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Review

Mitophagy and mitochondrial integrity in cardiac ischemia-reperfusion injury

Mingjie Yang[a], Becky S. Linn[b], Yingmei Zhang[a,b,*], Jun Ren[a,b,*]

[a] Department of Cardiology and Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai 200032, PR China
[b] School of Pharmacy, University of Wyoming College of Health Sciences, Laramie, WY 82071, USA

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ABSTRACT

Ischemia-reperfusion injury (IR injury), produced by initial interruption and subsequent restoration of organ blood flow, is an important clinical dilemma accompanied by various cardiac reperfusion strategies following acute myocardial infarction (AMI). Although the restored blood flow is necessary for oxygen and nutrient supply, reperfusion often results in pathological sequelae leading to elevated ischemic damage. Among various theories postulated for IR injury including vascular leakage, oxidative stress, leukocyte entrapment, inflammation and apoptosis, mitochondrial dysfunction plays an essential role in mediating pathophysiological processes with recent evidence depicting a pivotal role for impaired mitophagy in mitochondrial injury. Given the critical role for mitophagy in mitochondrial quality control and the recent reports supporting a tie between mitophagy and IR injury, this review will revisit the contemporary understanding of mitophagy in the regulation of cardiac homeostasis and update recent progresses with regards to mitophagy and cardiac IR injury. We hope to establish a role for mitophagy as a potential therapeutic target in the management of IR injury.

1. Introduction

Based on the epidemiological data from the Global Burden of Disease study 2013 (GBD 2013), cardiovascular disease (CVD) remains as the most common cause of death worldwide, accounting for 31.5% of all-cause mortality – more than doubling the number of cancer [1]. For example, over 4 million people die of CVD across the Europe each year, a phenomenon commonly found in many other developed countries [2]. Coronary artery disease, the most common form of CVD, has seen a reduction in mortality over the past decades courtesy of the in-time reperfusion medical strategies, such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) [3,4]. However, at the same time reperfusion promotes the recovery of blood flow and salvage of cardiomyocytes in the myocardial infarct border zone, it imposes a detrimental outcome to aggravate the myocardial damage. Much effort has been engaged to clarify the precise cellular and molecular mechanisms in cardiac ischemia-reperfusion injury (IR injury) although limited consensus has been reached. Several mechanisms have been postulated for cardiac IR injury including mitochondrial Ca^{2+} overload, reactive oxygen species (ROS) generation, autophagy failure, platelet activation and micro-thrombosis formation [3,5,6], among which mitochondria seem to be cardinal to myocardial integrity and energy fuel.

As a vital intracellular organelle responsible for adenosine triphosphate (ATP) generation and energy metabolism, loss of integrity and function in mitochondria is deemed a pathological factor for altered cardiac structure and function [7]. Mitophagy or mitochondrial selective autophagy has received some recent attention in the regulation of mitochondrial quality control. In most cases, mitophagy is considered as a protective or adaptive mechanism given its ability to clear defective mitochondrial built-up from ischemia-reperfusion injury. Nonetheless, uncontrolled or excessive (maladaptive) mitophagy may result in the shortage of functional or healthy mitochondria for ATP generation, leading to compromised cell survival. Here we will discuss the current contemporary understanding for the possible role of mitophagy in pathophysiology of myocardial ischemia-reperfusion injury.

2. Overview of mitochondrial quality control mechanism

Mitochondria are double-membraned intracellular organelles mainly responsible for ATP production and regulation of cellular energy metabolism. Most cells possess abundant mitochondria such that mitochondria account for over 30% of cardiomyocyte volume to meet the constant high energy demand [8]. In addition, mitochondria participate

* Corresponding authors at: Department of Cardiology and Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai 200032, PR China.
E-mail addresses: zhangym197951@126.com (Y. Zhang), ren.jun@zs-hospital.sh.cn (J. Ren).

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in many other physiological functions including Ca^{2+} signaling and generation of ROS [9,10]. Meanwhile, mitochondria are more prone to cellular stress such as hypoxia, leading to ROS production and pro-apoptotic proteins, ultimately cell death from damaged mitochondria. To this end, mitochondrial quality control plays an important role in maintaining cellular homeostasis and cell survival, including mitochondrial biogenesis, fusion and fission and mitophagy. Removal of damaged, aged (long-lived) and dysfunctional mitochondria is mediated by mitophagy, and new mitochondria are generated for replacement via mitochondrial biogenesis, with the help of proper change in mitochondrial dynamics.

Mitochondrial quality control serves as an essential governing machinery to regulate the size, quantity, morphology, quality and biological activity for mitochondria [11–13]. When cellular stress prompts mitochondrial injury, cells first react to maintain original structure and composition via antioxidants, DNA repair, protein folding and degradation. If this first line of defense fails, a broader quality control system including mitochondrial biogenesis, fusion and fission, and elimination of damaged ones through mitophagy will kick in. When damaged mitochondria cannot be reinstated to a healthy state, mitophagy is likely the final safeguard to remove damaged mitochondria and maintain cell viability prior to apoptosis and necrosis [14]. In other words, mitochondrial biogenesis, clearance, dynamics and their intricate interplay make up an efficient quality control system to combat pathological stress and maintain mitochondrial function.

2.1. Mitophagy

Mitophagy refers to a special subtype of autophagy, a mechanism leading to lysosomal degradation of cellular components such as protein aggregates, waste lipids and dysfunctional organelles [11,12]. Autophagy is an important component of quality control system together with ubiquitin/proteasome system (UPS) in order to maintain cellular homeostasis. Targeted substrates are ubiquitinated through posttranslational modification and then recognized by ubiquitin receptors, which transfer substrates for proteasomal or autophagic degradation through binding with LC3 on phagophore [15]. Autophagy is divided into macroautophagy (commonly termed as “autophagy”), microautophagy and chaperone-mediated autophagy, among which macroautophagy is studied most widely [12,13]. Autophagy is usually maintained at basal levels under normal conditions to maintain homeostasis but is induced in cellular stress such as nutrition deprivation and hypoxia. Reduced energy level can be sensed by AMPK (AMP-activated protein kinase), which activates autophagy through inhibition of mTORC1 (mechanistic target of rapamycin kinase complex 1) or phosphorylating ULK1 (Unc-51 like autophagy activating kinase 1). Once initiated, phagophores expand and enclose waste proteins and organelles, and then fuse with lysosomes to form autolysosomes. Degraded contents are released into cytosols where they are recycled for synthesis of cellular components, nutrients and energy in the form of ATP.

Depending on the nature of cellular components to be engulfed by autophagosomes and targeted for degradation, autophagy can be further classified into selective and non-selective autophagy. Selective autophagy is mediated by unique autophagy receptors and is classified based on specific substrates for lysosomal degradation, including aggrephagy (proteins aggregates), mitophagy (mitochondria), ER-phagy (endoplasmic reticulum) and xenophagy (pathogens) [16–19]. Mitophagy is a form of selective macroautophagy, to specifically recognize and degrade defective mitochondria. Not surprisingly, genetic ablation of autophagy proteins or impaired mitophagy results in accumulation of damaged mitochondria and cell death.

Mitochondrial stress induces mitophagy as well as cell death through a complex mechanism, and the outcome is determined by intrinsic balance. Stress increases permeability of outer mitochondrial membrane (OMM) via BAX (BCL2 associated X) and BAK (BCL2 antagonist/killer 1) and releases proapoptotic proteins such as AIF (apoptosis-inducing factor) and cytochrome *c* [20]. Stress also contributes to the opening of mPTP (mitochondrial permeability transition pore) in IMM and mitochondria swelling and rupture due to rapid influx of water [21]. Although mitochondrial Ca^{2+} buffering is generally cellular protective in most cases, too much intake caused by stress will result in Ca^{2+} overload and mPTP opening [22]. To the contrary, mitophagy functions as a cardioprotective measure to remove defective mitochondria and maintain cellular homeostasis. Too much cellular stress impairs mitophagy to favor apoptosis, while improper mitophagy is also detrimental due to the shortage of healthy mitochondria for ATP generation [21]. Mitophagy and mitochondrial pro-apoptotic pathways are maintained in a delicate balance to govern cellular fate in concert.

2.2. Mitochondrial biogenesis

Mitochondrial biogenesis is responsible for replenishment of new mitochondria in order to meet energy demands [7]. A rather complicated interplay exists between mitophagy and mitochondrial biogenesis. The transcription coactivator peroxisome-proliferator-activated receptor γ coactivator 1α (PGC-1α) is induced during mitochondrial biogenesis. Meanwhile, starvation or fasting may also rapidly increase PGC-1α expression in the heart along with activation of mitophagy [23]. Parkin (PRKN, RBR E3 ubiquitin protein ligase), as a key regulator of mitophagy, may also regulate mitochondrial biogenesis through degradation of PARIS (Parkin-interacting substrate) and activation of PGC-1α transcription [24,25].

2.3. Mitochondrial dynamics/fusion and fission

Besides mitochondrial biogenesis, mitochondrial fusion and fission is another important mechanism for quality control. Mitochondria are constantly dividing and elongating through fission and fusion, thus maintaining their morphology in a dynamic fashion. Mitochondrial fission results in small fragmented mitochondria while fusion forms elongated interconnected network. Upon fission, mitochondria are divided into polarized and depolarized daughter mitochondria. Depolarized mitochondria are targeted towards mitophagy, in which case fission promotes mitophagy while inhibiting fission or enhancing fusion prevents mitophagy [10].

Mitochondrial fission is regulated by proteins including Drp1 (dynamin-related peptide-1), Fis1 (fission protein-1), Mff (mitochondrial fission factor) and MiD49/51 (mitochondrial dynamics proteins 49 and 51) [26]. Drp1 translocates to OMM and undergoes post-translational modification processes including phosphorylation, dephosphorylation, ubiquitination and sumoylation. Then Drp1 interacts with four receptors including Fis1, Mff, Mid49 and Mid51, where it constricts and cleaves mitochondria afterwards. Fis1 is a bounded to mitochondria and can help to recruit Drp1 and assemble the fission complex [27]. Due to its central role in mediating fission, Drp1 deletion was embryonic lethal with reduced cardiac contractility in embryos [28]. Korobova and colleagues reported a rather unique manner of regulating mitochondrial fission through ER (endoplasmic reticulum)-mitochondria contact. ER-localized INF2 (inverted formin 2) mediates ER tubule wrapping around and restricting mitochondria, and also offers sites for Drp1 recruitment and secondary restriction [29].

Mitochondrial fission is usually considered as the prerequisite for the occurrence of mitophagy. Ablation of DRP1 is reported to disrupt mitochondrial fission, promote elongated mitochondria and inhibit mitophagy, resulting in aggravated cardiac dysfunction in the face of IR injury [30]. Inhibition of fission leads to progression of cardiovascular diseases due to impaired mitophagy, while excessive Drp1-mediated mitochondrial fission promotes maladaptive apoptosis or mitophagy-mediated cell death [31,32]. However, it is noteworthy that mitophagy is not necessarily dependent upon mitochondrial fission process. For example, conditional cardiomyocyte-specific knockout Drp1 in mice

increases mitophagy, triggers a loss of mitochondria and prompts onset of dilated cardiomyopathy [33]. It was also noted that Drp1 ablation interrupts mitochondrial fission and leads to overactivation of Parkin-mediated mitophagy, and Parkin deletion in Drp1-deficient mice improves heart function and reduces cardiac remodeling [34]. NR4A1 (nuclear receptor subfamily 4 group A member 1) was shown to aggravate IR injury by way of elevated fatal mitochondrial fission through Mff phosphorylation and Drp1 translocation while suppressing mitophagy, which resulted in the disturbance of cellular homeostasis and microvasculature dysfunction. Genetic ablation of NR4A1 protects against pathological fission and mitochondrial dysfunction, a phenomenon that appears to be contradictory to the current understanding of the relationship between mitochondrial fission and mitophagy [35].

In contrast to fission, mitochondrial fusion forms elongated networks mediated by Mfn1, Mfn2 (mitofusin 1 and 2) and OPA1 (optic atrophy protein-1). Mfn1/2 may regulate outer mitochondrial membrane fusion and prevent damaged mitochondria from fusing with healthy ones, in which case they serve as substrates for Parkin to promote mitophagy. Mfn2 also acts as a tethering molecule between mitochondria and ER, and the contact contributes to mitophagosome formation to prompt mitophagy. Genetic ablation of Mfn2 in cells loosens ER-mitochondria contacts and reduces Ca^{2+} uptake into mitochondria (thus to alleviate mitochondrial Ca^{2+} overload) [36–38]. OPA1 functions to maintain normal cristae structure of inner mitochondrial membrane (IMM) and mediate its fusion, and its depression led to cardiomyopathy in Drosophila [26,39,40].

3. Mitophagy pathways and its role in cardiac ischemia-reperfusion injury

Impaired mitophagy and mitochondrial dysfunction are well known to participate in the onset and development of neurodegenerative diseases, cancers, cardiovascular diseases, lung diseases, acute kidney injury and fatty liver diseases [14,41–43]. The potential contribution of mitophagy to cardiac ischemia-reperfusion injury has drawn recent attentions given the clinical importance of IR injury. It is generally perceived that mitophagy is cardioprotective while mitophagy impairment contributes to mitochondrial dysfunction and interrupted cardiac homeostasis.

It remains somewhat controversial with regards to how dysfunctional mitochondria are selectively recognized and engulfed and how adaptors on mitochondrial membrane would interact with autophagosomes to promote mitophagy. As depicted in Fig. 1, mitophagy is under the close scrutiny of a number of cellular signal mechanisms including PINK1 (PTEN-induced putative kinase 1), Parkin, mitophagy receptors, as well as certain mitophagy adaptors. Mitophagy receptors are constitutively anchored at OMM via transmembrane domains and attach autophagosomes to mitochondria through LIR motif, including ATG32 in yeast, BNIP3 (BCL2 interacting protein 3), BNIP3L/NIX (BCL2 interacting protein 3 like), FUNDC1 (FUN14 domain containing 1), Bcl2L13 (Bcl2-like 13), PHB2 (prohibitin 2) and FKBP8 (FKBP prolyl isomerase 8) in mammalian cells. With the help of the LIR motif, these mitophagy receptors are capable of recruiting the ATG8 family proteins LC3 and its homolog GABARAP (gamma-aminobutyric acid receptor-associated protein) to the mitochondrial membrane and initiate mitophagy in an ubiquitin-independent pathway [44,45].

3.1. PINK1-Parkin

The serine/threonine kinase PINK1 and E3 ligase Parkin play essential roles in the canonical ubiquitin-mediated mitophagy pathway. PINK1 serves as a sensor for mitochondrial polarization. In polarized mitochondria, PINK1 transports into the mitochondrial intermembrane space through TOM (translocase of outer mitochondrial membrane) and integrates with inner membrane via insertion into TIM (translocase of inner mitochondrial membrane). PINK1 is degraded and is cleaved by a number of mechanics including PARL (presenilin-associated rhomboid-like protein), proteasome and mitochondrial membrane peptidase. These mechanisms help to maintain PINK1 at a low basal level in physiological situations [46–49].

The function of TIM relies on steady mitochondrial membrane potential and the function may be lost when mitochondria are depolarized in cellular stress, in which case PINK1 can no longer be imported and degraded. Autophosphorylated and activated PINK1 accumulates on OMM and recruits Parkin to mitochondria from cytosol, through phosphorylating Mfn2 or directly phosphorylating ubiquitin-like domain of Parkin. Once recruited and activated, Parkin polyubiquitylates several OMM proteins VDAC1 (voltage dependent anion channel 1), Mfn1/2 and Miro1 (mitochondrial rho GTPase 1), which can be recognized by LC3 adapters [50,51]. These ubiquitinated proteins undergo proteasomal degradation and the degradation of Mfn1/2 induces mitochondrial fission and mitophagy initiation [52].

Besides Parkin and ubiquitin, PINK1 also phosphorylates TBK1 (TANK binding kinase 1) at Ser^{172}, resulting in further phosphorylation of the autophagy receptors p62/SQSTM1, OPTN (optineurin) and NDP52 (nuclear dot protein 52). Autophagy receptors recognize and bind to ubiquitinated mitochondria and autophagosome proteins. P62 mediates aggregation of defective mitochondria, while OPTN and NDP52 recruit related proteins to mitochondrial membranes such as ULK1 (Unc-51-like autophagy activating kinase 1), DFCP1 (double FYVE-containing protein 1), WIPI1 (WD repeat domain phosphoinositide-interacting protein 1) to engage their binding with autophagosomes via ubiquitin and LC3 binding domains prior to mitophagy [53,54]. DFCP1 and WIPI1 are important proteins in early phases of autophagosome biogenesis although they are not detectable in cells with OPTN and NDP52 ablation. Besides, Parkin ubiquitinates OMM proteins, allowing recruited OPTN to stably bind with ubiquitinated mitochondria via LIR (LC3 interacting region). Then DFCP1 transiently translocates to damaged mitochondria and initiate autophagosome formation and LC3 recruitment [55].

Considering the importance of PINK1/Parkin-mediated mitophagy, much effort has been engaged to learn about its role in cardiac ischemia-reperfusion injury. PTENα (phosphatase and tensin homolog α) interacts with E3 ligase Parkin to promote its recruitment to damaged and abnormal mitochondria, thus facilitating mitophagy. PTENα deficiency was found to compromise Parkin-mediated mitophagy and promote the build-up of abnormal mitochondria, resulting in a higher risk of injury with exposure to isoprenaline and IR injury [56]. Heart ischemic preconditioning (IPC) is universally acknowledged as an effective method to protect cardiomyocytes against IR injury with permissive roles for autophagy and mitophagy in ischemic preconditioning. As shown in Table 1, levels of WDR26 (WD repeat domain 26) were found elevated after cardiac IPC in rats. Following hypoxia, WDR26 was reported to promote Parkin-mediated mitophagy and inhibit apoptosis, protecting cardiomyocytes against oxidative stress [57]. Besides, statin-offered cardioprotective effects were related to Parkin-mediated mitophagy. HL-1 cardiomyocytes treated with Simvastatin exhibited mitochondrial translocation of Parkin and p62, mitochondrial fission and mitophagy activation. Simvastatin also decreased the infarct size in wild-type mice subjected to ischemia-reperfusion injury by upregulating autophagy and Parkin-mediated mitophagy, which was not observed in Parkin knockout mice [58].

The PINK1/Parkin-mediated mitophagy is considered a novel therapeutic target for cardiac IR injury. A grape-derived antioxidant was reported to be cardioprotective in rats subject to IR injury by promoting PINK1/Parkin-mediated mitophagy in a Sirt3 (sirtuin 3)- and Foxo3 (forkhead box O3)-dependent manner [59]. In addition, certain biologically active neuropeptides such as PPENK (preproenkephalin) offer postconditioning protection against IR injury and reduce myocardial infarct size through PINK1/Parkin-mediated mitophagy [60]. Zinc ion has also been demonstrated to facilitate autophagy and PINK1-dependent mitophagy through the MAPK/ERK (mitogen-activated protein

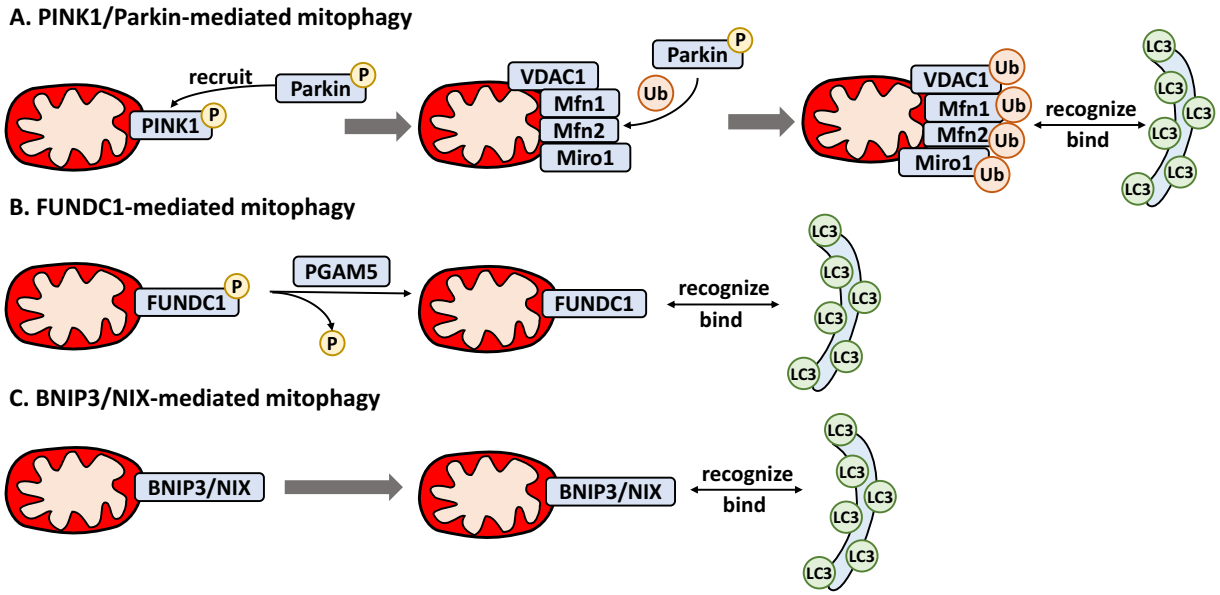

Fig. 1. Mitophagy pathways. A. PINK1/Parkin-mediated mitophagy. When mitochondria are depolarized in cellular stress, PINK1 can no longer be imported into mitochondria. Then autophosphorylated PINK1 accumulates on OMM and recruits Parkin to mitochondria. E3 ligase Parkin polyubiquitylates OMM proteins VDAC1, Mfn1, Mfn2 and Miro1, which will be recognized by LC3 adaptors on phagophore. B. FUNDC1-mediated mitophagy. Under hypoxic condition, PGAM5 dephosphorylates FUNDC1 and activates mitophagy. C. BNIP3/NIX-mediated mitophagy. BNIP3 and BNIP3L/NIX act synergistically and share an overlapping biological function in activating mitophagy when mitochondria have stable membrane potential.

kinase 1) signaling pathway, leading to suppressed mitochondrial superoxide generation and oxidative stress in cardiomyocytes challenged with hypoxia-reoxygenation (H/R) [61].

PINK1/Parkin-mediated mitophagy also participates in cardioprotective responses of a number of necrosis regulatory factors. TRAF2 (tumor necrosis factor receptor-associated factor 2), a novel E3 ubiquitin ligase localized at mitochondria, partially restores defective mitophagy triggered by Parkin knockout, leading to alleviation of cell death in neonatal rat cardiomyocytes challenged with hypoxia/reoxygenation. Moreover, tumor necrosis factor (TNF) was also reported to protect against cardiac ischemic-reperfusion injury through transcriptional upregulation of TRAF2 in mitochondria [62].

3.2. FUNDC1

FUNDC1 acts as a mitophagy receptor under hypoxic condition, the function of which is mainly regulated by phosphorylation modifications at site Tyr^{18}, Ser^{13} and Ser^{17}. FUNDC1 knockout in cardiomyocytes compromises mitochondrial function and disrupts MAMs (mitochondrial-associated membranes) and Ca^{2+} influx into mitochondria and cytosol via interacting with IP3R2 (inositol 1,4,5-trisphosphate receptor) [63]. The mitochondrial protein PGAM5 (phosphoglycerate mutase family member 5) dephosphorylates FUNDC1 at Ser^{13} and activates mitophagy through binding to LC3 on phagophores [64]. PGAM5 also offers cytoprotection against necroptosis by promoting PINK1-mediated mitophagy and PGAM5 impairment worsens necroptosis in response to IR injury in both hearts and brains [65].

Up-to-date, most studies have depicted a protective property of FUNDC1-mediated mitophagy in cardiac IR injury. Mst1 (mammalian STE20-like kinase 1) upregulation in IR injury represses FUNDC1-mediated mitophagy, increases ROS production, and promotes apoptosis, leading to increased cardiac injury through MAPK/ERK-CREB (cAMP responsive element binding protein) pathway. Genetic ablation of Mst1 was found to preserve FUNDC1 levels and mitophagy, reduce myocardial infarct size and protect against cardiac function [66].

Levels of CK2α (casein kinase 2α) is reported to be upregulated in IR injury, which suppresses FUNDC1-mediated mitophagy. Cardiac-specific deletion of CK2α was reported to rescue mitochondrial damage and preserve cardiac function through reversing mitophagy in a FUNDC1-dependent manner [67]. Moreover, NR4A1 activates CK2α in cardiac ischemia-reperfusion, resulting in suppressed FUNDC1-mediated mitophagy and aggravated IR injury [35]. Along the same line, reperfusion injury disrupts FUNDC1-mediated mitophagy and leads to caspase9-related apoptosis through upregulating Ripk3 (receptor interacting serine/threonine kinase 3). Ripk3 deficiency protects the heart against IR injury by activating mitophagy and inhibiting apoptotic pathway [68].

Platelet activation and micro-thrombosis formation result in occlusion of microcirculation and secondary ischemic event after reperfusion [45]. Hypoxia preconditioning was found to promote extensive FUNDC1-mediated mitophagy in platelets and reduced IR injury. This beneficial effect was ablated by a synthetic peptide encompassing LIR motif of FUNDC1 to interrupt its interaction with LC3 in wild-type mice. Platelet-specific FUNDC1 ablation worsened cardiac injury by mitophagy inhibition and platelet activation [69,70]. Zhou and coworkers reported seemingly contradictory results that loss of PPARγ (peroxisome proliferator-activated receptor γ) activates FUNDC1-mediated mitophagy, and enhances mitochondrial function and ATP generation, resulting in platelet aggregation and cardiac dysfunction in IR injury. Melatonin is capable of reducing infarct size and preserving cardiac function through restoration of PPARγ in platelets and inhibition of FUNDC1-mediated mitophagy and platelet activation [71].

3.3. BNIP3 and BNIP3L/NIX

Both BNIP3 and BNIP3L/NIX are BCL2 (B cell CLL/lymphoma 2) related proteins and can activate mitophagy when mitochondria possess stable membrane potentials. Ablation of either gene leads to a drop in mitophagy although much pronounced mitochondrial defect in hearts with BNIP3-BNIP3L/NIX double knockout [72–74]. Cardiac-specific knockout of NIX in BNIP3-deficient mice had a poor cardiac function compared with the BNIP3 positive mice, suggesting overlapping but synergistic regulation of these proteins on mitochondrial function [75].

The role of BNIP3-mediated mitophagy remains controversial in IR injury. ROS was shown to promote autophagosome formation via mTOR (mechanistic target of rapamycin) inhibition and BNIP3-

Table 1
Preconditioning, postconditioning and drugs alleviating cardiac ischemia-reperfusion injury through mitophagy regulation.

Treatments	Mitophagy	Mechanisms	Cardiac IR/HR injury	References
Mitophagy protects against cardiac IR injury				
Heart ischemic preconditioning (IPC)	PINK1/Parkin-mediated mitophagy ↑	IPC → WDR26 ↑→ mitophagy ↑ and apoptosis ↓	Protection against oxidative stress	[57]
Hypoxia preconditioning	FUNDC1-mediated mitophagy in platelets ↑	Platelet activation ↓	Protection against cardiac IR injury	[70]
PPENK postconditioning	PINK1/Parkin-mediated mitophagy ↑	PPENK-MIDGE-NLS signaling pathway	Protection against IR injury in rats	[60]
Statin	PINK1/Parkin-mediated mitophagy ↑	Mitochondrial translocation of Parkin and p62 ↑ and mitochondrial fission ↑	Protection against IR injury in mice	[58]
A grape-derived antioxidant	PINK1/Parkin-mediated mitophagy ↑	Sirt3 and Foxo3 activated	Protection against IR injury in rats	[59]
Zinc	PINK1/Parkin-mediated mitophagy ↑	MAPK/ERK pathway → mitochondrial superoxide generation ↓	Protection against oxidative stress in cardiac cells treated with H/R	[61]
Mitophagy aggravates cardiac IR injury				
Post-ischemic GPER activation	PINK1/Parkin-mediated mitophagy ↓	Mitochondrial structural integrity preserved, ROS ↓	Protection against IR injury	[103]
Melatonin	FUNDC1-mediated mitophagy ↓	PPARγ in platelets restored	Platelet aggregation ↓ and protection against IR injury	[71]

mediated mitophagy [76]. Inhibition of p53 and TIGAR (TP53-induced glycolysis and apoptosis regulator) was found to protect against ischemic injury through activation of BNIP3-mediated mitophagy and thus reduced apoptosis [77]. However, another research showed that BNIP3 overexpression triggers apoptosis and increases myocardial infarction in IR injury, which could be reversed with genetic ablation of BNIP3 [76]. DUSP1 (dual-specificity protein phosphotase1) deficiency promotes BNIP3 phosphorylation and mitophagy activation via JNK (JUN N-terminal kinase) signaling pathway, while DUSP1 supplementation suppresses BINP3-mediated mitophagy and alleviates cardiac IR injury [78]. To this end, Anzell and colleagues suggested possible existence of “a threshold” in the role of BNIP3 in determination of cell fate in the face of IR injury [79].

3.4. Other mitophagy receptors/adaptors

In addition to the canonical pathways discussed above, several novel mitophagy receptors or adaptors may also contribute to the pathogenesis and management of cardiac ischemia-reperfusion injury. For example, the aforementioned mitophagy adaptors including p62, OPTN and NDP52 may serve as downstream effectors in the PINK-Parkin signaling cascade. P62 binds with ubiquitinated proteins through UBA (ubiquitin-associated) domain and with LC3 on the phagophore via LIR motif. However, recruitment of p62 alone is not sufficient for sustained mitophagy [80]. AMBRA1 (autophagy and Beclin1 regulator 1) translocates to ER and mitochondria, binds with Beclin1 and initiates phagophore formation at mitochondria, as well as interacts with Parkin to promote mitophagy [81]. Kubli and Gustafsson proposed that p62 tends to recruit pre-existing phagophores to mitochondria while AMBRA1 stimulates new phagophore formation at mitochondria, which can be tethered to ubiquitinated mitochondria through p62 following LC3 incorporation [21].

One recently reported mitophagy adaptor choline dehydrogenase (CHDH) is known to accumulate on OMM upon mitophagy activation, interact with p62 and recruit the autophagy adaptor onto the depolarized mitochondria. LC3 is then loaded onto the damaged mitochondria via p62 and choline-p62-LC3 complex is required for Parkin-mediated mitophagy [82]. More evidence has depicted the roles of other mitophagy adapters such as NBR1 (neighbor of BRCA1 gene 1) and TAX1BP1 (Tax1-binding protein 1) in governing the mitophagy process [80]. NBR1, a functional homolog of p62, plays an important role in Parkin-mediated mitophagy regardless of the presence or absence of p62 [83]. The ubiquitin binding protein TAX1BP1 mediates autophagosome induction by regulating mTOR and enables metabolic transition of activated T cells [84]. The mitochondrial Rab GTPase-activating protein TBC1D15/17 (TBC1 domain family member 15/17) inhibits Rab7 (Ras-associated protein 7), binds with mitochondria and autophagosome through Fis1 and LC3, respectively, to function as a downstream regulator of Parkin [85]. Besides, mitochondria-lysosome contacts regulate mitochondrial fission through Rab7 hydrolysis. The mitochondria-lysosome contact is promoted by active GTP-bound lysosomal Rab7, while the contact release (dissociation) is mediated by recruitment of TBC1D15 to mitochondria by Fis1 and Rab7 hydrolysis [86]. Further studies are warranted to better understand the precise roles of these mitophagy adaptors in cardiac ischemia-reperfusion injury.

3.5. Lipid-mediated mitophagy

Ceramide and cardiolipin can directly bind to LC3 and promote mitophagy when localized at OMM. Ceramide acts as a receptor for anchoring LC3B-II autolysosomes to mitochondria to induce mitophagy. Exogenous treatment or endogenous generation of C(18)-ceramide mediates autophagic cell death through binding with LC3B-II upon Drp1-dependent mitochondrial fission, resulting in mitochondrial dysfunction and oxygen consumption. Genetic ablation of LC3B-II impairs

LC3B-ceramide binding, thus protecting against ceramide-dependent mitophagy [87]. More recent evidence also suggested a role for ceramide-dependent mitophagy in tumor repression and chemotherapy resistance [88–90].

Cardiolipin localizes at IMM in normal conditions, specifically around the folds of cristae, and redistributes to OMM when oxidized or faced with mitochondrial stress, mediated by NDPK-D (nucleoside diphosphate kinase-D) [91]. Then the externalized cardiolipin is recognized and bind with LC3 on phagophore to activate mitophagy [92,93]. Tafazzin (TAZ) catalyzes the remodeling of cardiolipin that is selectively needed for mitophagy initiation. TAZ deficiency in primary mouse embryonic fibroblasts (MEFs) triggers defective mitophagosome biogenesis and mitochondrial dysfunction, and mutation of TAZ leads to Barth syndrome, which is characterized by mitochondrial dysfunction and dilated cardiomyopathy [94].

3.6. Cell signaling regulation of mitophagy in IR injury

Besides the canonical cell signaling pathways mentioned, many other mechanisms may also participate in the regulation of mitophagy in IR injury. Apelin/APJ (a G-protein-coupled receptor) system alleviates IR injury through reducing mitochondrial ROS, delaying mPTP opening and initiating mitophagy [95]. AMPK is known to confer protection in IR injury although ischemia AMPK activation is blunted with aging. Sestrin2 (Sesn2) as a scaffold protein mediates AMPK activation through interacting with AMPK upstream regulator LKB1 (liver kinase B1). Decreased Sesn2 with aging is believed to compromise AMPK-Sesn2 complex and blunt ischemic AMPK activation, making the heart more prone to IR injury [96]. Another study suggested that melatonin intake promotes mitochondrial fusion and mitophagy through AMPK-OPA1 signaling pathway and protects against cardiac ischemia-reperfusion injury, the effect of which may be eliminated by OPA1 knockout [97].

Micro-RNAs are now considered as important regulatory factors in many physiological and pathophysiological processes although their role in mitophagy regulation is rarely reported. For example, microRNA-410 was significantly upregulated in a murine IR model, leading to worsened mitochondrial function and mitophagy via interaction with HMGB1 (high-mobility group box 1 protein). In cultured human adult cardiac myocytes (HACMs), miRNA-410 overexpression was found to lower cell viability, ATP level and mitophagy possibly associated with facilitated cell death via cytochrome *c* release and caspase-3 activity [98]. More evidence indicated that Bicarbonate, a buffer widely used in resuscitation after cardiac arrest, may aggravate IR injury through inhibition of mitophagy [99].

3.7. Mitophagy paradox in ischemia and reperfusion phases

As we have summarized in Fig. 2, whether mitophagy is protective or detrimental in IR injury still remains controversial. Different hypotheses have been put forward to explain the seemingly contradictory roles of mitophagy in IR injury, such as the paradox in ischemia and reperfusion phase. Our group discovered autophagy paradox in the cardioprotective role of ALDH2 (mitochondrial isoform of aldehyde dehydrogenase) in ischemia-reperfusion injury several years ago. ALDH2 promotes autophagy through AMPK-mTOR signaling during ischemia whereas it inhibits autophagy by Akt (AKT serine/threonine kinase 1)-mTOR signaling during reperfusion. Therefore, autophagy was considered to be cardioprotective in ischemia phase while being detrimental in reperfusion phase [6]. Likewise, ALDH2 was capable of increasing cell viability and protecting against IR injury through suppressing PINK1/Parkin-mediated mitophagy. But the measurement of mitophagy in this study remains challenging, such as colocalization of PINK1, Parkin and mitochondria electron transport chain protein COXIV (cytochrome *c* oxidase subunit IV) [100].

Anzell and associates speculated mitophagy possesses different roles in ischemic and reperfusion phase, which supported our hypothesis of mitophagy paradox [79]. During ischemia phase, the interruption of ATP production activates AMPK-ULK1 signaling pathway, which promotes FUNDC1-dependent mitophagy and offers cardioprotection against ischemia [101]. Genetic ablation of Parkin leads to impairment of mitophagy, accumulation of dysfunctional mitochondria and aggravation of cardiac injury induced by myocardial infarction [102]. Many other studies have also suggested a cardioprotective role of mitophagy during ischemia while it is noteworthy that mitophagy may be detrimental to myocardium in reperfusion. Excessive mitochondrial fission and fragmentation together with enhanced mitophagy greatly reduced ATP production and energy supply for cell survival, especially when mitochondrial biogenesis was also impaired by IR injury [79]. GPER (G protein-coupled estrogen receptor 1) activation at the beginning of reperfusion phase by post-ischemia estrogen administration ameliorates cardiac ischemia-reperfusion injury through preserving mitochondrial integrity, reducing ROS and inhibiting PINK1/Parkin-mediated mitophagy [103].

In sum, we believe there may be a mitophagy paradox in cardiac ischemia-reperfusion injury (Fig. 2). Most studies have depicted the cardioprotective role of mitophagy in myocardial infarction and IR injury. However, excessive mitophagy and unnecessary mitochondrial clearance may sharply reduce the number of mitochondria and cellular energy production, prompting oxidative stress, ROS production and cardiac injury, especially during reperfusion phase. The precise role of mitophagy in reperfusion still remains controversial, mainly due to the technical difficulty to distinguish cardiac injury originated from ischemia and reperfusion phase.

4. Conclusions and future perspectives

Mitochondria are indispensable organelles for energy metabolism and therefore quality control system plays an important role in maintaining mitochondrial integrity and cellular homeostasis. Damaged, aberrant or dysfunctional mitochondria are cleared by mitophagy and new born mitochondria are supplemented through mitochondrial biogenesis in order to meet cellular demand, thus necessitating adaptation in mitochondrial dynamics. Drp1-mediated mitochondrial fission is commonly considered as the prerequisite for mitophagy given that fragmented mitochondria are in proper size to be engulfed by autophagosomes, while some other studies displayed contradictory results that fission and mitophagy don't always change synchronously. Disrupted fission and mitophagy is seen to aggravate myocardial dysfunction in IR injury (detailed information as shown in Table 2).

Mitophagy is regulated by multiple cell signaling pathways including PINK1/Parkin, FUNDC1 and BNIP3/NIX. These receptor- or Parkin-mediated mitophagy components share complex crosstalk mechanism although compelling experimental evidence is still lacking. For example, as a well-known regulator of FUNDC1, PGAM5 activation was also associated with increased DRP1 translocation and PINK1/Parkin-mediated mitophagy. Treatment with carbonyl cyanide *m*-chlorophenylhydrazone (CCCP) in SH-SY5Y cells was found to upregulate PGAM5 with concurrent overt mitochondrial damage [80]. Anti-apoptotic protein BCL2L1/BCL-XL (BCL2 like 1) inhibits FUNDC1-mediated mitophagy by interacting with PGAM5 and regulates FUNDC1 phosphorylation at Ser^{13} [104]. In addition, BCL2L1 itself can be phosphorylated by PINK1 upon mitochondrial depolarization, therefore dampening its pro-apoptotic cleavage and apoptotic cell death [105].

Besides these canonical pathways and lipid-mediated mitophagy, some other new mitophagy receptors and adaptors have also been discovered, such as p62, OPTN, NDP52, CHDH, NBR1 and TAX1BP1. Most studies are in favor of the cardioprotective role of mitophagy in cardiac IR injury and defective mitophagy results in the accumulation of waste mitochondria and cellular apoptosis, thus increasing myocardial infarct size and deteriorating ventricular function (as shown in Fig. 2). However, several studies suggest mitophagy may be the culprit

Fig. 2. Hypothesis of mitophagy paradox in cardiac ischemia-reperfusion injury. Mitophagy is protective (adaptive) during ischemia phase since it helps to remove abnormal mitochondria. However, excessive mitochondrial fission, fragmentation and mitophagy (maladaptive) compromise mitochondrial integrity and function, which may be harmful to cell survival, especially during reperfusion.

Table 2
Regulatory proteins and microRNA in cardiac IR injury by modulating mitophagy.

Molecules	Mitophagy	Mechanisms	Cardiac IR/HR injury	References
Mitophagy protected against cardiac IR injury				
Mst1	FUNDC1-mediated mitophagy ↓	MAPK/ERK-CREB pathway	IR injury ↑	[66]
CK2α	FUNDC1-mediated mitophagy ↓	Phosphorylation of FUNDC1 at Ser13 and its inactivation	Mitochondrial damage ↑ and IR injury ↑	[67]
Ripk3	FUNDC1-mediated mitophagy ↓	Caspase9-related apoptosis	IR injury ↓ with Ripk3 deficiency	[68]
Apelin/APJ system	Mitophagy initiated	Mitochondrial ROS ↓ and mPTP opening delayed	IR injury ↓	[95]
MicroRNA-410	Mitophagy ↓	Interaction with HMGB1	Mitochondrial function ↓ and cell death ↑	[98]
Mitophagy aggravated cardiac IR injury				
DUSP1	BINP3-mediated mitophagy ↓	JNK signaling pathway	IR injury ↓	[78]
ALDH2	PINK1/Parkin-mediated mitophagy ↓	4-hydroxynonenal, ROS, mitochondrial superoxide ↓	Cell viability ↑ and IR injury ↓	[100]

in IR injury and cardiac dysfunction can be alleviated by suppressing mitophagy related proteins, especially in the reperfusion phase [103]. Therefore, we speculate that there exists a mitophagy paradox between ischemia and reperfusion phase. Activated mitophagy is cardioprotective in ischemia whereas it is detrimental in reperfusion phase through different regulatory pathways (as summarized in Fig. 2 and Table 2).

In general, evidence has depicted a rather unique protective role for mitophagy in myocardial mitochondrial homeostasis and IR injury. Defective and excessive mitophagy may both prompt mitochondrial dysfunction and myocardial cell death. Different time period and stimulation should also be taken into account, as well as the complex interplay between mitochondrial dynamics and mitophagy. Besides, more effective technologies and methods are needed to measure mitophagy in order to reach a consensus on its role in IR injury.

Ischemia-reperfusion injury also occurs in other organs and tissues, including brain, liver, kidney and intestine, which contributes to the increased mortality of organ transplantation and surgery [106]. Mitophagy is turned on in cerebral IR injury through increasing PINK1 accumulation on outer mitochondrial membrane and Parkin translocation [107]. Reactive nitrogen species peroxynitrite (ONOO-) aggravates cerebral ischemia-reperfusion injury by recruiting Drp1 to abnormal mitochondria and activating PINK1/Parkin-mediated mitophagy [108]. Hepatic IR injury may also activate autophagy and mitophagy, as manifested by higher levels of PINK1/Parkin and LC3-II [109]. It was shown that hepatic IR injury promotes mitochondrial fission (Drp1 and PINK1) while suppressing mitochondrial biogenesis and fusion (mitofusion 2) [110]. PINK1/Parkin-mediated mitophagy activation is found to be protective in renal IR injury and acute kidney injury (AKI), and PINK1 or Parkin deficiency aggravates mitochondrial damage [111]. Conclusively, there is no consensus on whether PINK1/Parkin-mediated mitophagy may ameliorate or aggravate IR injury in other organs (except hearts). BNIP3 also regulated mitophagy in a HIF-1α (hypoxia-inducible factor-1 α)-dependent manner in renal IR injury [112], but few studies have addressed the precise role of BNIP3 and FUNDC1-mediated mitophagy in other organs.

Mitochondrial dysregulation is an important cell biological issue, which deserves careful investigation and may become a novel therapeutic target for cardiac ischemia-reperfusion injury. Ischemic preconditioning and postconditioning reduce infarct size and protect myocardial function partially through modulation of mitophagy, and redox balance. Although there are no FDA-approved drugs directly targeting mitophagy at this time, many regulatory proteins and miRNAs can be considered as possible drug targets to modulate mitophagy in future, thus conferring cardioprotection against IR injury. Urolithin A, a natural compound that induces mitophagy, extends lifespan and promotes health aging via mitophagy induction [113]. Recent evidence also depicted beneficial role of urolithin A in alleviating myocardial ischemia/reperfusion injury through PI3K/Akt pathway [114]. Several mitochondrial drugs may also have some effects on mitophagy as summarized in our recent review [11] and deserve further investigation. Due to the important role of mitochondrial dynamics in regulating mitophagy and mitochondrial function, modulating mitochondrial biogenesis, fusion and fission could be a novel therapeutic target for many other diseases beyond cardiac IR injury.

Transparency document

The Transparency document associated with this article can be found, in online version.

Declaration of Competing Interest

None of the authors declare any potential conflict of interest.

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