

The Role of Parkin-Mediated Mitophagy in Cardiovascular Diseases

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Abstract: Parkin is a protein encoded by the PARK2 gene, whose mutations were first found in patients with Parkinson's disease. Recent studies reveal that Parkin plays an important role in the development of cardiovascular diseases (CVD) in addition to its contribution in neurological and malignant diseases. The abnormalities of mitochondrial functions and structures play crucial role in the development of many pathological disorders, including CVD. Parkin is a vital component of mitophagy process, in which the damaged mitochondria is selectively removed to maintain the cellular homeostasis. This article summarizes the latest current updates of researches related to Parkin-mediated mitophagy and its functions in CVD. This would improve our understanding about the development of CVD and provide new therapeutic targets for the treatment of CVD.

Keywords: Parkin, Mitophagy, Cardiovascular Disease

Background

Cardiovascular disease seriously endangers human health. Although cardiovascular disease research has made important progress, but the precise mechanism remains unclear. Cardiomyocytes are rich in mitochondrial. The abundance of mitochondrial in cardiomyocytes is highly dynamic to meet the high energy requirements of the heart. Mitochondrial structural damage and dysfunction involves the etiology and progression of cardiovascular disease. In the present study, Parkin is highly expressed in the heart, and Parkin-mediated mitophagy is known to serve important roles in cardiac development and cardiac function maintenance. The abnormal expression of Parkin is closely related to the occurrence of cardiovascular disease.

1 Parkin protein structure and function

1998, Japanese scholars discovered that the PARK2 gene is a causative gene of autosomal recessive Parkinson's disease, and the expression product of PARK2 gene is Parkin protein [1]. Parkin protein is a cytoplasmic protein with 465 amino acid residues. Its N-terminus is homologous to ubiquitin, called ubiquitin-like domain, and has RING1-IBR-RING2 at its C-terminus. The RING1-IBR-RING2 domain is referred to as the loop finger domain, in which RING1 and RING2 are loop finger structures, and the IBR (in-between ring) is the cysteine rich region between the two loop fingers [2].

Parkin protein is widely distributed in the brain, heart and skeletal muscle, suggesting its extensive roles in physiology. Under normal conditions, Parkin is mainly

free in the cytoplasm [3], but when cells are damaged, such as mitochondrial stress and endoplasmic reticulum stress [4-6], Parkin transferred to the outer membrane of mitochondria, together with ubiquitin to initiate mitophagy. The process of Parkin transfer to mitochondria is the key to activation mitophagy. It has also been reported that Parkin can be localized to endoplasmic reticulum, Golgi and synaptic vesicles, but the specific mechanism is unclear and needs further study [7-9].

Parkin acts as ubiquitin-protein ligase, which is associated with ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin to modify the outer membrane proteins of damaged mitochondria, which promote the degradation of damaged mitochondria, thereby exerting the ubiquitination function of Parkin protein [5]. A number of substrate proteins that can be modified by Parkin have been discovered, such as synphilin [10], Pael receptor [11], and CDCrel-1 [12].

2 Parkin's role and mechanism in mitophagy

Autophagy is a process of lysosomal-dependent degradation pathway that allows macromolecules and damaged organelles in cells to be degraded into small molecules in lysosomes for cell reuse, thereby maintaining a stable homeostasis [13]. As a kind of autophagy, mitophagy plays a key role in the body [14].

Mitophagy is first discovered in mammalian cells [15]. Multiple signaling pathways can mediate mitophagy. PTEN-induced kinase 1 (PINK1)/Parkin pathway is the

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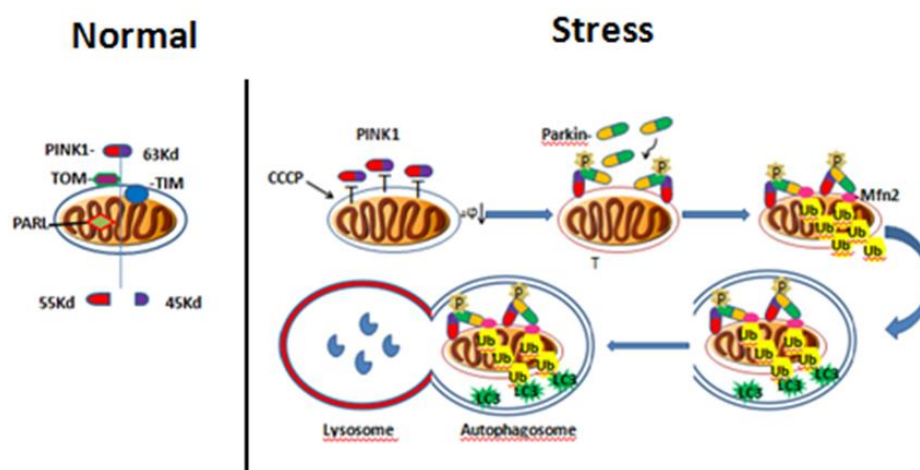
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most typical mitophagy pathway [16,17]. PINK1, which is a silk/threonine kinase, enters mitochondria through mitochondrial outer membrane transposase and endomembrane translocating enzyme and is degraded by proteolytic enzymes, so the expression level of endogenous PINK1 in mitochondria is low [18,19]. When mitochondria upon depolarization and loss of membrane potential, PINK1 rapidly accumulates in the mitochondrial outer membrane and recruits Parkin to the mitochondrial outer membrane to initiate the mitophagy process, and finally enters the autophagic lysosomal pathway for degradation [20] (Figure.1). Thus, PINK1/Parkin mediates mitophagy to regulate mitochondrial biogenesis.

In addition to PINK1/Parkin-mediated mitophagy, Bcl-2 and adenovirus E1B19 kDa-interacting protein 3 (BNIP3) and mitochondrial outer membrane proteins NIP3-like protein X (NIX) signaling pathway also involve in the regulation of mitophagy [21,22]. BNIP3 and NIX can directly link microtubule-associated protein light chain 3 (LC3) proteins and recruit autophagosome-degrading target proteins [23]; NIX can also directly mediate ubiquitination of Parkin substrate to regulate mitophagy [24], but whether PINK1/Parkin-mediated mitophagy pathway is associated with this pathway will be a new field for future studies of mitophagy.



Note: When mitochondria cause membrane potential decrease due to external stimulation, PINK1 phosphorylates Parkin protein, and phosphorylated Parkin protein is translocated from the cytoplasm to the outer membrane of the damaged mitochondria, ubiquitinating and modifying the outer membrane protein of mitochondria, and binding to lysosome, ultimately to remove damaged mitochondria.

Figure 1 Mechanism of PINK1/Parkin in mitophagy

3 The regulation mechanism of Parkin

3.1 Ubiquitination

Ubiquitination is a post-translational modification required to regulate many critical mechanisms, including cell cycle control, endocytosis, inflammation, and DNA repair. As a ubiquitinated E3 ligase, Parkin protein plays a key role in ubiquitin proteasome system (UPS) [25]. However, Parkin initially showed ubiquitin ligase activity by self-ubiquitination assays [12], but whether Parkin's own ubiquitination occurs under normal cell conditions is unclear. When Parkin itself is ubiquitinated, it degrades in a proteasome-dependent manner [26, 27], rendering the Parkin protein inactive. However, Parkin's own ubiquitination may also be an effective regulatory mechanism required for ubiquitination of substrate proteins. In conclusion, the ubiquitination process involved in Parkin protein plays a key role in protein localization, metabolism and

degradation.

3.2 S-nitrosylation

S-nitrosylation is a reversible post-translational modification involving the covalent attachment of a nitric oxide (NO) group to a cysteine residue to form an S-nitrosothiol species, thereby stabilizing the structure of the protein [28, 28]. Nitrosylated stress is a key factor in protein misfolding and neurodegeneration. Parkin is rich in cysteine and coordinates eight zinc atoms to ensure Parkin's correct folding [30]. Therefore, the S-nitrosylation of any zinc-coordinated cysteine will affect the function of Parkin. However, The regular functions of S-nitrosylation of Parkin protein are controversial. On the one hand, it was found that S-nitrosylation of Parkin protein increase E3 ligase activity after mitochondrial depolarization, which induce mitochondrial aggregation and degradation. In addition, some reports found that Cys323 in parkin is S-nitrosylation key site [31]. On the other hand, it was found that S-nitrosylation of Parkin protein attenuates E3 ligase activity after mitochondrial depolarization [32]. Therefore, the specific regulatory mechanisms of S-nitrosylation of Parkin protein requires further investigation.

3.3 SUMO

SUMO (small ubiquitin-related modifier) is a small

ubiquitin-like modification with certain sequence homology and structural similarity with ubiquitin, and plays an important role in stabilizing protein conformation and regulating protein subcellular localization [33]. Parkin protein lies not only in the cytoplasm but also in the nucleus [34, 35]. Studies have shown that non-covalent binding of Parkin protein to SUMO-1 enhances Parkin's nuclear translocation and increases its own ubiquitination [33], but no significant Parkin protein levels were detected after overexpression of SUMO-1. Therefore, a positive regulator of Parkin like SUMO-1 may simply disintegrate the self-inhibiting conformation of Parkin protein, or enhance the binding of E2 to the substrate without causing degradation of Parkin protein. These are new field requires further study.

4 Parkin's relationship with cardiovascular disease

In recent years, it has been found that Parkin-mediated mitophagy plays an important role in the maintenance of normal function of nerve cells and is essential for maintaining normal cardiac function. The heart is a highly energy-consuming organ, rich in mitochondria, mitochondrial structural damage and dysfunction involving the development and progression of cardiovascular disease. At present, Parkin-mediated mitophagy has become a hot spot for the study of cardiovascular diseases, as shown in Figure 2.

4.1 The role of Parkin in the normal heart

Parkin protein is highly expressed in the heart, but whether it has a key role in normal stress-free myocardial tissue is still unclear. On the one hand, the myocardial tissue morphology has not changed significantly and the functions of the heart have not been influenced in Parkin knockout mice, but the myocardial mitochondria were significantly reduced, its arrangement was not neat, and abnormal electron aggregation occurred over time compared with the control group [36]. Therefore, the expression of Parkin may be related to mitochondrial membrane stability, mitochondrial morphology, and release of ROS under the unstressed state. On the other hand, Parkin expression plays a crucial role in the mitochondrial maturation of the heart of newborn mice. In the first 3 weeks after birth, the mitochondria gradually mature due to changes from anaerobic glycolysis to mitochondrial respiration in the metabolic environment. It was found that Parkin knockout mice had mitochondrial development arrest and gradually died after 21 days of birth [37]. In summary, these results suggest that Parkin may play an important role in maintaining normal cardiac function and cardiac development.

4.2 Parkin regulation in myocardial ischemia-reperfusion

Parkin protects against cardiomyocyte damage induced by ischemia. Ischemia-reperfusion leads to impaired

programmed cell death [38]. Recent studies have shown that ischemic precondition and enhanced autophagy are effective ways to reduce myocardial infarct size and protect cardiomyocytes [39]. In the myocardial ischemia reperfusion model, Parkin protein expression is significantly increased after ischemic precondition, and then P62 is translocated to mitochondria. After the translocation of P62, it increased the level of mitophagy by ubiquitination binding protein (Sequestosome 1, SQSTM1), controlling the number of mitochondria in cardiomyocytes to protect cardiomyocytes from damage [40]. The mice whose Parkin is knockout is sensitive to ischemic precondition. In addition, Parkin-mediated mitophagy is also a related signal pathway for many proteins to protect cardiomyocytes from ischemia-reperfusion injury. Under ischemic conditions, ischemic precondition upregulated gene 2 (WD repeat domain 26, WDR26) promotes the translocation of Parkin to the mitochondrial membrane to cause mitophagy, thereby reducing the release of lactic dehydrogenase (LDH) to protect cardiomyocytes [41]. In neonatal rat cardiomyocytes, exogenous hepatic growth factors enhance the expression of Parkin, thereby increasing mitophagy to protect against hypoxia-induced myocardial damage [41]. Therefore, Parkin-mediated mitophagy plays an important role in ischemia-reperfusion injury.

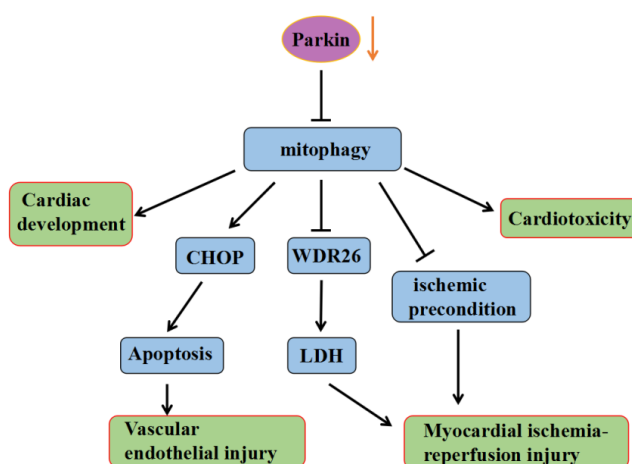
4.3 Parkin regulation in vascular endothelial injury

Endothelial injury is the main cause of coronary heart disease caused by atherosclerosis in coronary angiogenesis [42]. Endoplasmic reticulum stress is a key factor in the injury of myocardial vascular endothelial cells. It has been reported that Parkin protein is up-regulated during endoplasmic reticulum stress, and is involved in the regulation of endoplasmic reticulum stress-related proteins to protect myocardial vascular endothelial cells from damage [43]. CCAAT/enhancer binding protein homologous protein (CHOP) is an important apoptotic signaling molecule initiated by endoplasmic reticulum stress, which is expressed in cells, but the expression of CHOP increased significantly when endoplasmic reticulum is stressed, eventually leading to increased apoptosis. Recent studies have found that CHOP is one of the substrates of Parkin ubiquitination. Parkin binds to CHOP and degrades CHOP by ubiquitination, thereby reducing cardiomyocyte apoptosis; In addition, mice with myocardial hypertrophy were significantly aggravated by hypertension induced by thoracic aortic coarctation or tunicamycin-induced endoplasmic reticulum stress [44]. Therefore, Parkin protein plays an important role in heart diseases caused by vascular endothelial damage induced by endoplasmic reticulum stress.

4.4 Parkin protects against drug-induced myocardial toxicity

Arsenic trioxide (ATO), is used as a drug for acute promyelocytic leukemia, but it is harmful to the skin, liver, kidney, and heart, but Parkin-mediated mitophagy can protect against ATO-induced myocardial damage [45]. Doxorubicin (DOX) is an anthracycline antibiotic and is a widely used antitumor drug. DOX can induce cardiotoxicity and form irreversible degenerative cardiovascular disease, therefore, it is limited in

clinical application [46]. More and more evidence demonstrate that mitophagy is critical for DOX-induced cardiac damage. Importantly, Parkin-mediated mitophagy plays an important role in DOX-induced cardiotoxicity, but the specific mechanism is unclear [47]. Therefore, elucidating the role of Parkin in drug-induced cardiotoxicity to balance mitophagy is essential for maintaining healthy mitochondrial and cellular homeostasis.



Note: Parkin protein plays an important role in maintaining cardiac development in mice, but inhibits Parkin-mediated mitophagy, resulting in cardiac arrest, vascular endothelial injury, ischemia-reperfusion injury, myocardial cell senescence and myocardial toxicity.

Figure 2 Mechanism of Parkin-mediated mitophagy in cardiovascular disease

5 Summary and outlook

A large number of studies have shown that Parkin protein plays an important role in neurodegenerative diseases. In recent years, it has been found that Parkin protein has gradually gained attention in cardiovascular diseases. Especially, Parkin-mediated mitophagy plays an important regulatory role in maintaining normal cardiac function, cardiac development, myocardial ischemia-reperfusion, vascular endothelial injury, diabetic cardiomyopathy, myocardial toxicity, and aging cardiomyocytes, and becomes a potential regulatory mechanism of cardiovascular disease. Although the role of Parkin protein in the heart has been established, there are still many problems to be solved. For example, the mutation of the PARK2 gene which encodes Parkin protein is the main cause of Parkinson's syndrome, but whether there are mutations of PARK2 gene in various cardiovascular diseases will be worthy exploring.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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