrogen bonds; on the other hand, phosphorylated Tyr18 and Ser13 in FUNDC1 significantly hinder their interaction with the hydrophobic pocket and Atg10 of LC3B [132]. Knockdown of FUNDC1 in SH-SY5Y cells does not affect Pink1 translocation or Parkin recruitment, indicating that FUNDC1 was not involved in Pink1/Parkin-dependent mitophagy [133]. FUNDC1 is also associated with mitochondrial dynamics. FUNDC1 is located in MAMs where it binds to IP3R2, which is localised to the endoplasmic reticulum. FUNDC1 maintains the concentration of Ca^{2+} in the cytoplasm through this effect, thus maintaining the expression of FIS1, mitochondrial fission, and mitophagy [134]. FUNDC1 interacts with OPA1 through its lysine 70 (K70), and the K70a mutation, lacking interaction with OPA1, reduces the recruitment of LC3 [135]. Current studies support a protective role of FUNDC1 in the heart. Alpha-lipoic acid (α-LA) is a coenzyme present in mitochondria that reduces cardiac hypertrophy induced by pressure overload [136]. Li et al. [137] found that α-La increases the expression of Nrf1 by activating ALDH2; Nrf1 directly binds to the 5′ promoter of FUNDC1 to regulate its expression, thus reducing cardiac hypertrophy and myocardial remodelling caused by pressure overload. Therefore, the regulation of FUNDC1 in mitophagy to alleviate the damage caused by stress overload is expected to be extensively explored and utilised.

4.4. MCU and Mitochondrial Calcium Homeostasis. Mitochondrial Ca^{2+} homeostasis imbalance is an important feature of heart failure caused by pressure overload; mitochondrial calcium overload or insufficient uptake is aggravating factors of pressure overload heart failure. Thai et al. [138] found that TAC caused damage to mitochondrial Ca^{2+} uptake in mouse cardiomyocytes. Silencing the translocator protein of the outer mitochondrial membrane to restore mitochondrial Ca^{2+} uptake can protect the heart

from pathological myocardial hypertrophy and cardiac remodelling caused by pressure overload. Elrod et al. [139] confirmed that Ppif gene deficiency in mice led to a decrease in physical opening of MPTP and an abnormal increase in mitochondrial Ca^{2+}, aggravating myocardial hypertrophy and heart failure after pressure overload. MCU anchored in the inner mitochondrial membrane is the most important one-way channel responsible for Ca^{2+} influx into mitochondria [140]. Ca^{2+} is a ubiquitous intracellular signal messenger that participates in many cellular functions, including mitophagy [141]. However, there is still no unified conclusion on how mitochondrial Ca^{2+} triggers and regulates mitophagy in different disease models. In myocardial ischaemia–reperfusion injury model, mitochondrial calcium overload caused by MCU upregulation activated calpain, thus inhibiting OPA1 and mitochondrial fusion, resulting in the inhibition of mitophagy [142]. In vascular smooth muscle cells, MCU-dependent mitochondrial Ca^{2+} uptake promotes mitophagy [143]. MCU is closely related to a variety of mechanisms that mediate mitophagy. The use of MCU inhibitor RU360 in vascular endothelial cells inhibits mitochondrial division by inhibiting DRP1 phosphorylation and oligomers [144]. MCU-dependent mitochondrial Ca^{2+} uptake can also induce mtROS production [145]. The use of RU360 reduces mtROS generation [146]. MPTP opening is a main pathway of physiological mitochondrial Ca^{2+} efflux. MPTP opening plays a decisive role in the activation of Pink1–Parkin-mediated mitophagy [147]. It has been proved that inhibiting MCU will reduce the opening of MPTP, and activating MCU will increase the opening of MPTP [148]. MCU also regulates mitochondrial metabolism by targeting the key enzymes involved in the TCA, through mitochondrial Ca^{2+} uptake [149]. An abnormal TCA cycle will change the biosynthesis of metabolites that have an impact on myocardial hypertrophy. A paper by Ritterhoff et al. [150] showed that remodelling of the TCA cycle promotes the increase of glucose-derived aspartate and promotes myocardial hypertrophy. AKG is an important intermediate of the TCA cycle that regulates a variety of important physiological functions, including cell metabolism and signal transduction. Dietary AKG supplementation inhibits cardiac hypertrophy and fibrosis induced by TAC [48]. An et al. [48] confirmed that TAC causes a decline of Pink1/Parkin, and the use of AKG inhibits this trend and reduces the production of ROS. Current research has established a direct link between MCU, mitophagy, and pressure overload-induced heart failure. In heart failure induced by pressure overload, MCU expression is upregulated, and autophagic flux is blocked. After the use of MCU inhibitors, Parkin and Pink1 are upregulated, mitophagy is enhanced, and cardiac function is improved [151]. These findings suggest that the regulation of mitophagy by MCU is a potential therapeutic target for heart failure induced by pressure overload.

4.5. Signalling Pathways Potentially Influencing Mitophagy. AMPK is a key sensor of cellular energy state and is considered a participant in mitophagy. The relationship between AMPK, mitophagy, and pressure overload-induced heart failure has been established. Wang et al. [152] constructed AMPK catalytic α2-subunit knockout mice and demonstrated that its absence exacerbates heart failure after TAC by inhibiting mitophagy. Pink1 phosphorylation and Pink1/Parkin-mediated mitophagy were enhanced after AMPKα2 overexpression. Several sites on Pink1 can be phosphorylated by AMPKα2, but Ser495 residue is considered the optimal site, as Ala mutation reduces mitophagy and induces ROS production there [152]. Phosphorylation of ULK1 is also necessary for mitophagy in the verified case [153]. AMPK can trigger autophagy by activating ULK1 directly or by inhibiting the mTORC1 complex. AMPK mediates the phosphorylation of Ser772 and Ser792 of mTOR binding partner Raptor and is also able to phosphorylate TSC2 upstream of mTOR to jointly inhibit the activity of mTORC1 [154]. Egan et al. [155] identified four AMPK phosphorylated sites in ULK1 (Ser 467, Ser 555, Thr 574, and Ser 637) and confirmed that AMPK or ULK1 knockdown leads to autophagy defects. A recent study determined that GPR39, as an inhibitor of AMPK, increases after TAC to activate mTOR and promotes cardiac hypertrophy [156]. AMPK is also involved in mitochondrial dynamics. DRP1 receptor MFF has two AMPK phosphorylation sites, Ser155 and Ser172, and phosphorylation dysfunction at these two sites prevents DRP1 recruitment to mitochondria [157]. AMPK has also been identified as an upstream signal of OPA1, and inhibition of AMPK results in a decrease in OPA1 expression [51]. Although existing studies have directly linked only part of the mechanism of AMPK regulation of mitophagy to the cardiac phenotype under pressure overload, current results still provide a blueprint for applying the AMPK–mitophagy pathway to the model of pressure overload.

SIRT1 is an NAD^+-dependent deacetylase that mediates a variety of physiological effects, such as cell metabolism, proliferation, and differentiation [158]. SIRT1 was earlier shown to activate autophagy, but it was also found that there is a significant accumulation of abnormal mitochondria after SIRT1 knockout [159]. Subsequent studies by Huang et al. [160] proved that nicotinamide promoted the increase of $[NAD^+]/[NADH]$ ratio through the salvage pathway, mediated the enhancement of SIRT1 activity, and thus improved mitophagy. This is favourable evidence that SIRT1 is directly associated with mitophagy. Existing theories are gradually clarifying how SIRT1 is involved in mitophagy through different pathways. Resveratrol is a natural compound with an antiageing effect. It activates SIRT1/SIRT3 to exert cardiac protection through the Pink–Parkin pathway via FOXO3 [161]. Available evidence suggests that SIRT1 plays a protective role in cardiac hypertrophy induced by pressure overload. After SIRT1 knockout, the indexes of myocardial hypertrophy β-MHC and ANP increase [162]. SIRT1 can also negatively regulate the mTOR signalling pathway and affect autophagy and mitophagy-mediated mitochondrial clearance [163]. SIRT1 also enables PGC-1α deacetylation, which in turn activates the Pink–Parkin pathway [164]. Although the current study is optimistic about the positive role of PGC-1α in pressure overload models [165], studies have not established a direct correlation between PGC-1α-

induced mitophagy and cardiac remodelling induced by pressure overload. Future studies may not rule out the possibility of SIRT1/PGC-1α-mediated mitophagy as a therapeutic target for pressure overload.

PTEN is a phosphatase of lipids and proteins that inhibits tumour growth, regulates glucose and lipid metabolism, and adjusts mitochondrial function [166]. PTEN can inhibit the PI3K/AKT pathway and promote autophagy [167]. However, several studies have found that PTEN can inhibit mitophagy. Li et al. [168] confirmed that PTEN restricts mitophagy by inhibiting the TLR4–JNK–BNIP3 pathway. Knockout of PTEN increases the activity of mitophagy by increasing the expression of MFN2 [169]. In the TAC model, inhibition of PTEN degradation led to AKT/mTOR inactivation and AMPK signal activation, thereby ameliorating cardiac hypertrophy and dysfunction caused by pressure overload [170]. The results of Tian et al. [171] showed that in TAC model or ISO induced cardiomyocyte hypertrophy, LKB1IP activates AKT signal transduction by inhibiting the phosphatase activity of PTEN, thereby aggravating pathological cardiac hypertrophy. However, there is no study on the direct connection between PTEN, mitophagy, and pathological cardiac hypertrophy.

The functions of P53 include but are not limited to tumour inhibition, ageing, metabolism regulation, and oxidative stress regulation. Hoshino et al. [172] revealed its role in mitophagy, wherein residues 81–160 of P53 interact with the RING0 region of Parkin and inhibit mitochondrial translocation of Parkin, thereby inhibiting mitophagy. P53 increases significantly one week after TAC [173]. Overexpression of Canopy 2 inhibits the expression of P53 and maintains cardiac structure and function after TAC [173]. Nrf2 is an antioxidant involved in oxidative stress and mitophagy in a variety of disease models. The expression levels of Pink and Parkin are reduced after Nrf2 is knocked out by siRNA [174]. Nrf2 can also be combined with the ARE sequence of P62 to activate the expression of P62. P62 has also been proved to lead to the activation of Nrf2. Their mutual regulation forms a cycle and regulates the homeostasis of mitophagy [175]. Finally, peroxiredoxin 1 was shown to inhibit TAC-induced cardiac remodelling and cardiac dysfunction. Peroxiredoxin 1 increases the expression of Nrf2 after TAC, and knockout of Nrf2 inhibits the protective effect of peroxiredoxin 1 [176].

5. Mitophagy and Cardiac Nonmyocytes

Cardiac nonmyocytes actively participate in the development of cardiac hypertrophy under pressure overload. Fibroblasts, vascular endothelial cells, and macrophages are all important in pressure overload-induced cardiac remodelling [177]. Activation of cardiac fibroblasts is a hallmark of cardiac remodelling and fibrosis caused by pressure overload [178]. Cardiac fibroblasts can also promote cardiomyocyte hypertrophy through paracrine communication [177]. Therefore, the control of myocardial fibrotic remodelling is considered a possible target for the treatment of heart failure induced by pressure overload [179]. Activation of cardiac fibroblasts can be regulated by mitophagy. Mitophagy plays a role in tissue fibrosis remodelling [180]. ADAM17, known as disintegrin and metalloproteases, whose knockdown inhibited TGF-β1, induced collagen synthesis in cardiac fibroblasts by enhancing mitophagy [181]. However, a study of Zhang et al. [182] suggested that Mir-24-3p reduced myocardial fibrosis by inhibiting mitophagy in mice undergoing TAC surgery. A growing number of studies have reported the complex role of macrophages in cardiac remodelling induced by pressure overload. Huo et al. [128] observed an increase in the infiltration of macrophages in heart tissue at 4 and 8 weeks after TAC. A single-cell sequencing of cells isolated from mouse hearts after TAC showed that macrophage subtype conversion is a key event in the progression of pathological myocardial hypertrophy 2 to 5 weeks after TAC [183]. Macrophages can release cytokines to promote cardiomyocyte hypertrophy and myocardial fibroblast activation [184]. However, cardiac resident macrophages can inhibit myocardial fibrosis and stimulate angiogenesis under pressure overload [185]. Patoli et al. [186] revealed the regulation of mitophagy on macrophage activation; they found that LPS/IFN-γ-mediated mitophagy inhibition triggers macrophage activation through ROS. The reduction of adaptive angiogenesis under pressure overload aggravates cardiac dysfunction [187]. Overexpression of SIRT3 in cardiac microvascular endothelial cells enhances Pink/Parkin-mediated mitophagy, reduces the production of ROS, and promotes angiogenesis [188]. The effect of mitophagy on the phenotype of cardiac nonmyocytes reflects the extensive regulation of mitophagy in pathological changes of the heart under pressure overload and further clarifies the significant impact mitophagy will have in the identification of new therapeutic targets for cardiac remodelling and heart failure under pressure overload.

6. Active Compounds with the Potential to Intervene in the Effects of Pressure Overload on the Heart by Regulating Mitophagy

There is as yet no general clinical consensus on intervening in mitophagy under pressure overload. However, the current research provides promising pathways and new starting points for the treatment of heart injury caused by pressure overload, covering as it does multiple aspects of mitophagy. The latest view takes a short-term high-fat diet as a measure to inhibit cardiac hypertrophy after TAC. A short-term high-fat diet enhances the utilisation of fatty acids in the myocardium and enhances mitophagy by upregulating Parkin, which provides novel evidence for the effect of diet on mitophagy [189]. The researchers in the cited study also found that a long-term high-fat diet did not enhance mitophagy and even caused lipotoxic damage to the myocardium. Therefore, it is indicated that the regulation of mitophagy by diet requires precise timing and careful use [189]. There is broad consensus that statins improve the outcomes of heart failure. In the case of pressure overload, the combination of simvastatin and losartan reduces cardiac remodelling. In the detection of Parkin and observation of ultrastructure by transmission electron microscope, mitophagy was considered involved in the protective effect of

simvastatin [190]. A variety of natural herbal active compounds have also been shown to regulate mitophagy in the pressure overload model. Berberine is extracted from Coptis Chinensis, and its protective effect on the heart has been confirmed in recent years [191]. Abudureyimu et al. [113] found that Berberine alleviates the inhibition of mitophagy after TAC through the Pink–Parkin pathway, reduces the accumulation of swelling and damaged mitochondria, and reduces ROS levels. Inhibition of the mTOR pathway by Berberine has also been demonstrated in vivo and in vitro in response to cardiac remodelling induced by TAC [191]. Baicalein can be combined with FOXO3a, which plays a protective role in the pressure overload model, and increases the mRNA and protein levels of FUNDC1 after TAC [192].

7. Conclusion and Future Perspectives

In pressure overload-induced cardiac remodelling, mitochondrial damage exerts negative effects by interfering with normal energy metabolism and mediating oxidative stress and mtDNA imbalance. Many studies support that mitophagy is a cell-initiated protective mechanism to protect the heart from various effects of mitochondrial damage. Mitophagy not only plays a role in the TAC model but also plays a protective role in Ang II-induced myocardial injury and hypertensive cardiac remodelling [188, 193]. However, the regulation of mitochondrial dynamics, mitophagy pathways, and related signal transduction in pressure overload must be the comprehensively investigated. The roles of genes, drugs, and active molecules in mitophagy indicate many meaningful targets for ameliorating the adverse effects of pressure overload. This paper has also summarised the protective effects of conventional clinical drugs on the heart under stress overload by regulating mitophagy. However, a limitation is that most studies have been conducted at cytological and zoological levels, and few studies have been used for clinical validation. Precise targets and drugs for manipulating mitophagy need to be developed to treat cardiac dysfunction caused by pressure overload.

Abbreviations

mtDNA: Mitochondrial DNA
TAC: Transverse aortic constriction
ETC: Electron transport chain
AMS: Allyl methyl sulfide
ROS: Reactive oxygen species
RNS: Reactive nitrogen species
NOXs: NADPH oxidases
BH4: Tetrahydrobiopterin
NOS: Nitric oxide synthase
Ffar4: Free fatty acid receptor 4
JMJD: JmjC domain-containing
Pol γ: DNA polymerase γ
NDUFS1: NADH-ubiquinone oxidoreductase 75 kDa subunit
TGF-β1: Transforming growth factor β1
TIGAR: TP53-induced glycolysis and apoptosis regulator
BNIP3: BCL2 and adenovirus E1B 19 kDa-interacting protein 3
NIX: BNIP3-like
ATG: Autophagy-related proteins
FOXO3: Factor forkhead box O-3
Nrf2: Nuclear factor erythroid 2-related factor 2
ATAD3B: AAA-domain-containing protein 3B
OPA1: Optic atrophy 1
MFN: Mitochondrial fusion protein
IMS: Intermembrane space
DRP1: Dynein-related protein 1
FIS1: Mitochondrial fission protein 1
MFF: Mitochondrial fission factor
MID: Mitochondrial dynamics proteins
MEF: Murine embryonic fibroblasts
CCCP: Carbonyl cyanide m-chlorophenylhydrazone
STX: Syntaxin
TNFR2: TNFα receptor 2
MTS: Mitochondrial targeting sequence
Tom: Mitochondrial outer membrane transporter
TIM: Mitochondrial inner membrane transporter
MOM: Mitochondrial outer membrane
VDAC1: Voltage-dependent anion channel 1
Miro: Rho GTPase of mitochondrial
RAGE: Receptor for advanced glycation end products
MAM: Mitochondria-associated membrane
IP3R2: Inositol 1,4,5-trisphosphate type 2 receptor
FUNDC1: FUN14 domain-containing 1
α-LA: Alpha-lipoic acid
MPTP: Mitochondrial permeability transition pore
MCU: Mitochondrial calcium uniporter
mtROS: Mitochondrial ROS
TCA cycle: Tricarboxylic acid cycle
AKG: α-Ketoglutarate
mTOR: Mechanistic target of rapamycin
ULK1: Unc-51 like autophagy activating kinase 1
SIRT1: Sirtuin1
PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1 alpha
PTEN: Phosphatase and tensin homolog deleted on chromosome 10

Data Availability

The figures used to support the findings of this review were included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Ruochen Shao and Junli Li contributed equally to this work.

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