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OVERVIEW

Mitophagy in Ischaemia/Reperfusion Induced Cerebral Injury

Kangyong Liu · Yinyi Sun · Zhaohua Gu · Nan Shi · Ting Zhang · Xiaojiang Sun

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Abstract Mitochondrial autophagy (Mitophagy), the specific autophagic elimination of mitochondria, has been related with several forms of degenerative disease and mitochondrial dysfunction. It is involved in multiple cellular processes. In addition to one of its established key roles in the maintenance of normal cellular phenotype and function, there is growing interest in the concept that targeted modulation of mitophagy may reduce cerebral ischaemia/reperfusion injury. Induction of mitophagy results in selective clearance of damaged mitochondria in cells. In response to stress such as ischaemia/reperfusion, prosurvival and prodeath pathways are concomitantly activated in neuronal cells.

Keywords Autophagy · Mitophagy · Ischaemia/reperfusion · Cerebral injury

Introduction

Autophagy, widely existing in eukaryotic cells, is a lysosomal degradation pathway with an astonishing number of connections to human disease and physiology. For example, autophagic dysfunction is associated with cancer, neurodegeneration, microbial infection and ageing [1, 2]. The ubiquitin–proteasome system (UPS) and autophagy-lysosome pathway (ALP) are the two most important mechanisms that normally repair or remove abnormal proteins. In contrast to the UPS, the major inducible pathway autophagy is likely to be the primary mechanism involved in the degradation of long-lived, stable proteins and is the only mechanism by which entire organelles such as mitochondria are recycled. Large membrane proteins and protein complexes that fail to pass through the narrow proteasome barrel can be degraded by autophagy [3]. Autophagy regulation is very complex. The mammalian target of rapamycin (mTOR), such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/PKB), adenosine triphosphate/adenosine monophosphate-activated protein kinase (ATP/AMPK), is involved in the occurrence and form of autophagy [4–6] (Fig. 1). mTOR, a negative regulator of autophagy, is a serine/threonine protein kinase which controls cells reaction when the nutrition conditions change and regulates many pathways of energy metabolism. mTOR is considered to be the regulatory mechanism of autophagy [7, 8]. 3-Methyladenine (3-MA), a special inhibitor of autophagy, can activate target of rapamycin (TOR) to reduce the occurrence of autophagy by inhibiting the PI3K pathway [9]. TOR kinase mainly inhibits autophagy through two mechanisms. One is that TOR can be the signaling cascade to control transcription and translation by the downstream factor, such as ribosomal p70S6 kinase (S6K1) and eukaryotic initiation factor 4E-binding protein 1(eIF-4E). The other is that TOR, in the role of autophagy-related proteins, can directly or indirectly influence the formation of autophagosome [10]. Regulation of autophagy in recent reports mainly focuses on mTOR dependence or independence pathways [11–13] (Fig. 1). Rapamycin activate macroautophagy by inhibiting

Kangyong Liu and Yinyi Sun contributed to this work equally.

K. Liu · Z. Gu · N. Shi
Department of Neurology, Shanghai Pudong New Area Zhoupu Hospital, Shanghai, People's Republic of China

K. Liu · Y. Sun · T. Zhang · X. Sun (✉)
Department of Neurology, Affiliated Sixth People's Hospital of Shanghai Jiaotong University, Yishan Road, Xuhui District, Shanghai 200233, People's Republic of China
e-mail: sunxj155@sohu.com

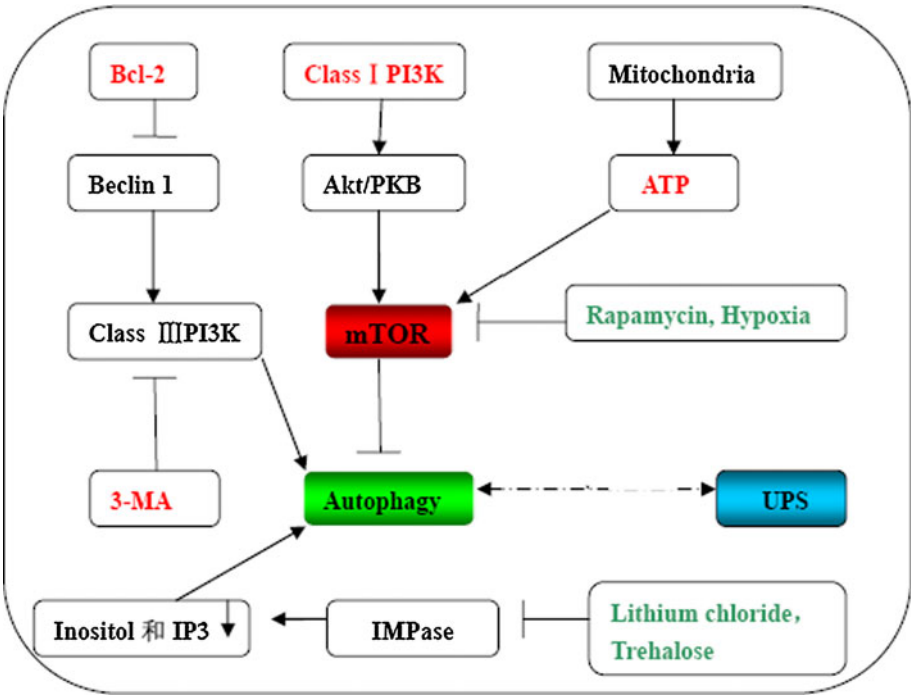

Fig. 1 Regulation pathways of autophagy

mTOR, the contra lateral site of autophagy [14]. Our latest research also confirmed that rapamycin is able to prevent the apoptosis of dopaminergic neurons following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced treatment, likely via activation of autophagy pathways. The rapamycin pretreatment may therefore be a promising protection effect [15, 16].

Concurrent mitochondrial elimination and autophagy in many systems has led to the proposal that autophagy is the main mechanism of mitochondrial turnover during development and under pathological conditions. The term mitophagy was coined to describe the selective removal of mitochondria by autophagy but the process itself is still contentious [17]. There is a delicate balance between life and death in the neuronal cells during stress such as ischaemia/reperfusion (I/R), and the final outcome depends on the complex cross-talk between these pathways [18]. In this review, we provide a brief review of the roles of mitophagy in cerebral I/R injury, and discuss the controversies and challenges in exploiting mitophagy as a therapeutic strategy.

The Concept of Mitophagy

Mitochondria have double membranes and are essential organelles involved with oxidative phosphorylation, calcium homeostasis, reactive oxygen species (ROS) management, and programmed cell death [19–21]. In normal mammalian brains, it has been shown that mitochondria have an average half-life of 10–25 days [22]. Mitophagy was first observed in mammalian cells by Lemaster [17, 23]. During starvation, mitochondrial turnover can be accelerated by an autophagic process specifically called mitophagy [23–25]. Mitophagy and macroautophagy can be separated not only based on their different triggers, molecular mechanisms, consequences, but also based on the mitochondrial morphologies that characterize them: mitophagy is preceded by organelle fragmentation, while autophagy is accompanied conversely by their elongation [26].

Mitophagy is controlled either in conjunction with general macroautophagy or selectively through specific mitophagy genes. As in yeast and in mammalian cells, mitophagy can be selective and specific. Youth protein 1 (Uth1p), ancient ubiquitous protein 1 (Aup1p) and autophagy-related 32 (Atg32) are necessary for mitophagy in yeast. Uth1p is a member of the so-called SUN family [27], which is required for the removal of excessive mitochondria during starvation [28]. In addition, Aup1p, one of a family of protein phosphatase homologs, is also required for efficient mitophagy in stationary-phase cells. Atg32 is a 59-kDa protein which is critical for its interaction with Atg8 and Atg11. Recent studies found that Atg11 is also required for mitophagy [29, 30]. It was found that Atg32 is phosphorylated after nitrogen starvation, and the phosphorylation of Atg32 is required for mitophagy [31]. High osmolarity glycerol response protein 1 (Hog1) is a mitogen-activated protein kinase in yeast. Deletion of either Hog1 leads to inhibition of Atg32 phosphorylation as well as mitophagy [32].

Mammalian homologues of Atg32, Uth1p, and Aup1p have not been found. NIP3-like protein X (NIX), unc-51-like kinase 1 (ULK1) and Parkin are three proteins that can signal specific mitophagy in mammalian cells. AMPK is activated in response to decreased intracellular ATP and then phosphorylates ULK1 and ULK2 (two Atg1 homologues) to activate both general macroautophagy and mitophagy [25, 33]. ULK1, a serine threonine kinase, is a critical regulator of mitochondrial and ribosomal clearance during the final stages of erythroid maturation. Thus, many more reticulocytes with normal/numerous mitochondria that retained normal membrane potential accumulated in ULK1 knockout mice. As with all the other studies that show specificity, expression of ULK1p was not essential for induction of macroautophagy in response to nutrient deprivation or for survival of newborn mice. It should be noted that eventually, ULK1−/− cells cleared their organelles. The authors implicate NIX in this process [34, 35]. Together, these data suggest that the Atg1 homologue ULK1 is a component of the selective autophagy machinery that leads to the elimination of organelles in erythroid cells. Unlike Atg1, it is not an essential mechanistic component of mitophagy in erythrocyte maturation [16, 31].

Some studies found NIX, which is a homologue of BCL2/adenovirus E1B interacting protein 3 (BNIP3), and a member of inducible BCL2 homology domain 3 families, is regulated by hypoxia. The induction of mitophagy by NIX is thought to be mediated by direct binding to microtubule-associated protein 1 light chain 3 (LC3) and gamma-aminobutyric acid receptor associated protein (GABARAP) [36, 37]. NIX could be involved in the maturation of immature red blood cells by mitophagy and potentially induce mitophagy through apoptotic signaling [17, 37]. NIX mitochondria were robustly filled with a loss of mitochondrial membrane potential ($\Delta\Psi$m)-dependent mitochondrial dye [17]. In mammalian cells, NIX is involved in mitochondrial clearance during erythrocyte maturation [25, 32].

Parkin is an E3 ubiquitin ligase, dysregulation of which is linked to Parkinson's disease and loss of neurons of the substantia nigra [37]. Upon mitochondrial damage, mitochondria-localized phosphatase and tensin homolog-induced putative kinase 1 (PINK1) recruits E3-ligase Parkin to mitochondria. Ubiquitinated mitofusins are then degraded by proteasome that is recruited to mitochondria together with p97. Mitofusin degradation blocks fusion events and mitophagy can be activated. At the same time, Parkin can polyubiquitinate voltage-dependent anion channel 1 (VDAC1) creating K27-linked Ub-chains that recruit p62. Binding of p62 to VDAC1 on the mitochondria and Atg8/LC3/GABARAP on the developing autophagosome, results in mitochondrial sequestration and removal by autophagic machinery [17, 32, 36, 37].

Regulators of calcineurin 1 (RCAN1s) are identified as regulators of mitophagy. Recent research demonstrates that induction of RCAN1-1L can cause dramatic degradation of mitochondria. The mechanisms of such degradation involve the adenine nucleotide translocator and mitochondrial permeability transition pore opening [38].

Attention to date has focused largely on the mitophagy programmed cell death in cerebral I/R. In the past few years, the evidence of mitophagy for cell function is critically examined [39]. The modulation of mitophagy mechanisms of neural cells has recently been implicated as well [17, 25, 26, 37, 40]. Mitophagy functions as an eneuronal protective response, favoring adaptation to stress by removing damaged mitochondria. In contrast, increased oxidative stress and apoptotic proteases can inactivate mitophagy, allowing for the execution of cell death [18] (Fig. 2).

Autophagy in Cerebral Ischaemia/Reperfusion

Hypoxia is involved in the ischemic stroke [41]. Autophagy is markedly activated after neonatal ischaemia. The amount of LC3-II increases and highly correlates with the

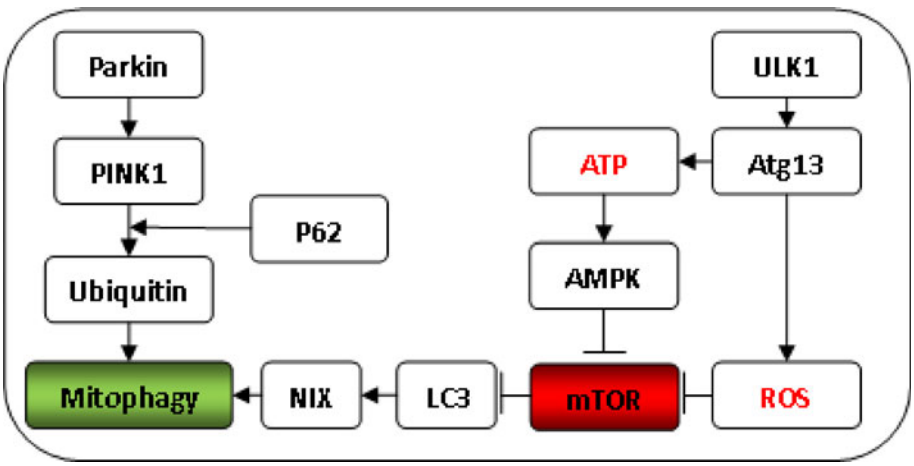

Fig. 2 Mitophagy in mammalian cells

number of autophagosome [42]. Beclin 1, a component of the PI3K complex that is required for autophagy and LC3, a microtubule-associated protein that is lipidated upon activation of autophagy, rapidly increase in cells of the injured side [43–45]. Furthermore, during reperfusion period in stroke and brain trauma, inflammation response occurs and causes injury. Because this reperfusion induced injury is involved in the brain's ischemic cascade and reintroduction of oxygen within cells may cause damage to cellular proteins, DNA, and the plasma membrane [46, 47]. Recent study found that rapamycin administration increases autophagy, decreases apoptosis and significantly reduces brain damage. After hypoxia–ischaemia, when autophagy is blocked neuronal cells rapidly progress toward necrotic cell death [48]. Rapamycin can reduce infarct volume, brain edema and motor deficits induced by permanent focal ischaemia and increase the protein levels of LC3-II and beclin [49]. In contrast, this increased cell death was inhibited by the specific autophagy inhibitor, 3-MA [47, 50]. 3-MA reduced the increased Beclin 1 expression, the neuroprotective effect of rapamycin without affecting Akt phosphorylation. However, both compounds significantly increased necrotic cell death. Taken together, these data indicate that in neonatal hypoxia–ischaemia autophagy can be part of an integrated prosurvival signaling which includes the PI3K/Akt-mTOR axis. When the autophagic or the PI3K/Akt-mTOR pathways are interrupted cells undergo necrotic cell death [48].

Mitophagy in Cerebral Ischaemia/Reperfusion

Ischaemia and reperfusion are two fundamental events that cause cerebral damage. Different mechanisms may take a lead in the evolution of brain injury: initiated by mitochondrial dysfunction, cellular injury, followed by the neuroinflammation [51]. Mitochondrial dysfunction is the key mechanism of cell damage in cerebral hypoxia–ischaemia and reperfusion. Neurons rely heavily upon mitophagy for normal development and function [52]. Neurons are particularly dependent on mitochondria, the power generators, for ATP production. These cells are more sensitive to mitochondrial dysfunction. Dynamic mitochondrial changes in their shape and populations are critical for normal cellular energy homeostasis. Many recent studies suggest that neuronal cell death is related to mitochondrial dysfunction in stroke [19, 53].

Mitochondria are the major sites of generation and action of ROS in brain cells [25]. Mitophagy is up-regulated in a neuroprotective effort to protect the nerve cells from excessive damage due to an accumulation of dysfunctional mitochondria [54]. $\Delta\Psi m$ appears to be a common feature of mitophagy. A damaged mitochondrion signals the autophagic machinery to remove it—perhaps via ROS production [17].

The different steps of mitophagy are regulated by Atg proteins. Mitophagy describes the engulfment of mitochondria into vesicles that are coated with the autophagosome marker mannosidase processing 1 (MAP1) LC3 [37]. Mitochondrial respiratory chain is increasingly recognized as a source for ROS in the postischemic tissue [51]. ROS activates the protease Atg4B, the enzyme that cleaves the c-terminus of LC3-I, an essential precursor to conversion of LC3I to LC3II. Via ROS production, the autophagic machinery is signaled to remove a damaged mitochondrion [55]. ROS, such as superoxide, hydrogen peroxide, and hydroxyl radical, attack proteins, lipids and nucleic acids and initiate peroxidation chain reactions, contribute to the reperfusion-driven oxidative stress and promote mitochondrial membrane permeabilization. The loss of mitochondrial membranes integrity during reperfusion is considered as the major mechanism of secondary energy failure [23, 51]. Mitophagy regulates mitochondrial number to match metabolic demand and might also be a form of quality control to remove damaged mitochondria [37]. Excessive or damaged mitochondria may generate ROS and release proapoptotic proteins to promote cell death [56]. Tracking multiple proteins in different steps of the mitophagy could be employed to evaluate relative contributions of I/R injury.

Mitochondrial fission protein dynamin-related protein 1 (Drp1) and fusion protein optic atrophy 1 (Opa1) were both upregulated in the ischemic penumbra. In contrast, both Drp1 and Opa1 showed progressive decreases in the ischemic core because of necrotic brain damage. The present study suggests that there was a continuous mitochondrial fission and fusion during these periods in the ischemic penumbra after hypoxia–ischaemia, probably in an effort toward mitophagy and cellular survival. A mitochondrial fission and fusion in the dying neurons, probably in an effort toward mitophagy and cellular survival [19].

Rapamycin and Propofol Regulate Cerebral Ischaemia/Reperfusion

Rapamycin, a lipophilic macrolide antibiotic, has been found to reduce injury in different models of neurodegenerative disorders. The neuroprotective effect of rapamycin was associated with increased autophagy and decreased caspase-3 activation because after rapamycin treatment there was a marked reduction of Bax and Bad translocation to mitochondria, cytochrome c release, and caspase-3 activation. The TOR pathway, which senses nutrient availability and environmental stress, has recently emerged as a major regulator of lifespan. The TOR complex 1

(TORC1) and its downstream effectors influence lifespan by regulating cellular metabolism and mitochondrial functions. TORC1 can regulate mitochondrial biogenesis and turnover through the Atgs. TORC1 influences the levels of mitochondrial ROS. Defects in the clearance of damaged mitochondria by TORC1-regulated autophagy also contribute to ROS accumulation [57, 58]. Rapamycin administered before I/R injury prevents the apoptotic signaling taking place through the mitochondrial pathway [59].

In another research, propofol reduced the I/R-induced death of cells. The prevention of neuron death by the inhibition of autophagy after hypoxic-ischemic injury has been documented to be dependent on an autophagy induction-related gene, Atg7. The present results indicate that a group of factors including class III PI3K, Beclin 1 and Bcl2 are also engaged in the neuroprotection of propofol against oxygen-glucose deprivation-induced damage in neuronal PC12 cells [60].

Conclusion

Mitophagy is the specific degradation of the mitochondria in response to global signals, including starvation and oxidative stress, or specific signals including mitochondrial targeting of signaling proteins or modification of mitochondrial proteins. As it is an essential cellular pathway to eliminate damaged or depolarized mitochondria to maintain the homeostasis of cells, the dysfunction of mitophagy is closely related to cerebral diseases. Mitophagy pathway can be activated after focal cerebral I/R. It may be a therapeutic strategy to protect the nerve cells by regulating the mitophagy pathway after cerebral I/R injury.

In recent years, the research of mitophagic molecular mechanism has made great progress. However, the regulation of mitophagy, especially a variety of interaction between promotion and inhibition, has limited information. Therefore, while in the study of autophagy has achieved some successes; there are still many unknown issues to be researched. We believe that we will have a deeper understanding of mitophagy eventually, and regulate mitophagy as targets for treatment. This will help the treatment of ischemic stroke.

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