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Review

Role of mitophagy in spinal cord ischemia-reperfusion injury

Yanni Duan[1, 2, 3, #], Fengguang Yang[1, 2, 3, #], Yibao Zhang[1, 2, 3], Mingtao Zhang[1, 2, 3], Yujun Shi[1, 2, 3], Yun Lang[1, 2, 3], Hongli Sun[1, 2, 3], Xin Wang[1, 2, 3], Hongyun Jin[1, 2, 3], Xuewen Kang[1, 2, 3, *]

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From the Contents

Abstract

Spinal cord ischemia-reperfusion injury, a severe form of spinal cord damage, can lead to sensory and motor dysfunction. This injury often occurs after traumatic events, spinal cord surgeries, or thoracoabdominal aortic surgeries. The unpredictable nature of this condition, combined with limited treatment options, poses a significant burden on patients, their families, and society. Spinal cord ischemia-reperfusion injury leads to reduced neuronal regenerative capacity and complex pathological processes. In contrast, mitophagy is crucial for degrading damaged mitochondria, thereby supporting neuronal metabolism and energy supply. However, while moderate mitophagy can be beneficial in the context of spinal cord ischemia-reperfusion injury, excessive mitophagy may be detrimental. Therefore, this review aims to investigate the potential mechanisms and regulators of mitophagy involved in the pathological processes of spinal cord ischemia-reperfusion injury. The goal is to provide a comprehensive understanding of recent advancements in mitophagy related to spinal cord ischemia-reperfusion injury and clarify its potential clinical applications.

Key Words: BNIP3; BNIP3L/NIX; FUNDC1; mechanism; mitochondria; mitophagy; modulators; Parkin; PINK1; spinal cord ischemia-reperfusion injury

Introduction

Spinal cord injury (SCI) is widely-acknowledged as a debilitating neurological condition associated with high disability and mortality rates. All forms of SCI can result in significant motor, sensory, and autonomic dysfunctions below the injury level. Between 1990 and 2016, the global incidence of SCI reached 27.04 million cases, affecting approximately 368 individuals per 100,000 population. In 2016, approximately 30,000 new cases of SCI were reported worldwide, corresponding to an incidence rate of 13 per 100,000 individuals (GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators, 2019). The global annual incidence of SCI is estimated to range between 250,000 and 500,000 individuals (Khorasanizadeh et al., 2019). Among these, the incidence rates of postoperative neurological dysfunction and permanent paraplegia associated with spinal cord ischemia-reperfusion injury (SCIRI) are reported to be 9%–16% (Verhoeven et al., 2015) and 0.3%–6.5% (Estrera et al., 2005), respectively. Given its unpredictable nature and challenging treatment nature, SCIRI remains a significant concern within the medical community.

SCIRI refers to a condition wherein, following a period of spinal cord ischemia, neurological function fails to improve despite the restoration of blood circulation. This results in significant sensory and motor dysfunction (Smith et al., 2012; Long et al., 2024). SCIRI is commonly observed after surgical interventions involving the spine, spinal cord, or chest and abdominal aorta. If not prevented and treated promptly, spinal cord function may suffer long-term or permanent damage, potentially resulting in paralysis or even death (Wen et al., 2024). Current clinical practices aim to prevent SCIRI through several strategies, including intraoperative neurological function monitoring, minimizing spinal cord ischemia time, elevating spinal cord perfusion pressure, and enhancing spinal cord tolerance to ischemia through hypothermia. Techniques such as monitoring somatosensory and motor-evoked potentials during surgery demonstrate effectiveness in reducing the incidence of ischemic events (Shine et al., 2008). However, despite these preventive measures, treatment options for SCIRI remain limited.

Tissue damage caused by ischemia-reperfusion injury can be classified into ischemic and reperfusion injuries. Ischemic injuries lead to hypoxia and nutrient deprivation, causing cellular energy deficiency, metabolic acidosis, and the accumulation of metabolic byproducts. Upon reperfusion, oxidative stress, inflammatory responses, and increased production of reactive oxygen species (ROS) may occur, exacerbating secondary damage. Secondary SCI involves vascular spasms leading to insufficient oxygen and energy supply, disruption of mitochondrial electron transport chains, decreased membrane potential, and increased ROS production. This surge in ROS production can exceed the clearance capacity of the endogenous antioxidant system, thereby exacerbating oxidative damage at the SCI site (Hall et al., 2016). Cell death mechanisms after SCIRI include necrosis, apoptosis, and autophagic cell death (Yu et al., 2013). Recent research has focused extensively on the secondary injury stage. Owing to the limited regenerative capacity of neurons and the complexity of the associated pathological processes, effective treatment strategies for these stages remain insufficient. A growing body of literature

[1]Department of Orthopedics, The Second Hospital of Lanzhou University, Lanzhou, Gansu Province, China; [2]The Second Clinical Medical School, Lanzhou University, Lanzhou, Gansu Province, China; [3]Orthopaedics Key Laboratory of Gansu Province, The Second Hospital of Lanzhou University, Lanzhou, Gansu Province, China
*Correspondence to: Xuewen Kang, PhD, ery_kangxw@lzu.edu.cn.
https://orcid.org/0000-0002-5877-9198 (Xuewen Kang)
#Both authors contributed equally to this work and share first authorship.

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suggests that mitophagy may serve as a potential neuroprotective mechanism by regulating neuronal cell death in central nervous system diseases, particularly in the context of SCIRI (Lipinski et al., 2015; Nikoletopoulou et al., 2015). Consequently, enhancing mitophagy is considered a promising therapeutic strategy for protecting neurons from ischemic damage. Therefore, this review aims to investigate mitophagy in the context of SCIRI, emphasizing its pathophysiology. Furthermore, this review evaluates current and future treatment approaches. Given the crucial role of mitochondrial integrity and mitophagy in SCIRI, it comprehensively examines the following aspects: (1) a brief overview of mitochondrial damage in SCIRI; (2) an exploration of potential signaling pathways and regulators of mitochondria, their relevance to SCIRI, and an analysis of their underlying mechanisms; and (3) a summary of key molecules regulating mitophagy and their potential clinical significance in SCIRI. These mitophagy pathways and regulators may become important targets for the treatment of SCIRI. With the increasing research on mitophagy, it is believed that it will bring a brand new program for disease salvage in the future.

Literature Retrieval Strategy

On June 20, 2023, the first author initiated a search of multiple databases covering literature published from March 1998 to February 2024. The databases accessed included the China National Knowledge Infrastructure, Wanfang Database, and PubMed. The search strategy utilized keywords such as "spinal cord ischemia-reperfusion injury," "mitochondrial autophagy," "mitophagy," "autophagy," and "mitochondria" to establish selection criteria. Various combinations of these keywords were used during the retrieval process. The retrieved literature primarily consisted of original research articles, review papers, commentaries, case reports, and meta-analyses. The inclusion criteria included studies with relevance to mitophagy and SCIRI, a high degree of originality, clear conclusions, and publication in reputable journals within the past 20 years. Exclusion criteria included studies not relevant to the subject matter of this review or those with repetitive content. After the initial search, relevance to this study was determined by reviewing the title and abstract, followed by a thorough reading of the full text to assess the central theme of the selected studies.

Mitochondrial Damage Induced by Spinal Cord Ischemia-Reperfusion Injury

Mitochondria are double-membrane-bound subcellular organelles present in the cells of multicellular eukaryotes, functioning as the "powerhouses" of cells and contributing approximately 95% of the energy required for cellular activities (Lane and Martin, 2010; Zhang et al., 2024). Furthermore, mitochondria are crucial for various cellular processes, including apoptosis, necrosis, autophagy, lipid synthesis, Ca^{2+} metabolism, and the regulation of cell growth and the cell cycle (Kalkavan and Green, 2018; You et al., 2024). Under normal physiological conditions, mitochondria exhibit a highly dynamic, double-layer membrane-encapsulated cystic structure characterized by a distinct morphology and well-organized cristae. However, during SCIRI, mitochondria undergo volumetric expansion, structural irregularities, and disorganized cristae arrangement, which negatively affect electron transport and oxidative phosphorylation. Various pathophysiological mechanisms related to mitochondria dysfunction contribute to SCIRI. Ischemia-reperfusion injury leads to a decline in mitochondrial membrane potential (MMP), increased reactive oxygen species (ROS) production, reduced adenosine triphosphate (ATP) synthesis, the release of apoptotic factors such as cytochrome c, the opening of mitochondrial permeability transition pores, and the activation of inflammatory pathways (Sanderson et al., 2013; Panel et al., 2019). Additionally, SCIRI can disrupt mitochondrial dynamics, leading to reduced mitophagy (Huang et al., 2023). Given the critical role of mitochondrial dysfunction in SCIRI, therapeutic strategies aimed at targeting cellular processes to maintain or restore mitochondrial homeostasis have gained increasing attention (Han et al., 2020a).

Increasing evidence supports the critical involvement of mitochondria in both physiological and pathological processes, such as axonal degeneration and regeneration, apoptosis, and immune responses (Wang et al., 2021; Sun et al., 2024). Mitochondrial dysfunction significantly influences diverse cellular responses following SCIRI, affecting various cellular outcomes (Slater et al., 2022). Mitochondrial quantity and localization significantly influence cellular metabolism, which is crucial for modulating immune responses and inflammation, ultimately affecting axonal regeneration capacity (Kiryu-Seo and Kiyama, 2019; Afridi et al., 2020). Conversely, mitochondrial quality and substrate utilization are key factors in the self-renewal and differentiation of neural stem cells (Khacho et al., 2019). During SCIRI, mitochondrial dysfunction manifests early in axonal degeneration stages and is characterized by oxidative stress, energy depletion, disrupted mitochondrial dynamics, transport impairments, and defects in mitophagy, ultimately leading to cell necrosis, apoptosis, or ferroptosis (Hall et al., 2016). Furthermore, the direct injection of mitochondria into the SCI site is taken up by neurons, astrocytes, and macrophages, resulting in reduced apoptosis, improved motor function, and a decrease in SCI lesion size (Li et al., 2019). Consequently, precise regulation of mitochondrial quality and quantity and the timely removal of dysfunctional mitochondria through mitophagy are crucial for sustaining a healthy mitochondrial network and reducing the harmful effects of damaged mitochondria on neurons. However, the potential negative effects of excessive mitophagy on nerve cells remain uncertain, necessitating further investigation (Su et al., 2018; Yu et al., 2018; Wang et al., 2019; Deng et al., 2020; Wen et al., 2021).

Mitophagy Pathways After Spinal Cord Ischemia-Reperfusion Injury

Autophagy, an evolutionarily conserved metabolic process, degrades unwanted cytoplasmic proteins and damaged organelles by facilitating the fusion of autophagosomes with lysosomes (Nagayach and Wang, 2024). This intracellular degradation system, which is preserved across eukaryotes, significantly contributes to maintaining cell integrity and metabolic balance (Zhang et al., 2016a). The autophagy process progresses through four stages: phagophore formation, autophagosome development, autophagosome-lysosome fusion, and autophagosome degradation (Ohsumi, 2014). Under normal physiological conditions, autophagy is maintained at a basal level and responds to various microenvironmental triggering factors, including nutrient deprivation, metabolic disturbances, cellular damage, and exposure to physical or chemical stimuli (Kaur and Debnath, 2015).

Beyond the previously discussed non-selective degradation process, autophagy functions as a selective system that targets specific organelles for clearance (Gatica et al., 2018). Based on its selectivity, autophagy can be classified into two types: selective and non-selective autophagy. Mitophagy is the most prevalent form of selective autophagy. Lemasters (2005) were the first to introduce the term "mitochondrial autophagy" to describe the process by which mitochondria are engulfed by vesicles, characterized by the autophagosome marker microtubule-associated protein 1 (MAP1) light chain 3 (LC3), a homolog of yeast Atg8. This process can occur within approximately 5 min, highlighting its non-random and highly regulated nature (Lemasters, 2005; Kim et al., 2007). Mitophagy, a form of selective autophagy, specifically targets damaged or dysfunctional mitochondria by sequestering and engulfing them into autophagosomes. This process is crucial for maintaining mitochondrial function and cellular homeostasis by regulating the quality and quantity of mitochondria (Palikaras et al., 2018; Pickles et al., 2018). Under normal physiological conditions, mitophagy is essential for the maintenance and renewal of mitochondria. Additionally, various pathological stress responses, such as MMP depletion, hypoxia, and oxidative stress, significantly stimulate mitophagy. Consequently, mammals have evolved multiple mitophagy pathways to facilitate the clearance of damaged mitochondria under various physiological and pathological conditions (Youle and Narendra, 2011; Onishi et al., 2021). Ubiquitin-mediated mitophagy primarily depends on phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1)/Parkin pathways, which are activated by mitochondrial depolarization to facilitate the elimination of dysfunctional mitochondria. Growing evidence indicates that mitophagy receptors, such as BCL2/adenovirus E1B 19-kDa-interacting protein 3 (BNIP3), Nip3-like protein X (NIX)/BNIP3-like protein (NIX/BNIP3L), FUN14 domain-containing protein 1 (FUNDC1), FK506-binding protein 8 (FKBP8), and B-cell lymphoma 2-like 13 (BCL2L13), can be activated by various signals, independently facilitating mitophagy (Liu et al., 2012; Lou et al., 2020). Recent studies indicate that the PINK1/Parkin pathway plays a compensatory role in mitigating mitochondrial dysfunction induced by acute chemical injury (Palikaras et al., 2018), while receptor-mediated mitophagy is predominantly active under chronic stress conditions (Villa et al., 2018). A comprehensive overview of the mitophagy

pathway is provided below. **Figure 1** illustrates the timeline of some pioneering contributions to research on mitochondrial phagocytosis.

PINK1/Parkin-mediated mitophagy in spinal cord ischemia-reperfusion injury

In mammalian cells, the PINK1/Parkin-mediated pathway is the most extensively studied and functions as a receptor-independent mechanism (Eiyama and Okamoto, 2015; Yang et al., 2024). The functional loss of PINK1 or Parkin is primarily responsible for recessive Parkinson's disease. PINK1, a serine/threonine kinase, functions as a molecular sensor for mitochondrial health, continuously monitoring mitochondrial status. Upon detecting mitochondrial damage, PINK1 signals the recruitment and activation of Parkin (Nguyen et al., 2016). Parkin, an E3 ubiquitin ligase belonging to the inter-ring domain family, contains an N-terminal ubiquitin-like domain that shares a structural fold with ubiquitin. This domain facilitates the ubiquitination of mitochondrial membrane proteins, binds to LC3B, a protein associated with autophagosome, and induces mitophagy. In the cytoplasm, Parkin remains inactive due to self-inhibition of its conformation (Wauer and Komander, 2013).

PINK1/Parkin-mediated mitophagy comprises three primary components: the mitochondrial damage sensor (PINK1), the signal amplifier (Parkin), and the signal effector (ubiquitin chain) (Harper et al., 2018). Under basal conditions, PINK1 is localized in the inner mitochondrial membrane (IMM) and it is translocates into the mitochondrial matrix with the assistance of the mitochondrial outer membrane translocase (TOMM) and mitochondrial inner membrane translocase (TIMM) (Greene et al., 2012). During this process, PINK1 is cleaved by matrix processing peptidase (Jin et al., 2010) and the inner membrane protease known as PINK1/PCAM5-related rhombic protease (PARL) (Meissner et al., 2011). The resulting PARL-mediated cleavage product, characterized by an amino-terminal Phe104 residue, is released into the cytoplasm and subsequently degraded by proteasomes through the N-terminal regulatory pathway (Yamano and Youle, 2013; **Figure 2**). When mitochondrial damage occurs, it leads to changes in mitochondrial membrane permeability and a reduction in MMP, resulting in abnormal TIMM integration. This disruption hinders the entry of PINK1 into the mitochondria, leading to its aggregation on the outer mitochondrial membrane (OMM) (Bakthavachalam and Shanmugam, 2017). Subsequently, PINK1 homodimerizes, undergoes self-phosphorylation, and becomes a highly active kinase (Okatsu et al., 2013). Following this activation, PINK1 phosphorylates serine 65 (Ser65) of ubiquitin, which is present in low concentrations on the OMM. This phosphorylated ubiquitin serves as a mitochondrial receptor for the E3 ubiquitin ligase Parkin (Nguyen et al., 2016). After translocating from the cytoplasm to the OMM, Parkin is phosphorylated by PINK1 at the homologous Ser65 residue within its ubiquitin-like domain (Yamano et al., 2016; Malpartida et al., 2021; **Figure 3**). Fully activated, phosphorylated Parkin extends the ubiquitin chain, or alternatively, cytoplasmic ubiquitin is recruited to mitochondria through the ubiquitination reaction catalyzed by activated Parkin (Ordureau et al., 2014, 2015). Collectively, this process establishes a positive feedback loop of ubiquitination, accelerating the translocation of Parkin to damaged mitochondria and facilitating the formation of polyubiquitin chains (**Figure 4**). The PINK1/Parkin pathway serves as a signaling mechanism utilizing ubiquitin chains to label damaged mitochondria. Subsequently, these multi-ubiquitin chains are recognized by various ubiquitin-binding autophagic ligands belonging to the chelator-like receptor family. Key receptors in this family include chelator 1 (SQSTM1, referred to as p62), optic nerve phosphatase (OPTN), BRCA1 gene 1 protein (NBR1), adjacent calcium-binding and curly helix domain 2 (CALCOCO2, commonly known as NDP52), and Tax1 binding protein 1 (TAX1BP1). These receptors possess specific ubiquitin-binding domains (UBDs) and LC3-interacting regions (LIR motifs) that facilitate their interaction with ATG8 proteins in the autophagosome membranes. This interaction facilitates the clearance of damaged or excess mitochondria through autophagosomal and lysosomal pathways (Palikaras et al., 2018; Johansen and Lamark, 2020; **Figure 5A**). In the context of PINK1/Parkin-mediated mitophagy, phosphorylated Ub and polyUb chains can be hydrolyzed by ubiquitin-specific proteases, such as USP15, USP30, and USP35. These proteases antagonize Parkin-mediated mitochondrial ubiquitination events and act as key negative regulators of mitophagy (Gersch et al., 2017; Harper et al., 2018).

Mitochondrial dysfunction during SCIRI accelerates apoptosis. Moderately increased mitophagy exhibits a protective effect on neurons (Wu et al., 2021a; Jiang et al., 2023; Chen et al., 2024). Similarly, PINK1/Parkin-mediated mitophagy significantly protects neurons after SCI (Mao et al., 2022a). Additionally, in the extensively studied context of brain ischemia-reperfusion injury, the activation of PINK1/Parkin-dependent mitophagy has been shown to improve neuronal damage in the hippocampus (Mao et al., 2022b). Furthermore, the ubiquitination of proliferation-associated 2G4 facilitates PINK1/Parkin-mediated mitophagy, potentially contributing to neuroprotection (Hwang et al., 2024). The previously discussed molecules, which have regulatory effects on PINK1/Parkin-mediated mitophagy, may play significant roles in the treatment of SCIRI. However, given that mitophagy is a dynamic process, evaluating the effects of PINK1/Parkin-mediated mitophagy on SCIRI at a single static time point may result in misleading conclusions.

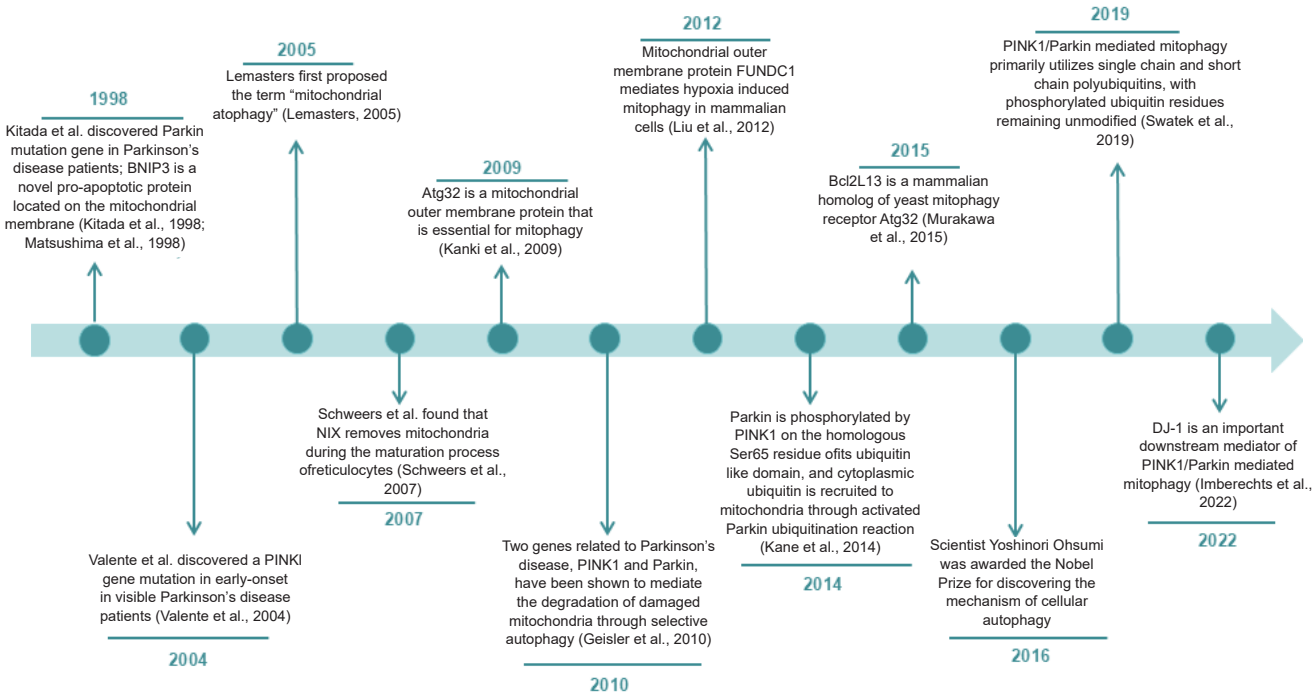

Figure 1 | **Timeline of seminal contributions to mitophagy research.**

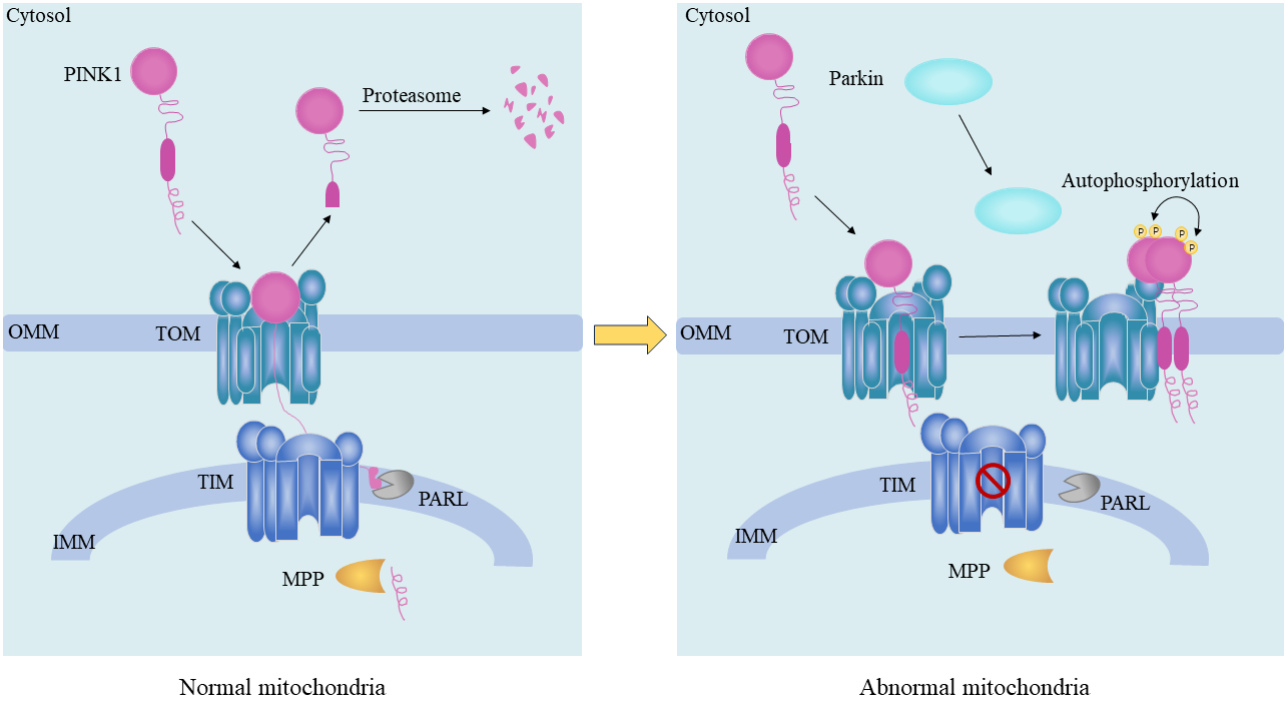

Figure 2 | **Degradation, homologous dimerization, and self-phosphorylation process of PINK1.**
In healthy mitochondria, the mitochondrial transmembrane potential drives PINK1 to move into the inner mitochondrial membrane (IMM) via translocases located on the outer mitochondrial membrane (OMM) and IMM. Once in the IMM, PINK1 has its N-terminal mitochondrial targeting signal cleaved by mitochondrial processing peptidase (MPP). Following this, the protein PARL, associated with early aging, cleaves the amino acid sequence between PINK1 residues A103 and F104. This cleavage leads to the rapid degradation of PINK1 in the cytoplasm via the ubiquitin-proteasome system. Under stress conditions, the mitochondrial membrane potential decreases, causing depolarization, which prevents PINK1 from entering the IMM. Consequently, PINK1 accumulates on the OMM, where it undergoes homologous dimerization and self-phosphorylation, transforming into a highly active kinase that ultimately recruits Parkin and facilitates ubiquitin linkage formation. In summary, the precise regulatory mechanism of PINK1 explains how it identifies individual dysfunctional organelles among a population of healthy organelles. IMM: Inner mitochondrial membrane; MPP: mitochondrial membrane potential; OMM: outer mitochondrial membrane; PARL: presenilin-associated rhomboid-like protein; PINK1: PTEN induced kinase 1; TIM: translocase of the inner mitochondrial membrane; TOM: translocase of the outer mitochondrial membrane.

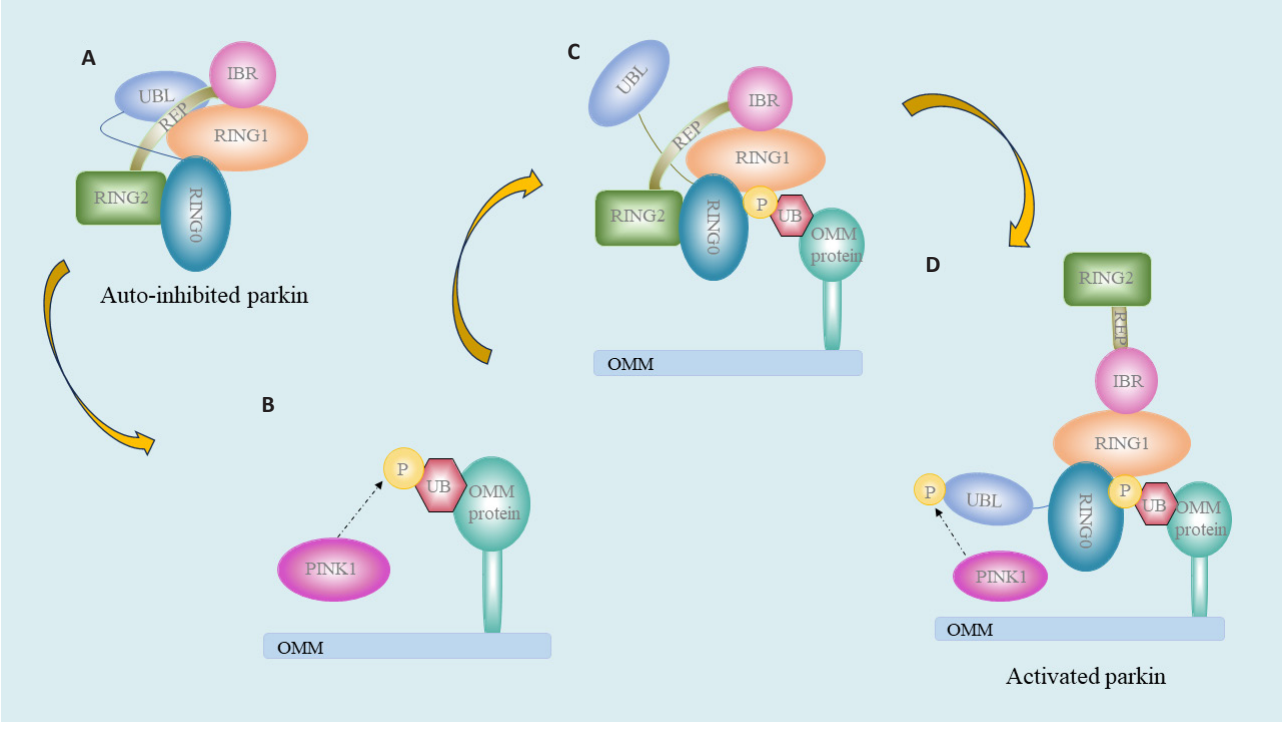

Figure 3 | **Parkin activation using PINK1.**
(A) Under normal conditions, Parkin exists in a self-inhibitory state within the cytoplasm. Parkin in RING2 catalyzes cysteine, but this is blocked by RING0. The binding site between RING1 and the ubiquitin ligase is obstructed by UBL and REP. (B) PINK1 initiates Parkin recruitment by phosphorylating ubiquitin bound to mitochondrial outer membrane proteins. (C) Parkin demonstrates a strong affinity for phosphorylated ubiquitin, driving its translocation to the OMM. At the OMM, the interaction with phosphorylated ubiquitin through RING0 and RING1 induces the displacement of inhibitory UBL and stretches REP, thereby disrupting the self-inhibitory state of Parkin. (D) Upon Parkin activation, the released UBL becomes readily phosphorylated by PINK1, further increasing its affinity for phosphorylated ubiquitin. OMM: Outer mitochondrial membrane; REP: repressor element; UB: ubiquitin; UBL: ubiquitin-like domain.

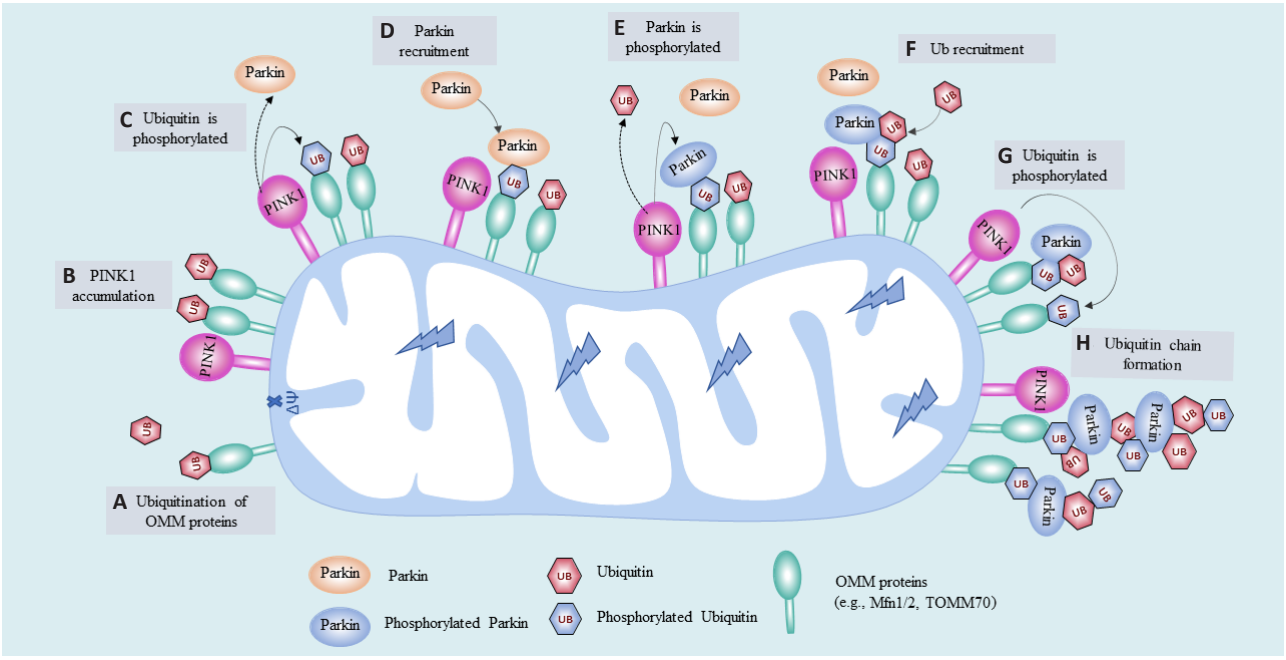

Figure 4 | **PINK1/Parkin-mediated mitophagy ubiquitin linkage formation process.**
(A) Under stress, damaged mitochondria undergo membrane depolarization, reducing membrane potential and promoting the binding of outer mitochondrial membrane (OMM) proteins to ubiquitin. (B) After mitochondrial damage, PINK1 is unable to enter the mitochondria for degradation, causing it to accumulate on the OMM. (C) Accumulated PINK1 undergoes homologous dimerization and self-phosphorylation, thereby inducing ubiquitin phosphorylation at S65. (D) Phosphorylated ubiquitin binds with high affinity to Parkin, facilitating its translocation to the OMM. (E) Once bound to phosphorylated ubiquitin, Parkin is also phosphorylated by PINK1. (F) Phosphorylated Parkin and ubiquitin recruit additional ubiquitin, promoting its aggregation. (G) Newly recruited ubiquitin is further phosphorylated by PINK1, leading to the recruitment of more Parkin. (H) PINK1 phosphorylates both ubiquitin and Parkin, leading to the formation of ubiquitin chains that mediate ubiquitin-dependent mitophagy. Mfn1/2: Mitofusin 1/2; OMM: outer mitochondrial membrane; PINK1: PTEN induced kinase 1; TOMM70: translocase of outer mitochondrial membrane 70; UB: ubiquitin.

BNIP3L/NIX-mediated mitophagy in spinal cord ischemia-reperfusion injury

Beyond the ubiquitin-dependent mitophagy pathway, the receptor-dependent mechanism for initiating mitophagy has garnered significant attention (Villa et al., 2018). NIX, commonly known as BCL-2 interacting protein 3-like (BNIP3L), is a mitochondrial outer membrane protein with a unique channel structure. The N-terminal BH3 domain of NIX interacts with Bcl-2 and Bcl-xL, facilitating the release of cytochrome c into the cytoplasm and inducing apoptosis (Ohi et al., 1999). Early research primarily focused on the pro-apoptotic role of NIX. However, Schweers et al. (2007) identified an upregulation of NIX-mediated mitophagy during the transformation of reticulocytes into red blood cells, indicating that NIX is crucial to reticulocyte maturation. Mice with NIX deficiency exhibited abnormalities in reticulocyte nuclear maturation, resulting in the accumulation of mitochondria due to impaired mitophagy (Schweers et al., 2007; Zhang et al., 2015). Furthermore, BNIP3L-induced mitophagy has been observed in neurons, retinal ganglion cells, and various tumor cells (Palikaras et al., 2017; Yuan et al., 2017; Humpton et al., 2019). The upregulation of hypoxia-inducible factor 1α is considered a typical stressor inducing BNIP3L-mediated mitophagy, as BNIP3L expression is responsive to hypoxia conditions (Sowter et al., 2001). Additionally, BNIP3L is transcriptionally regulated by FOXO3/FOXO3A, establishing a connection between mitophagy and fundamental signaling pathways (Chaanine et al., 2016).

NIX directly interacts with ATG8 family proteins on autophagosome membranes, facilitating mitochondrial sequestration within formed autophagosomes, particularly under hypoxic conditions (Novak et al., 2010; Ganley and Simonsen, 2022). The C-terminal transmembrane (TM) domain anchors BNIP3L to the mitochondrial membrane, while the N-terminal LIR domain remains exposed in the cytoplasm, facilitating interaction with LC3 on the autophagosome membrane. Autophagosomes engulf mitochondria, and their subsequent binding to lysosomes facilitates degradation (Marinković and Novak, 2021; **Figure 5B**). Ser212, located at the C-terminus of BNIP3L and extending into the intercellular space, serves as the primary amino acid residue responsible for dimerization. The phosphorylation of the LIR domain of BNIP3L and resulting receptor dimerization are essential for the initiation and progression of BNIP3L-dependent mitophagy (Marinković et al., 2021). Ser81, an evolutionarily conserved residue within the minimal essential region of BNIP3L and NIX, participates in hypoxia-triggered mitophagy via its phosphorylation (Yuan et al., 2017). Additionally, NIX enhances mitophagy by interacting with Parkin, thereby regulating Parkin translocation to the mitochondria, which facilitates the initiation of mitophagy (Ding et al., 2010). Parkin, an E3 ubiquitin ligase, ubiquitinates NIX, leading to the recruitment of adaptor proteins, such as p62 and OPTN, to autophagosomes for mitophagy (Gao et al., 2015).

Recent studies indicate that BNIP3L functions independently of the PINK1/Parkin-mediated mitophagy pathway. In patients with Parkinson's disease, BNIP3L can restore mitophagy and compensate for mitochondrial accumulation caused by mutations in Parkin and PINK1 (Koentjoro et al., 2017). Additionally, BNIP3L-mediated mitophagy is essential for the clearance of axonal mitochondria (Han et al., 2020b). The BNIP3L gene deletion significantly inhibits neuronal mitophagy induced by ischemia-reperfusion, exacerbating ischemic brain injury. Preventing BNIP3L degradation through the inhibition of the ubiquitin-proteasome pathway preserves mitophagy functionality and alleviates cerebral ischemic injury (Wu et al., 2021c). BNIP3L-mediated mitophagy exerts a neuroprotective effect in cerebral ischemia-reperfusion injury. The phosphorylation of Ser81 in BNIP3L is crucial for its mitophagy activity and may serve as a potential therapeutic target for ischemic stroke (Yuan et al., 2017). In summary, while the detailed mechanisms underlying BNIP3L-mediated mitophagy require further investigation, current evidence suggests that BNIP3L functions as a mitophagy receptor independent of the classical PINK1/Parkin pathway.

BNIP3-mediated mitophagy in spinal cord ischemia-reperfusion injury

The Bcl-2 protein family serves as a critical regulator of cell survival and death across various cellular environments. Among its members, BNIP3 and BNIP3L/NIX are distinct regulators of cell death (Field and Gordon, 2022). BNIP3 exhibits 56% homology with NIX/BNIP3L (Matsushima et al., 1998) and is typically associated with autophagy, particularly within the context of hypoxia-induced mitophagy (Tracy et al., 2007). BNIP3, a critical mitophagy receptor under hypoxic conditions, plays a protective role in mitigating ischemia-reperfusion injury-induced acute kidney injury through BNIP3-mediated mitophagy (Tang et al., 2019). Its TM domain is anchored to the mitochondrial outer membrane protein, while

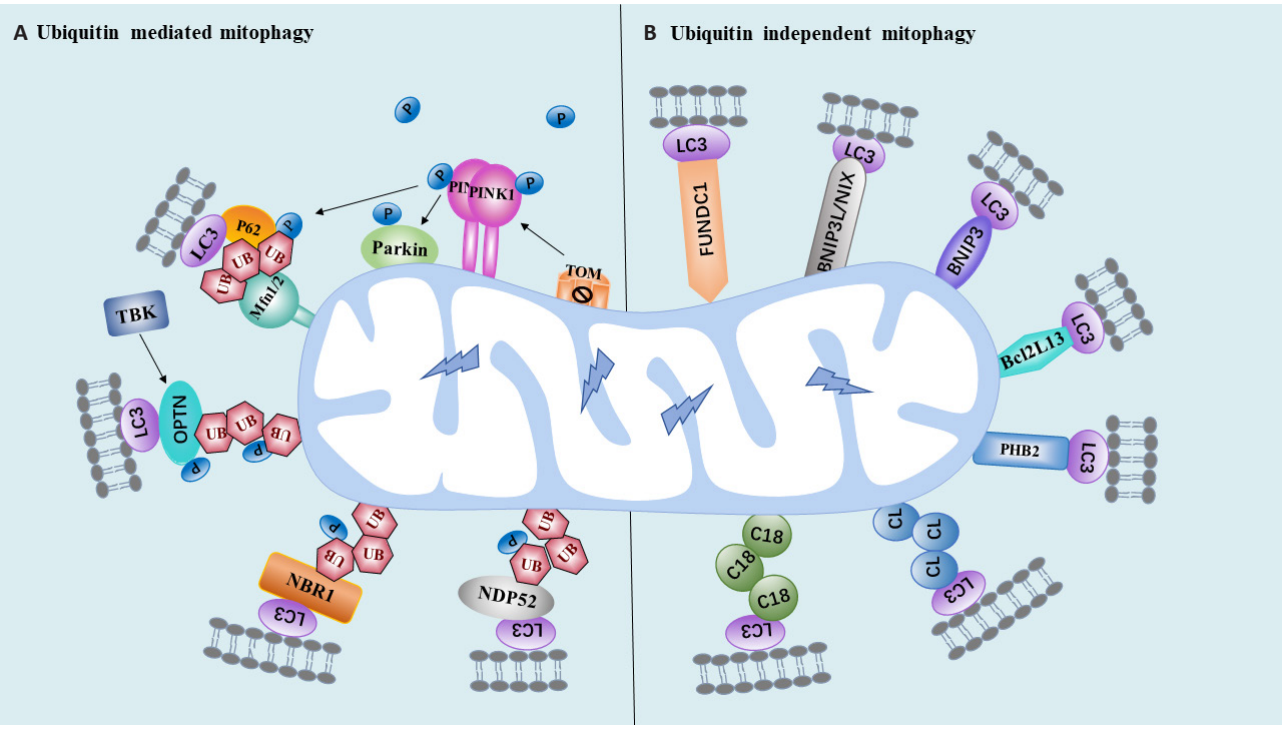

Figure 5 | **Schematic representation of the molecular mechanisms underlying the mitophagy pathways.**
The main mitophagy pathways include interaction between mitochondrial proteins and LC3 through linkers, direct interaction between mitochondrial receptor proteins and LC3, and direct interaction between lipids and LC3. These processes help maintain mitochondrial quality and quantity within cells. (A) Under stress, damaged mitochondria experience decreased membrane potential. PINK1 enters the mitochondria, but its degradation is blocked, causing it to accumulate on the outer mitochondrial membrane (OMM). PINK1 then undergoes homologous dimerization and self-phosphorylation, which phosphorylates ubiquitin and Parkin, leading to Parkin recruitment and the formation of ubiquitin chains, establishing a positive feedback loop. Activated PINK1/Parkin on the OMM binds to LC3 through linkers such as p62, OPTN, and NDP52, mediating ubiquitin-dependent mitophagy. (B) Hypoxia-induced mitophagy is mediated by mitochondrial proteins and lipid receptors. Mitochondrial receptors such as BNIP3L/NIX, BNIP3, FUNDC1, Bcl2L13, PHB2, and CL directly interact with LC3 through their LIR motifs, inducing mitophagy. BCL2L13: B-cell lymphoma 2-like 13; BNIP3: BCL2 and adenovirus E1B 19-kDa-interacting protein 3; BNIP3L/NIX: Nip3-like protein X (NIX)/BNIP3-like protein; CL: cardiophospholipids; FUNDC1: FUN14 domain-containing protein 1; LC3: microtubule-associated protein 1 light chain 3; Mfn1/2: mitofusin 1/2; NBR1: NBR1autophagycargoreceptor; NDP52/CALCOCO2: NDP52/calciumbindingandcoiled-coildomain2; OPTN: Optineurin; p62/SQSTM1: p62/Sequestosome1; PHB2: Prohibitin 2; PINK1: PTEN induced kinase 1; TBK: TANK-bindingkinase; TOM: translocase of the outer mitochondrial membrane; UB: ubiquitin.

the N-terminus extends into the cytoplasm, directly binding with LC3 or GABARAP (a homolog of LC3) to induce mitophagy (**Figure 5B**). BNIP3 is crucial in regulating PINK1 localization to the mitochondrial outer membrane, facilitating PINK1 protein cleavage, and modulating PINK1/Parkin-mediated mitophagy under normal physiological conditions (Zhang et al., 2016b).

BNIP3 is a hypoxia-responsive protein. Under hypoxic conditions, JNK1/2 (c-Jun N-terminal kinase 1/2) phosphorylates BNIP3 at Ser60 and Thr66, preventing proteasomal degradation and promoting its interaction with LC3. This phosphorylation enhances mitophagy, positioning BNIP3 as a potential therapeutic target for hypoxia-related diseases (He et al., 2022). Additionally, augmenting BNIP3-mediated mitophagy has demonstrated protective effects in cerebral ischemia-reperfusion injury (Peng et al., 2024). Similarly, BNIP3-mediated mitophagy activation exerts a protective effect in renal and cardiac ischemia-reperfusion injury (Tang et al., 2019; Zhang et al., 2019). However, some researchers suggest that NIX primarily regulates basal mitophagy under physiological conditions, while BNIP3 specifically activates excessive mitophagy, which may lead to cell death (Shi et al., 2014). For example, the long non-coding RNA small nucleolar RNA host gene 14 (SNHG14) induces excessive mitophagy in HT22 mouse hippocampal neurons through the miR-182-5p/BNIP3 axis, thereby exacerbating oxygen-glucose deprivation/reperfusion-induced neuronal damage (Deng et al., 2020).

FUNDC1-mediated mitophagy in spinal cord ischemia-reperfusion injury

The FUN14 domain-containing 1 (FUNDC1) was first identified as a hypoxia-induced mitophagy receptor in 2012, playing a crucial role in regulating mitophagy regulation, particularly under hypoxic conditions (**Figure 5B**). Endogenous FUNDC1 is specifically localized to the OMM and the mitochondria-associated endoplasmic reticulum (ER) membrane. Its C-terminal region extends into the mitochondrial intermembrane space, while its N-terminal region, which contains a conserved LIR motif, is exposed to the cytoplasm (Liu et al., 2012). Under normal physiological conditions, phosphorylation of the LIR motif by SRC kinase at tyrosine 18 and casein kinase 2 (CSNK2) at Ser13 inhibits the interaction between FUNDC1 and LC3, thereby suppressing mitophagy (Liu et al., 2012; Chen et al., 2014). Conversely, under conditions of hypoxia or MMP deficiency, UNC51-like Ser/Thr kinase 1 (ULK1) translocates to the mitochondria, phosphorylating FUNDC1 at Ser17. A deficiency in ULK1 impedes FUNDC1 activation (Wu et al., 2014; Lv et al., 2017). Additionally, membrane-associated RING-CH protein 5 (MARCH5), a mitochondrial E3 ubiquitin ligase, plays a crucial role in this process. Reduced endogenous MARCH5 expression significantly inhibits FUNDC1 degradation, thereby enhancing mitophagy (Chen et al., 2017b). Prior to FUNDC1 activation through phosphorylation, MARCH5 mediates its ubiquitination at Lys119, decreasing mitophagic activity and promoting proteasome-dependent degradation. This MARCH5/FUNDC1 axis regulation introduces a negative feedback mechanism, preventing the inappropriate removal of healthy mitochondria (Chen et al., 2017a, b).

Recent research has established a close association between FUNDC1 and ischemic diseases, tumors, and metabolic disorders (Tan et al., 2022). FUNDC1-mediated mitophagy inhibits mitochondrial-dependent apoptosis and improves mitochondrial function, thereby protecting against neuronal loss (Chen et al., 2024). In hypoxia-induced PC12 cells, UNC-51-like autophagy-activating kinase 1 (ULK1) promotes FUNDC1 activation, preventing apoptosis in a hypoxic environment. In conclusion, the ULK1/FUNDC1 pathway plays a critical regulatory role in hypoxia-induced neuronal autophagy and apoptosis (Wang et al., 2018). FUNDC1-mediated mitophagy has emerged as a novel therapeutic target for ischemia-reperfusion injury (Zhang et al., 2017). Further research is necessary to identify the specific determinants influencing different outcomes.

BCL2L13-mediated mitophagy in spinal cord ischemia-reperfusion injury

BCL2L13, a single-channel membrane protein localized in the OMM, contains two LIR motifs. In Atg32-deficient yeast cells, BCL2L13 induces mitophagy and may functionally resemble mammalian Atg32 (Otsu et al., 2015). In human embryonic kidney 293 (HEK293) cells, BCL2L13 initiates mitochondrial fragmentation and autophagy by interacting with LC3 through the WXXI motif (**Figure 5B**). The BCL2L13 BH domain predominantly facilitates mitochondrial fragmentation, while the WXXI motif is pivotal for the mitophagy process (Murakawa et al., 2015). In SH-SY5Y cells subjected to middle cerebral artery occlusion/reperfusion injury or oxygen-glucose deprivation/reoxygenation in rats, miR-874-3p mitigates ischemic injury by negatively regulating BCL2L13 (Jiang et al., 2019). BCL2L13 is suggested to play a detrimental role in ischemia-reperfusion injury models; however, whether this effect is mediated through the mitophagy pathway remains unclear.

FKBP8-mediated mitophagy in spinal cord ischemia-reperfusion injury

FKBP8, commonly known as FKBP38, is a distinct member of the FK506 binding protein (FKBP) family, primarily located in the OMM. FKBP8 inhibits apoptosis by recruiting the anti-apoptotic proteins BCL-2 and BCL2L1 to the mitochondria (Choi et al., 2010). During PINK1/Parkin-induced mitophagy, FKBP8 translocates from the mitochondria to the endoplasmic reticulum through a microtubule-dependent pathway, thereby preventing its degradation (Saita et al., 2013). Additionally, FKBP8 effectively recruits lipid-loaded LC3A to damaged mitochondria in an LIR-dependent manner, thereby facilitating mitophagy. This recruitment exceeds the capabilities of BNIP3 and NIX, even post-mitochondrial damage (Bhujabal et al., 2017). Currently, no relevant reports exist regarding FKBP8 in SCIRI.

NIPSNAP1/2-mediated mitophagy in spinal cord ischemia-reperfusion injury

NIPSNAP1/2, which are mitochondrial matrix proteins, function as mitophagy receptors promoting mitophagy. Upon mitochondrial damage and depolarization, NIPSNAP1 and NIPSNAP2 aggregate on the OMM, facilitating the recruitment of autophagy receptors, linkers, and Atg8 family proteins to drive mitophagy. Additionally, NIPSNAPs ensure the continuous recruitment of SQSTM1-like receptors, enhancing the efficacy of mitophagy (Abudu et al., 2019). Zebrafish brains deficient in NIPSNAP1 exhibit decreased mitophagy, resulting in increased ROS production, dopaminergic neuron loss, and a significant decline in motor activity (Mukherjee and Dikic, 2019). Furthermore, NIPSNAP1 and NIPSNAP2 exhibit redundant functions, with NIPSNAP1 able to compensate for the absence of NIPSNAP2 during PINK1-PRKN-mediated mitophagy (Princely Abudu et al., 2019). A recent report indicates that the NLRX1/FUNDC1/NIPSNAP1-2 axis regulates mitophagy and alleviates intestinal ischemia/reperfusion injury. However, no relevant studies have been published regarding SCIRI (Li et al., 2021).

AMBRA1-mediated mitophagy in spinal cord ischemia-reperfusion injury

Autophagy and Beclin 1 regulator 1 (AMBRA1) acts as a mitophagy receptor that selectively removes damaged mitochondria in mammalian cells. This process occurs through the action of CHUK/IKKα nuclear factor κB kinase complex inhibitors, phosphorylating, and binding to LC3, thereby acting as mitophagy receptors (Di Rita et al., 2018). Additionally, AMBRA1 interacts with PINK1 and ATAD3A, both transmembrane proteins that mediate mitochondrial import and PINK1 degradation, thereby regulating mitophagy and enhancing PINK1 stability (Strappazzon et al., 2015; Di Rienzo et al., 2022). Recent studies suggest that AMBRA1 serves as a valuable molecular target for promoting skeletal muscle mitophagy, which is essential for maintaining functional mitochondria (Gambarotto et al., 2022).

PHB2-mediated mitophagy in spinal cord ischemia-reperfusion injury

Prohibitin 2 (PHB2), a highly conserved inner membrane scaffold protein of the PHB domain family, serves as a key receptor for mitophagy. Recent studies have shown its involvement in targeted mitophagy degradation (Lahiri and Klionsky, 2017). PHB proteins consist of N-terminal transmembrane, evolutionarily conserved PHB, and C-terminal coiled helical domains, which interact within the IMM to stabilize mitochondria. During mitochondrial depolarization and proteasome-mediated outer membrane rupture, PHB2 promotes mitophagy by binding to LC3 through its LIR domain (Wei et al., 2017; **Figure 5B**). PHB2-mediated mitophagy depends on the mitochondrial inner membrane protease PARL, which interacts with PHB2 to regulate PINK1-PRKN-mediated mitophagy (Yan et al., 2020). Research has shown that PHB can directly bind to NO, leading to S-nitrosylation at the PHB residue Cys69. This modification helps preserve neuronal function under hypoxic stress (Qu et al., 2020). However, further research is required to determine if PHB2-mediated mitophagy has neuroprotective effects and to elucidate its specific mechanisms in the nervous system.

Mitophagy mediated by other protein receptors in spinal cord ischemia-reperfusion injury

The significant roles of MCL-1, FTMT, and SAMM50 in mediating mitophagy complement the previously discussed mitophagy receptors. MCL-1, which is located in various mitochondrial subregions, has diverse functions that affect mitochondrial activity and integrity. On the OMM, MCL-1 provides anti-apoptotic effects by inhibiting the activation of BAX, thereby preserving mitochondrial integrity. However, within the mitochondrial matrix, MCL-1 does not inhibit apoptosis but instead supports the maintenance of IMM structure (Perciavalle et al., 2012). MCL-1 is also crucial for nervous system development (Flemmer et al., 2021). FTMT, located on the OMM, interacts with NCOA4 to trigger mitophagy (Hara et al., 2020). This interaction also promotes the colocalization of FTMT and LC3 (Zhang et al., 2022). Overexpression of FTMT can enhance mitochondrial dysfunction, regulate glucose metabolism, reduce excessive ROS production, and prevent apoptosis caused by cerebral ischemia-reperfusion injury (Wang et al., 2022). SAMM50, a key receptor in basal mitophagy, recruits ATG8 family proteins via typical LIR motifs and interacts with p62/SQSTM1 to facilitate mitophagy (Abudu et al., 2021a, b).

Lipid receptor-mediated mitophagy in spinal cord ischemia-reperfusion injury

Mitochondrial lipid molecules, such as cardiophospholipids (CL) and ceramides (CE), serve as mitophagy receptors alongside mitochondrial proteins. These lipids mediate the specific isolation of damaged mitochondria by autophagosomes. CL, a phospholipid located in the IMM, interacts with various proteins to support ridge folding, stabilize respiratory chain complexes, and regulate autophagy and cell death (Paradies et al., 2014; Praharaj et al., 2019). Following mitochondrial damage, CL translocates from the IMM to OMM via the ligase PLSCR3. Once anchored to the OMM, CL directly interacts with LC3B, promoting mitophagy (Antón et al., 2016; **Figure 5B**). Research indicates that CL is crucial in mitochondrial dysfunction and neuronal death after SCI, and restoring mitochondrial CL homeostasis can reduce neuronal cell death and promote recovery of neuronal function after SCI (Liu et al., 2022).

CE are novel mitophagy receptors and are bioactive sphingolipids found in biological membranes. Long-chain CE, produced by ceramide synthase 1, primarily accumulates in the OMM and directly interacts with LC3B, triggering lethal mitophagy during Drp1-dependent mitochondrial division. A mutant form of LC3B that cannot bind to CE blocks the selective targeting of mitochondria for mitophagy (Sentelle et al., 2012).

In summary, as research into "mitophagy" expands, scientists are uncovering a growing number of mitophagy pathways (**Table 1**). The connection between mitophagy and various diseases underscores the importance of understanding its molecular regulatory mechanisms (Lisanti et al., 2010). Consequently, mitophagy is emerging as a potential therapeutic strategy for SCI.

Mitophagy Regulators in Spinal Cord Ischemia-Reperfusion Injury

Mitophagy inducers

Mitochondrial dysfunction is strongly associated with various diseases, making mitophagy a potential therapeutic strategy. Mitophagy inducers, classified by their targets, include targeted and non-targeted small-molecule mitophagy inducers (Li et al., 2024). The PINK1/Parkin-mediated mitophagy pathway, one of the most common, can be naturally enhanced by active modulators. Kinetin triphosphate, a novel substrate, shows a higher affinity for PINK1 than the natural substrate ATP (Hertz et al., 2013). Kinetin, the precursor to kinetin triphosphate, significantly increases PINK1 activity, promoting parkin recruitment to depolarized mitochondria (Lu et al., 2023). Additionally, the tumor suppressor p53 not only regulates PINK1 but also directly binds to Parkin, preventing its translocation to damaged mitochondria. Pifithrin-α, a specific inhibitor of p53, improves mitophagy (Hoshino et al., 2013).

Table 1 | A summary of the identified mitophagy receptors in mammals

Mitophagy receptor	Receptor type	Mitochondrial localization	Activated condition	Mitophagy interacting molecule	Regulator	Biologic function	Reference
BNIP3L (NIX)	MAR	OMM	Hypoxia; Erythrocyte maturation	GABARAPL1 LC3B LC3A	HIF1A↑	Binding to LC3 facilitates mitochondrial elimination during erythrocyte maturation, while deletion of the Bnip3l gene significantly impairs ischemia-reperfusion-induced neuronal mitochondrial autophagy	Novak et al., 2010; Wu et al., 2021c
BNIP3	MAR	OMM	Hypoxia	LC3B ATG8	FOXO3↑ HIF1A↑ MA-5↑ ULK1↑ JNK1/2↑ PP1/2A↓	In mediating mitophagy under hypoxic conditions, BNIP3 is more sensitive to hypoxia than any other BH3-only proteins on the outer membrane of the mitochondria	Hanna et al., 2012; Zhang et al., 2018
FUNDC1	MAR	OMM	Hypoxia FCCP	LC3B	ULK1↑ SRC↓ PGAM5↑ CK2↓ MIR137↓ USP19↑	Combining with LC3 induces mitophagy, which inhibits cell apoptosis and protects neurons. Binding to Drp1 promotes mitochondrial division	Chen et al., 2016; Cai et al., 2021
BCL2L13	MAR	OMM	Mitochondrial depolarization CCCP	LC3B LC3C GABARAP GABARAPL	ULK1↑	BCL2L13, a functional mammalian homolog of Atg32, induces mitochondrial fragmentation and autophagy in HEK293 cells	Murakawa et al., 2015; Otsu et al., 2015
FKBP8	MAR	OMM	Hypoxia Starvation Iron depletion	LC3A	RHEB↓	Recruiting LC3A mediates Parkin-independent mitophagy, allowing mitochondria to escape and enter the endoplasmic reticulum to avoid degradation	Yoo et al., 2020
NIPSNAP1/2	MAR	OMM	Mitochondrial depolarization	SLR	FBXL14↑ c-Myc-Miz1↓	NIPSNAP1/2, a mitochondrial matrix protein, accumulates on the outer mitochondrial membrane after depolarization, recruiting autophagic receptors and adaptors	Abudu et al., 2019; Gao et al., 2023
AMBRA1	MAR	OMM	FCCP Mitochondrial depolarization	LC3 BECN1 GABARAP	CHUK↑ MCL1↓ GSK3B↑	Regulates mitophagy by interacting with ATAD3A and enhancing PINK1 stability	Chaikovsky et al., 2021; Di Rienzo et al., 2022
PHB2	MAR	IMM	Mitochondrial depolarization	LC3B	AURKA↑	As a highly conserved membrane scaffold protein, it is recognized as a novel mitochondrial autophagy receptor.	Yan et al., 2020
MCL-1	MAR	OMM	Oxygen-glucose deprivation FCCP Early stage of hypoxia	LC3A	GSK3B↓	Participate in regulating mitophagy through various pathways	Perciavalle et al., 2012; Moyzis et al., 2022
FTMT	MAR	OMM	Iron loss	LC3	HIF1A↑	Participate in iron loss-mediated mitophagy	Hara et al., 2020; Yanatori et al., 2023
SAMM50	MAR	OMM	Under normal conditions	ATG8 protein	–	SAMM50-mediated piecemeal mitophagy maintains mitochondrial homeostasis	Lionello et al., 2020; Abudu et al., 2021b
Cardiolipin	Lipid	OMM/IMM	Rotenone CCCP	LC3A LC3B BECN1	PKC↑ CRLS1↑ PLSCR3↑ SNCA↑	Supports proper ridge folding, stabilizes respiratory chain complexes, and regulates autophagy and cell death	de la Ballina et al., 2020; Falabella et al., 2021
Ceramide	Lipid	OMM	C18-ceramide	LC3B	DNM1L↑	LC3B-ceramide binds to the mitochondrial membrane to recruit autophagosomes, leading to lethal mitophagy in cancer cells	Jiang and Ogretmen, 2013

IMM: Inner mitochondrial membrane; MAR: membrane-anchored autophagy receptors; OMM: outer mitochondrial membrane.

GeB, a novel flavonoid from vine plants, stabilizes PINK1, leading to Parkin translocation to damaged mitochondria and initiating mitophagy (Wu et al., 2021b). Mitophagy is inhibited by USP30, a mitochondria-specific deubiquitinase that opposes Parkin-mediated ubiquitination of mitochondrial protein (Bingol et al., 2014). The USP30 inhibitor MTX115325 improves mitochondrial autophagy (Fang et al., 2023). SIRT1, a NAD-dependent deacetylase, stimulates PINK1-Parkin-mediated mitophagy (Liu et al., 2020), while SIRT3 deficiency impairs mitophagy by increasing PINK1/Parkin acetylation (Deng et al., 2024). Rapamycin, an autophagy inducer, suppresses mTOR in spinal cord tissue post-injury, activating non-selective autophagy and mitophagy, which reduces apoptosis and promotes recovery from SCI (Zhang et al., 2020). In BNIP3-mediated mitophagy, the mTOR inhibitor Torin1 decreases BNIP3 levels, leading to increased death of hypoxic tumor cells (Park et al., 2013). Mitochondrial division is essential for mitophagy. Drp1, the key protein regulating mitochondrial division in mammalian cells, must be active for mitophagy to occur, as inhibiting Drp1 prevents its initiation (Han et al., 2020a). Antimicrobial A, an inhibitor of respiratory complex III, is commonly used to induce mitophagy in neuronal cells (Cai et al., 2012; Ashrafi et al., 2014). It causes mitochondrial depolarization and increases the accumulation of mitophagy receptors on the OMM, triggering mitophagy.

Non-targeted small-molecule mitophagy inducers trigger mitophagy by disrupting mitochondrial membrane potential (Elmore et al., 2001). Mitochondrial uncoupling agents transport H^+ from the intermembrane space back into the mitochondria matrix, neutralizing the proton gradient across the inner mitochondrial membrane. In cellular biology research, these weakly acidic proton (H^+) ion carriers, also known as proton carriers, are commonly used to induce mitophagy. Typical proton carriers include carbonyl cyanide chlorophenylhydrazone, carbonyl cyanide para-trifluoromethoxyphenylhydrazone, and 2,4-dinitrophenol. Carbonyl cyanide chlorophenylhydrazone, an early drug used to induce mitophagy, is highly toxic and causes non-physiological mitochondrial damage, especially in neurons. Mitochondrial toxins such as valinomycin and salinomycin, which are K^+ ion carriers, also induce mitophagy. Valinomycin, a respiratory chain inhibitor, triggers mitophagy by promoting K^+ influx and lowering mitochondrial membrane potential, while salinomycin induces mitochondrial K^+ efflux and H^+ influx (Managò et al., 2015; Xiong et al., 2020). Additionally, metal complexes designed to target mitochondria can

effectively overcome resistance mechanisms and trigger cell death programs (Lu et al., 2023). One significant metal complex is an iron chelator, which binds to free iron ions, leading to iron deficiency and subsequently inducing mitophagy (Allen et al., 2013). Additionally, Urolithin A is a novel enhancer of mitophagy that induces this process both *in vitro* and *in vivo* (Ryu et al., 2016). Ligustilide, a natural compound extracted from Ligusticum chuanxiong and Angelica sinensis, promotes mitophagy through the PINK1/Parkin pathway and mitigates neuronal damage following cerebral ischemia-reperfusion injury (Liu et al., 2022).

Mitophagy inhibitors

Currently, several pharmacological agents, including 3-methyladenine, bufloxacin A1, and chloroquine, are used as mitophagy inhibitors. Although commonly employed to investigate the role of mitophagy in ischemia-reperfusion injuries, these drugs have limitations in terms of selectivity and specificity. For example, 3-methyladenine, a non-selective PI3 kinase inhibitor, is widely used but it blocks all forms of macroautophagy by preventing autophagosome formation. Mitochondrial division, a prerequisite for mitophagy, is regulated by Drp1. Mitochondrial division inhibitor 1, a compound targeting Drp1, regulates its conformational changes (Xu et al., 2021). This inhibitor reduces blood–brain barrier disruption and cell death in traumatic brain injury by correcting autophagy dysfunction and suppressing mitophagy activation (Wu et al., 2018). ULK1, a homolog of yeast ATG1, is a kinase that initiates autophagy by activating the ULK1 complex. This activation triggers the recruitment of the VPS34 complex, which generates phosphatidylinositol 3-phosphate, a key molecule in autophagosome formation (Wong et al., 2013). IGS2.7, a regulator that inhibits ULK1 expression, plays a role in controlling mitophagy (Maestro et al., 2022). Analogue 6, a potent inhibitor of autophagy and mitophagy, selectively enhances autophagy flux while preventing the fusion of autophagosomes with lysosomes (Maestro et al., 2022).

Natural mitophagy inhibitors also exist alongside chemically synthesized small-molecule mitochondrial inhibitors. Quercetin, a polymethoxyflavone found in citrus peels, has anti-inflammatory, antiviral, antioxidant, and anti-atherosclerotic properties (Lu et al., 2023). It enhances mitochondrial function in bronchial epithelial cells by suppressing mitophagy (Son et al., 2018). Liensinine, a recently identified mitophagy inhibitor, is a plant-derived isoquinoline alkaloid that is effective in treating cardiovascular diseases. It mitigates doxorubicin-induced cardiac dysfunction and cell apoptosis by preventing excessive mitochondrial division via Drp1 inhibition (Liang et al., 2020). **Table 2** summarizes drugs associated with mitophagy regulators.

Role of Activated Mitophagy in Spinal Cord Ischemia-Reperfusion Injury

In recent years, despite advances in clinical and basic research, neuronal regeneration disorders following SCIRI remain a major barrier to restoring neurological function. Mitochondrial injury is a key factor driving neuronal loss in SCI. Such damage disrupts the mitochondrial quality control system, causes an imbalance in mitochondrial dynamics, and triggers excessive mitophagy, leading to neuronal cell death. The spinal cord is particularly vulnerable to ischemia-reperfusion injury, and mitochondria have become critical targets for therapeutic intervention. SCIRI activates mitophagy through multiple signaling pathways (Anzell et al., 2018; **Figure 6**). Mitophagy, when balanced with mitochondrial biosynthesis, supports the energy demands of the central nervous system. Under moderate hypoxia, selective removal of damaged mitochondria via mitophagy protects neurons by preventing the accumulation of dysfunctional organelles. Rapamycin significantly promotes mitophagy by increasing the recruitment of p62 and Parkin to damaged mitochondria, blocking Bax translocation to mitochondria, reducing cytochrome c release, and lowering levels of apoptosis-related mitochondrial proteins. These effects collectively alleviate SCIRI, leading to improved motor function (Li et al., 2018). Additionally, mild acidosis through acid post-treatment enhances ischemia-reperfusion injury-induced mitophagy via a PARK2-dependent pathway, reducing ischemic damage and extending the reperfusion window (Shen et al., 2017). GPCR kinase 2-interacting protein-1 regulates Beclin-1 phosphorylation at Thr119, promotes Parkin translocation to the mitochondrial outer membrane, enhances mitophagy, and protects neurons from ischemia-reperfusion injury. This protein may become a key focus for developing therapies to protect against ischemia-reperfusion injury (Huang et al., 2020). Recent studies have demonstrated that mesenchymal stem cells can transfer healthy mitochondria to neurons after SCI, where these mitochondria fuse with the neuronal mitochondrial membrane, restoring homeostasis and inhibiting mitochondrial division and autophagy (Yao et al., 2023). Therefore, targeted mitophagy holds potential as a therapeutic approach for SCIRI.

However, prolonged ischaemic injury increases the accumulation of dysfunctional mitochondria and triggers excessive mitophagy, leading to irreversible cellular damage (Jendrach et al., 2008). This indicates that mitophagy can harm the central nervous system, partly owing to neuronal ATP depletion. A controlled or moderate increase in mitophagy is protective; however, when upregulated excessively, it becomes maladaptive and harmful (Sciarretta et al., 2011). Mitophagy is a complex process regulated by multiple molecules and receptors, influencing various biological functions. Maintaining a balance between mitophagy and mitochondrial biogenesis is essential for proper mitochondrial function. Since mitophagy can act as a double-edged sword, both inadequate removal of damaged mitochondria and excessive degradation of functional mitochondria can result in neuronal cell death. Some scientists suggest that mitochondrial quality control operates at an equilibrium point, with mitophagy serving as the balancing mechanism. If a threshold can be identified where mitophagy removes dysfunctional mitochondria while preserving enough ATP to repair damaged cells, regulating mitophagy could become a promising therapeutic strategy (Anzell et al., 2018). Consequently, further research is necessary to determine whether the role of mitophagy in SCIRI is beneficial or detrimental, alongside exploring the potential pathogenesis and exogenous manipulation of SCIRI (Yang et al., 2018). **Table 3** schematically represents the effects of mitophagy during spinal cord ischemia-reperfusion injury.

Considerations and Future Directions

Mitophagy is a highly complex process primarily activated through pathways including PINK1/Parkin, NIX, BNIP3, FUNDC1, and lipid receptor pathways. The interactions among these pathways, particularly how the PINK1/Parkin pathway influences the Nix pathway and how PGAM5 and FUNDC1 interact with the PINK1/Parkin pathway, necessitate further investigation to uncover these complex interrelationships. Additionally, newly identified pathways, including the regulation of GPCR kinase 2-interacting protein-1 and the downregulation of the miRNA-124 induction pathway, warrant further research. Developing novel therapeutic strategies to reverse SCIRI remains a crucial priority. Although no FDA-approved drugs directly target mitochondria, several of the mentioned modulators have potential as drug targets. These modulators regulate mitochondrial function, biogenesis, fusion, division, and autophagy, thereby providing neuroprotective effects against SCIRI. Furthermore, exercise activates mitophagy, removes damaged mitochondria, stimulates mitochondrial biosynthesis, and improves mitochondrial function across various tissues (Memme et al., 2021). Mitochondrial transfer—the process of transferring functional mitochondria to damaged neurons—has gained attention and requires further investigation. With the growing interest in mitophagy research, the use of mitophagic pathways in SCIRI treatment is expected to expand and advance. However, current research on the mechanism of mitophagy in SCIRI remains limited, and this review may not fully capture it. More research on mitophagy in SCIRI is needed.

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Table 2 | **Drugs associated with mitophagy modulators**

Classification	Pharmaceutical	Target of action	Mechanism	Disease	Advantage or limitation	Reference
Targeting small molecule mitophagy inducers	Kinetin triphosphate	PINK1	Enhances the biological activity of PINK1 kinase	No application at present	The affinity for PINK1 is higher than that of the natural substrate, ATP	Hertz et al., 2013
	Kinetin	PINK1	As a precursor of KTP, it enhances the kinase activity of PINK1	Mainly employed for preventing and treating liver fibrosis	Does not affect the stability of PINK1 under resting conditions	Lu et al., 2023
	Pifithrin-α	P53	Effectively inhibits P53 and prevents its binding to Parkin	Has a protective effect on the central nervous system	Low specificity	Hoshino et al., 2013
	Vine Yellow Flavonoids B	PINK1	Regulating Parkin translocation and activation by stabilizing PINK1	Provides a protective effect against cerebral ischemia-reperfusion injury	Has a stabilizing effect	Wu et al., 2021b
	MTX115325	USP30	Inhibits USP30, thereby promoting ubiquitination	No application at present	Low specificity	Fang et al., 2023
	Resveratrol	SIRT1	Activates SIRT1	Antioxidant and anti-tumor	Induces non-selective autophagy with low specificity	Yang et al., 2019
	ADTL-SA1215	SIRT3	Activates SIRT3	Anti-tumor	Induces non-selective autophagy with low specificity	Zhang et al., 2021
	Rapamycin	mTOR	Inhibits mTOR expression and upregulates Beclin1 and phosphorylated Akt	Used to treat patients with kidney transplants and prevent rejection reactions following organ transplantation	Induced nonselective autophagy with low specificity	Zhang et al., 2020
	Antimycin A	Respiratory complex III	Reduces MMP and increase ROS by inhibiting respiratory complex III	Anti-tumor	Limited effectiveness when used alone	Cai et al., 2012; Ashrafi et al., 2014
Non-targeting small molecule mitophagy inducers	CCCP	–	Proton mediated dissipation of MMP	No application at present	Low specificity, high toxicity	Narendra et al., 2008
	FCCP	–	Proton mediated dissipation of MMP	Has a cardioprotective effect	Low specificity, high toxicity	Brennan et al., 2006
	DNP	–	Proton mediated dissipation of MMP	Accelerates fat burning and aids in weight loss	Low specificity, high toxicity	Shrestha et al., 2021
	Valinomycin	–	Dissipation of MMP increases the permeability of the mitochondrial inner membrane to K^+	Antibacterial and antiviral	Inducing PINK1 activation, leading to Parkin Ser65 phosphorylation	Managò et al., 2015; Xiong et al., 2020
	Urolithin A	–	Dissipation of MMP	Anti-tumor	Readily available	Ryu et al., 2016
	Ligustilide	–	Upregulating PINK1/Parkin pathway	Has neuroprotective effects	Multiple pharmacological effects with significant practical applications	Mao et al., 2022b
Small molecule mitophagy inhibitors	3-MA	–	Inhibiting the activity of PI3K	Anti-tumor effect	Controversy regarding its role in the nervous system	He et al., 2022
	Mdivi-1	–	Inhibiting the activity of Drp1	Anti-inflammatory and antioxidant stress	Low specificity	Wu et al., 2018
	IGS2.7	–	Inhibition of ULK1 expression	Anti-inflammatory, antioxidant, and anti-tumor	Readily available	Wong et al., 2013
	Analogue6	–	Increases autophagic flux while blocking the fusion of autophagosomes and lysosomes	Anti-tumor	High toxicity	Maestro et al., 2022
	Quercetogetotin	–	Inhibits the expression of p-DRP1 and- PINK1	Anti-inflammatory, antiviral, and antioxidant	Readily available	Lu et al., 2023
	Liensinine	–	Inhibits Drp1-mediated mitochondrial fission	Provides a protective effect against cardiovascular disease	No toxicity	Liang et al., 2020

ADTL-SA1215: SIRT3 compound 33c; Akt: V-akt murine thymoma viral oncogene homolog; CCCP: carbonyl cyanide m-chlorophenyl hydrazone; DNP: 2,4-dinitrophenol; Drp1: dynamin-related protein 1; FCCP: carbonyl cyanide p-trifluoromethoxyphenylhydrazone; 3-MA: 3-methyladenine; Mdivi-1: mitochondrial division inhibitor 1; mTOR: mechanistic target of rapamycin; MMP: mitochondrial membrane potential; PI3K: phosphatidylinositol-3 kinase; PINK1: PTEN induced kinase 1; SIRT1/3: sirtuin 1/3; ULK1: unc-51-likeautophagyactivatingkinase1; USP30: ubiquitin specific protease 30.

Table 3 | **The role of mitophagy in spinal cord ischemia-reperfusion injury**

In vivo/*in vitro*	Model	Ischemia-reperfusion time	Intervention	Evidence of mitophagy	Mitophagy inhibitor	Mitophagy change and effect	Neuron cell damage	Reference
In vivo (rat spinal cord)	Clamp aortic arch	14 min I/6, 12, 24, 28 h R	microRNA-124	Beclin-1↑, LC3-II↑,	3-MA	↑Protection	Cell apoptosis↓	Liu et al., 2017
In vivo (mouse spinal cord)	Clamp abdominal aorta	45 min I/4–6 h R	Git1$^{-/-}$	Beclin-1↓, LC3-II↓, P62↑		↓Damage	Cell apoptosis↑	Huang et al., 2020
In vitro (HEK 293T cells)	OGD/R	1 h I/0–6 h R	si-Git1	Beclin-1↓, LC3-II↓, P62↑, Parkin↓	CCCP	↓Damage	Caspase-9↑ Cell apoptosis↑	Huang et al., 2020
In vivo (mouse spinal cord)	Clamp aortic arch	10 min I/24 h R	Rapamycin	P62↑, Parkin↓		↑Protection	Bax↓ Cytosolic cytochrome c↓ Apaf-1↓ Caspase-3↓ Caspase-9↓	Li et al., 2018
In vivo (mouse spinal cord)	Clamp aortic arch	10 min I/1, 3, 7, 14 d R	Salidroside	PINK1↑, Parkin↑, autolysosomes↑		↑Protection	Cytosolic cytochrome c↓ Cell apoptosis↓	Gu et al., 2020
In vitro (primary spinal neurons)	OGD/R	30 min I/12 h R	Salidroside	LC3-II↑, P62↓, TOMM20↓, PINK1↑, Parkin↑	Mdivi-1	↑Protection	ΔΨm↑ Bcl-2/Bax↑ Caspase-3/caspase-9↓ Cytosolic cytochrome c↓ Cell apoptosis↓	Gu et al., 2020

CCCP: Carbonyl cyanide m-chlorophenyl hydrazone; LC3: microtubule-associated protein 1 light chain 3; Mdivi-1: mitochondrial division inhibitor 1; OGD/R: oxygen-glucose deprivation/reperfusion; p62/SQSTM1: p62/sequestosome1; PINK1: PTEN induced kinase 1; TOMM20: translocase of outer mitochondrial membrane 20.

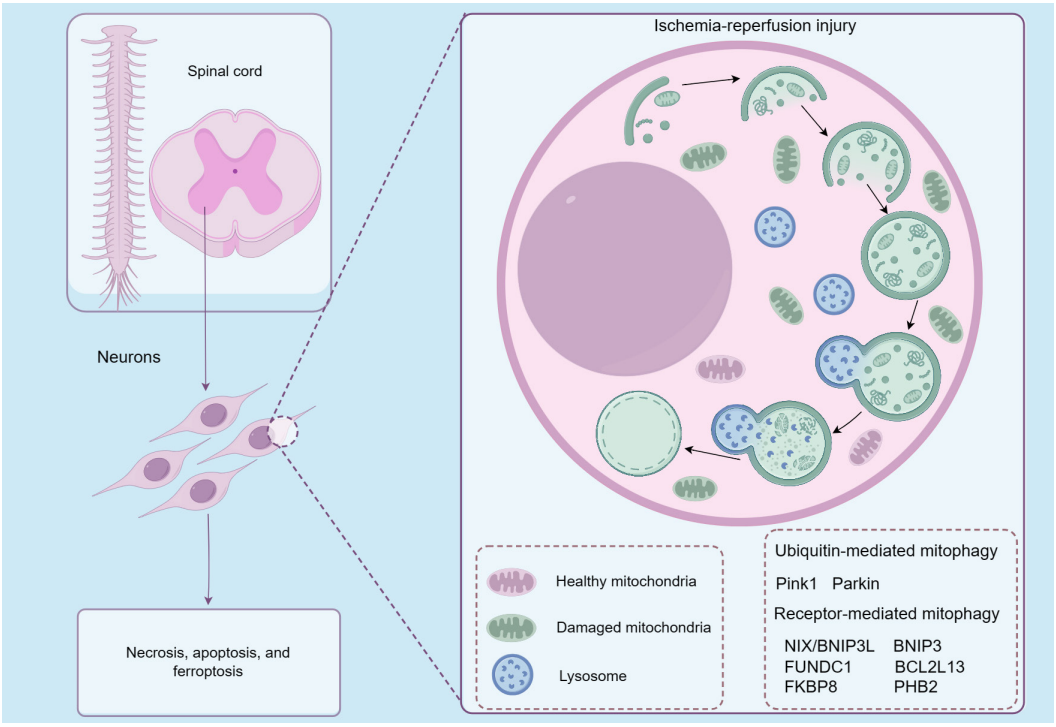

Figure 6 | **Schematic diagram of mitophagy occurring in neuronal cells in SCIRI.**
Following SCIRI, neurons undergo mitophagy, which primarily involves ubiquitin-dependent and ubiquitin-independent pathways. When mitophagy is activated, phagocytic vesicles first form, then gradually elongate and fuse to create double-membrane structures called autophagosomes. These autophagosomes bind to lysosomes and fuse via the microtubule network to form autolysosomes, which have digestive and degradation capabilities. The resulting degradation products are recycled for cellular use. Following SCIRI, cell death can occur through necrosis, apoptosis, or autophagic cell death. Created with Figdraw (www.figdraw.com). BCL2L13: B-cell lymphoma 2-like 13; BNIP3: BCL2 and adenovirus E1B 19-kDa-interacting protein 3; BNIP3L/NIX: Nip3-like protein X (NIX)/BNIP3-like protein; FKBP8: FK506-bindingprotein8; FUNDC1: FUN14 domain-containing protein 1; PHB2: Prohibitin 2; SCIRI: spinal cord ischemia-reperfusion injury.

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线粒体自噬在脊髓缺血再灌注损伤中的作用
文章特色分析

一、文章重要性
1. 临床问题的紧迫性
- 脊髓缺血再灌注损伤是脊髓手术、胸腹主动脉手术等常见并发症，可导致感觉与运动功能障碍，甚至永久性瘫痪，目前缺乏有效治疗手段。
- 文章指出，SCIRI 导致的术后神经功能障碍发生率为 9%–16%，永久性截瘫率为 0.3%–6.5%，凸显其临床重要性。
2. 聚焦关键病理机制
- 文章聚焦于线粒体功能障碍作为 SCIRI 的核心病理环节，并深入探讨线粒体自噬在其中的双重作用（保护性与破坏性），为理解该疾病的分子机制提供了系统视角。
3. 为治疗策略提供新方向
- 通过系统梳理多种线粒体自噬通路（如 PINK1/Parkin、BNIP3/NIX、FUNDC1 等）及其调控因子，文章为开发靶向线粒体自噬的药物或干预手段提供了理论基础。
二、文章创新性特色
1. 系统性综述多种线粒体自噬通路
- 不仅涵盖经典的 PINK1/Parkin 通路，还详细介绍了受体介导的线粒体自噬（如 BNIP3L/NIX、BNIP3、FUNDC1、BCL2L13、FKBP8、PHB2 等）以及脂质受体介导的线粒体自噬（如心磷脂、神经酰胺）。
2. 强调“适度自噬”的双刃剑作用
- 文章明确指出，适度线粒体自噬具有神经保护作用，而过度自噬则导致细胞死亡，提出“平衡调控”是未来治疗的关键。
3. 整合调控因子与药物研究进展
- 系统总结了多种调控线粒体自噬的小分子药物（如 Kinetin、Rapamycin、Urolithin A 等）及其作用机制，为转化医学研究提供候选分子。
4. 提出未来研究方向与治疗潜力
- 文章指出线粒体自噬通路之间的交叉调控、新型受体（如 GPCR kinase 2-interacting protein-1）的作用、以及线粒体移植等前沿方向，具有前瞻性。
三、对学科的启示
1. 推动神经再生与线粒体医学交叉研究
- 本文将线粒体质量控制机制与脊髓损伤修复紧密结合，促进了神经科学、细胞生物学与代谢医学的交叉融合。
2. 为精准调控自噬提供理论依据
- 文章强调“动态平衡”理念，提示未来治疗不应简单“激活”或“抑制”自噬，而应实现时空与程度上的精准调控。
3. 促进靶向线粒体的药物研发
- 通过系统梳理线粒体自噬的调控网络与药物靶点，为开发神经保护类药物提供了新思路，尤其针对缺血再灌注类疾病。
4. 启发多通路协同治疗策略
- 文章提示单一通路干预可能不足，未来需探索多通路协同调控（如 PINK1/Parkin 与 FUNDC1 的交互作用），以实现更有效的神经修复。
总结：本文是一篇具有高度系统性、前瞻性和转化潜力的综述，不仅深化了对脊髓缺血再灌注损伤机制的理解，也为开发针对线粒体自噬的神经保护策略提供了重要理论支撑和方向指引。其在机制梳理、靶点挖掘与治疗思路创新方面均表现出显著特色，对神经再生与线粒体医学领域具有重要推动意义。