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REVIEW

Autophagy and autophagy-related molecules in neurodegenerative diseases

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Abstract

Autophagy is one of the degradation pathways to remove proteins or damaged organelles in cells that plays an important role in neuroprotection. Different stages of autophagy are regulated by autophagy-related genes, and many molecules such as transcription factor EB (TFEB) are involved. The complete autophagy process plays an important role in maintaining the dynamic balance of autophagy and is crucial to the homeostasis of intracellular substance and energy metabolism. Autophagy balance is disrupted in neurodegenerative diseases, accounting for a variety of degeneration disorders. These impairments can be alleviated or treated by the regulation of autophagy through molecules such as TFEB.

KEYWORDS
autophagy, mitophagy, neurodegenerative, TFEB

1 | INTRODUCTION

Autophagy is the process by which cells degrade proteins or organelles through lysosomes. Intracellular proteins or organelles need to be cleared or renewed by autophagy or protease systems as the cells grow or are stimulated by external stimuli. Some small molecular substances or short-lived proteins are mainly degraded by the ubiquitin-proteasome pathway, whereas long-lived proteins or damaged organelles in the cytoplasm are degraded by the autophagy-lysosomal pathway.[1] Normally, autophagy mainly eliminates senescent organelles and macromolecular proteins that are difficult to clear by the proteasome system, which plays an important role in maintaining the intracellular homeostasis of energy and material metabolism.[2] In the 1860s, Duve et al. observed autophagy in hepatocytes. Then, in the 1980s, the signal pathway of autophagy was discovered in yeast cells.[3] Since then, autophagy has gradually become the focus of research, and the liver has become the main target for studying autophagy in mammals. Owing to its special relationship with blood supply, autophagy can be observed in hepatocytes under conditions of nutrient deficiency.

Thus, hepatocytes have always been an ideal material for studying autophagy under starvation conditions. Unlike the liver, the brain has priority in energy usage, which means it is difficult to observe neuronal autophagy even under starvation conditions.[4,5] Despite this difficulty, more and more studies have found that autophagy plays an important role in the development of nerve cells[6] and the function of synapses.[7,8] Abnormal levels of autophagy can cause damage to the nervous system, including autophagosome aggregation, neuronatrophy, mitochondrial depletion, and axonal and dendritic atrophy.[9,10] Neurodegeneration is the chronic progressive degeneration and loss of neurons in the brain and spinal cord, which can cause Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and dementia with Lewy body (DLB). Abnormal proteins accumulate in the brain of patients with neurodegenerative disease. Studies have shown that neurodegenerative diseases are closely related to abnormal autophagy function.

2 | AUTOPHAGY AND DEGRADATION

Autophagy can be divided into 3 types: microautophagy, chaperone-mediated autophagy, and macroautophagy. Microautophagy transports small molecules into the lysosomal cavity for degradation by endocytosis or budding of the lysosome itself.[11,12] Chaperone-mediated autophagy transports the target protein to lysosomes for degradation mainly by binding Hsc70 to LAMP2A on the lysosomal membrane.[13] When cells are stimulated by starvation or other stress, macroautophagy degrades most of the abnormal proteins or organelles. The autophagy described in this article refers to macroautophagy. The process of autophagy involves the formation of autophagosomes with bilayer membrane structure and the fusion and degradation with lysosomes.[6,14] Autophagosomes may be derived from the smooth endoplasmic reticulum and extend and mature under the action of ATG12-ATG5 complex and ATG8/LC3, forming a bilayer membrane structure with cytoplasm inside and outside. It is degraded and acidified by the inner membrane via endocytosis, and finally fuses with the lysosome to form a monolayer membrane of autophagosomes.[15,16] Therefore, the observation of double-layer or single-layer cell membrane structure under the ultrastructure is the gold standard for the observation of autophagosomes.[17]

Abnormal aggregation of proteins or mitochondrial damage[9,18,19] has been found in many neurodegenerative diseases, such as the aggregation of α-synuclein (α-syn) in PD,[20] and tangles of nerve fibers formed by β-amyloid and tau proteins in AD.[21,22] Abnormal aggregation of proteins can be degraded by proteasome or autophagy. The ubiquitin-proteasome system can only degrade proteins that are short-lived, are soluble, and can expand into the proteasome, and it is difficult to eliminate protein aggregates.[6] In contrast, the autophagy-lysosomal pathway can degrade abnormal protein aggregates, and even damaged mitochondria and other organelles.[23-25] When the function of proteasome or autophagy is impaired, a large number of abnormal proteins and damaged organelles accumulate in the cells, which disturbs the intracellular homeostasis of substance and energy metabolism (Figure 1). Studies have indicated that a mass of ubiquitinated protein inclusions was accumulated in the brain after the autophagy-related gene *ATG5/ATG7* was knocked out in mice.[26,27] More notably, the specific inhibition of autophagy in the mice brain can give rise to neurodegenerative diseases even without the accumulation of disease-related mutant proteins.

3 | REGULATION OF AUTOPHAGY

Autophagy-related genes (ATGs) regulate the autophagy process during different stages of autophagy.[28] Various molecules of ATG expression form different protein complexes to regulate the formation of autophagosomes, including induction of autophagy, generation of autophagosomes, expansion of autophagic vesicles, recognition and endocytosis of substrates, and clearance of autophagosomes[29-31] (Figure 2). In mammalian cells, mammalian rapamycin target protein complex (mTOR) can sense the level of amino acids and ATP in the cell and thus control the autophagy activity of the cell. When cells are suffering from starvation or external stimulus, mTOR is

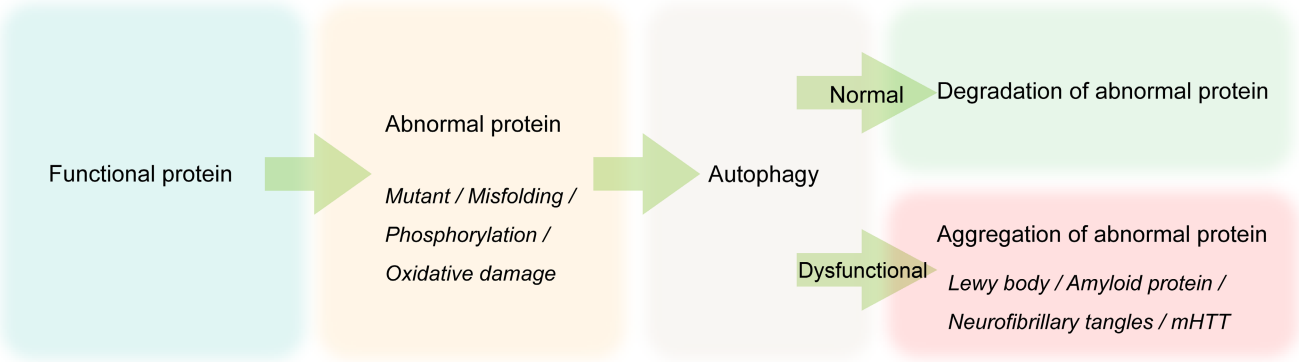

FIGURE 1 The role of autophagy in protein degradation

phosphorylated and autophagy is subsequently induced.[32] The formation of autophagosome is also known as the elongation stage, including the binding of ATG12 and the modification of LC3. Under the effect of E3 ligase, LC3-I is converted into LC3-II, binding to the forming autophagosomes.[33] Then cargos can combine with the autophagosomes through the LC3-interacting region (LIR), such as p62. The matured autophagosomes fuse with lysosomes to form autophagolysosomes, and finally, the combined cargos are degraded.[29]

Some important molecules are involved in the autophagy pathway, among which the TFEB is one of the important transcription factors regulating autophagy (Figure 3). Normally, TFEB binds to 14-3-3 protein in the cytoplasm[34-36] under the action of mTORC1 or MAPK1.[34-37] When cells are under stress due to starvation or impaired lysosomal function,[38] TFEB is activated by dephosphorylation and enters the nucleus to regulate the expression of lysosomal and autophagy-related molecules, thereby promoting the formation of autophagy and generation of lysosome.[36,39] A study found that upregulation of TFEB expression in PD can alleviate lysosomal collapse, autophagic vesicle accumulation, and the aggregation of α-syn in dopaminergic neurons, demonstrating an obvious protective effect.[40]

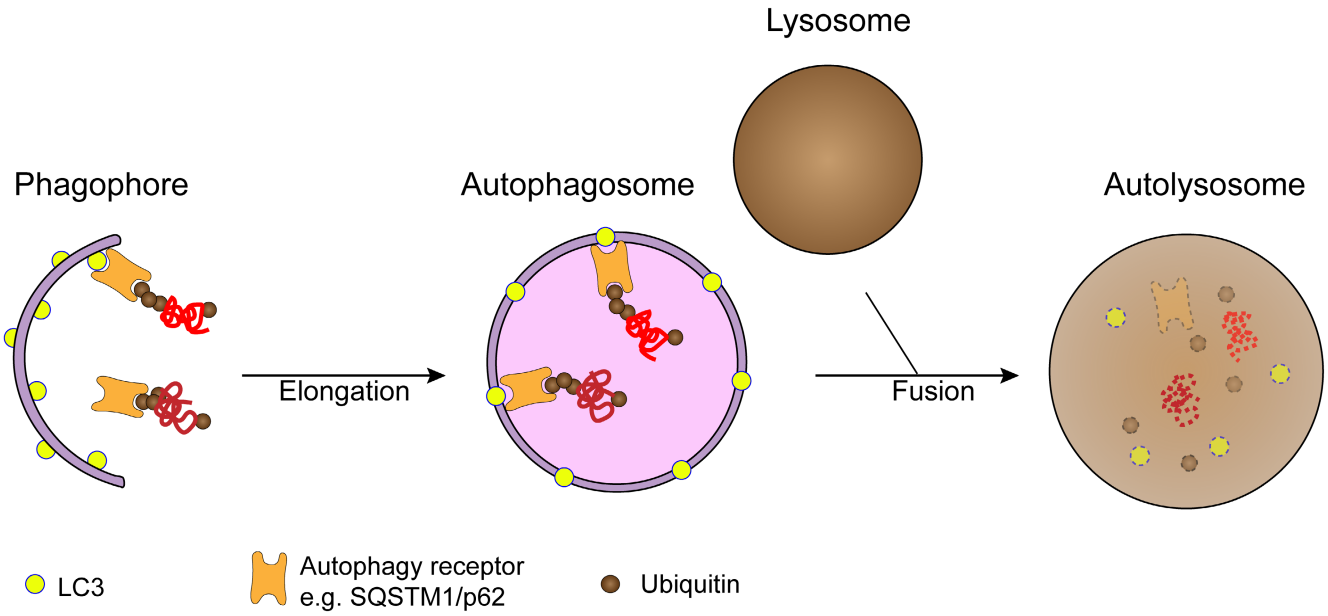

FIGURE 2 Different stages of autophagy

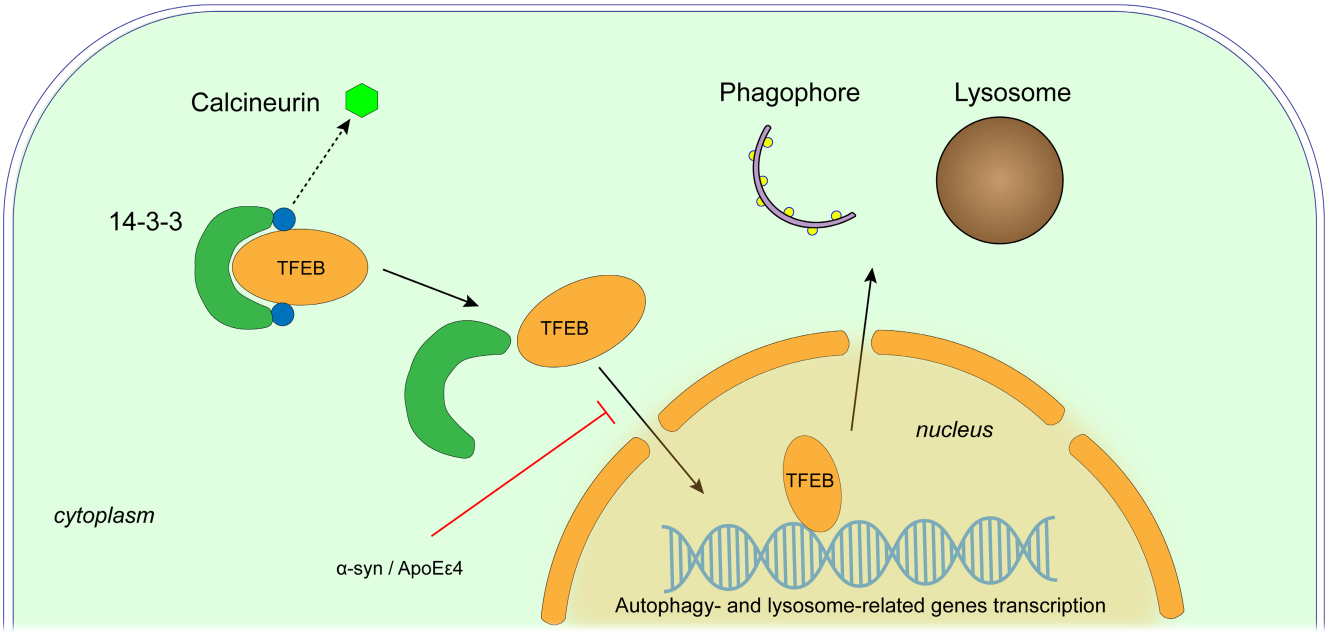

FIGURE 3 Regulation of TFEB in autophagy

Another study also showed that the activation of TFEB could rescue cells from the damage of injured mitochondria and reactive oxygen species (ROS).[41]

4 | MITOPHAGY AND NEURODEGENERATION

The damaged organelles in the cell are mainly degraded by selective autophagy, and the abnormal mitochondria in the neuron are mainly eliminated by mitophagy, to ensure the normal energy metabolism of neurons.[42,43] Mitophagy can be triggered by a variety of physiological or pathological factors.[6] In an animal model of PD, the mutation of PD-related gene *LRRK2* can cause mitochondrial damage and induce a mass of mitophagy in midbrain dopaminergic neurons.[44] Simultaneously, dysfunction of mitophagy is also observed, suggesting that abnormal mitophagy may play an important role in PD and other neurodegenerative diseases.[9,45,46,47,48,49,50]

4.1 | PINK1-parkin pathway

The damaged mitochondria can be labeled by ubiquitin and degraded and cleared through the PINK1-parkin pathway[51-53] (Figure 4). Impaired mitochondrial membrane potential decreases, leading to the accumulation of PINK1 protein in the mitochondrial outer membrane,[54-56] recruiting and activating the E3 ubiquitin ligase Parkin[57] by ubiquitin phosphorylation, ubiquitinating the mitochondrial outer membrane protein. It is further degraded by the ubiquitin-proteasome and autophagy pathway.[58,59] The ubiquitin-proteasome system also plays an important role in the degradation of mitochondrial outer membrane proteins, promoting the completion of PINK1-Parkin-mediated mitochondrial autophagy.[58] Some studies have found that TFEB is also involved in PINK1-Parkin-mediated mitochondrial autophagy after mitochondrial depolarization.[60] The recruitment of Parkin is regulated by TFEB, which is mTOR and ATG7 independent but requires the participation of ATG5 molecules,[60,61] and the specific process remains to be further studied.

4.2 | Other mitochondrial autophagy pathways

A variety of transmembrane receptors, including BNIP3L (Nix),[62,63] FUNDC1,[64,65] and FKBP8,[66] can mediate mitophagy through the non-PINK1-Parkin pathway (Figure 2). These transmembrane receptor proteins contain LIR domains that can bind to LC3 and induce mitochondrial autophagy.[6] In cortical neurons and neuroblastomas, the researchers observed mitophagy in the non-PINK1-Parkin pathway mediated by cardiolipin.[46] When the mitochondria are damaged, cardiolipin is exposed to the mitochondrial outer membrane from the inner membrane and directly interacts with LC3 to degrade the abnormal mitochondria through the autophagy pathway[46,67] (Figure 2). In addition to cardiolipin, ceramides and steroids also participate in the regulation of mitophagy.[68,69]

Thus, mitophagy-related molecules may play an important role in neurodegeneration. The dysfunction of mitophagy can induce neuronal damage. On the other hand, the regulation of these mitophagy-related molecules may attenuate the impact of mitochondrial dysfunction. Moreover, mitophagy-related molecules can be used to construct animal models of neurodegeneration disease.

5 | AUTOPHAGY HOMEOSTASIS AND NEURODEGENERATION

5.1 | The transport of autophagosomes in neurons

The entire autophagy process includes the formation, transport, and degradation of autophagosomes, and any abnormality in any of these steps will lead to autophagy dysfunction. Autophagosomes in neurons are mainly formed at the axon ends that are growing or have synaptic connections,[70,71] which is closely related to the synthesis and

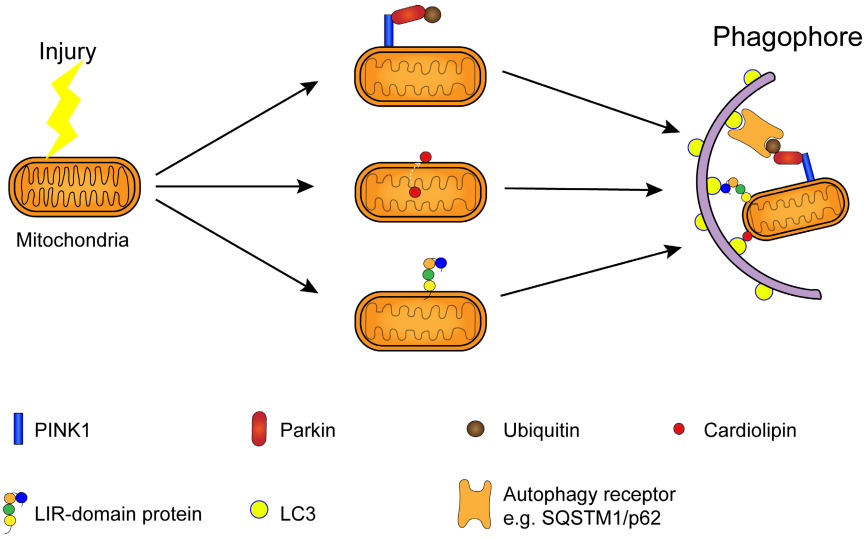

FIGURE 4 Mitochondrial autophagy mediated by different pathways

metabolism of synaptic vesicles.[5] The newly generated autophagic vesicles rapidly fuse with syntaxin-17 to obtain endolysosome markers LAMP1 and Rab17.[72,73] The vesicles are dependent on dynein to transport substances from the axon terminal to the nucleus via microtubules[74] and are degraded by fusion with lysosomes.[75,76] Studies have shown many neurodegenerative diseases to be associated with lysosomal dysfunction.[77-79] Researchers found a mass of lysosome accumulation in AD models,[73,80] suggesting that abnormal transport or degradation of autophagosomes and lysosomes may play an important role in degenerative diseases. Besides, TFEB has been shown to play an important role in the axonal transport of autophagosomes and lysosomes. Moreover, activated TFEB can transcribe lysosomal transmembrane proteins, which bind to dynein and exert a lasting effect on lysosomal transport.[76]

5.2 | Homeostasis in the process of autophagy

In normal autophagy process, the synthesis and degradation of autophagosomes are in a dynamic balance,[38] whereas in neurodegenerative diseases, multiple intermediate processes of autophagy process may be abnormal.[3,38,68,81,82] The decrease in transport, fusion, and degradation efficiency of autophagosomes and the increase in autophagy demand caused by continuous external stimulation all lead to an increase of intracellular autophagy pressure. Once the dynamic balance between autophagy synthesis and degradation is broken, autophagy stress will occur,[38] and induce abnormal autophagy. Thus, a large number of substances need to be transported between the neuron body and axon through microtubules. However, neurons are sensitive to energy changes. Even at a normal level of autophagy, energy depletion or Becin1/Bcl-2 imbalance may cause cell death when autophagy pressure increases.[83] The degeneration of dopaminergic neurons in the nigrostriatum of the midbrain in PD may be due to the autophagy stress resulting from damage to the neuron body or synapses.[38,44]

5.3 | Interference of abnormal proteins with autophagy homeostasis

On the other hand, abnormal proteins may interfere with autophagy homeostasis in some neurodegenerative diseases. In normal circumstances, the autophagy process can eliminate abnormally aggregated proteins or damaged organelles in cells, and play a protective role in nerve cells. However, cells are damaged or even killed by autophagy stress when the normal autophagy process is disturbed or inhibited.[38] At the same time, mutated LRRK2 or α-syn was shown to interfere with chaperone-mediated autophagy in some PD models.[84,85] The Jnk-Bcl-2 pathway was inhibited by E46K mutation,[86] which impaired the clearance of abnormal α-syn and damaged nerve cells. Besides, α-syn is structurally similar to the 14–3-3 protein, the chaperone of TFEB,[87] which binds to TFEB competitively and blocks TFEB entry into the nucleus, interfering with the entire autophagy process.[88,89] In AD, ApoEε4 competes with TFEB for the lysosomal protein promoter *SQSTM*, *MAP1LC3B*, *LAMP2*, leading to abnormal autophagy.[90,91] In neurodegenerative diseases such as PD and AD, the mutated molecules induce autophagy imbalance while causing structure damage, resulting in a vicious cycle and eventually leading to cell death. Therefore, the complete autophagy process plays an important role in maintaining the homeostasis of autophagy and is essential for the homeostasis of intracellular substances and energy metabolism.

6 | TREATMENT OF NEURODEGENERATIVE DISEASES BY REGULATING AUTOPHAGY

Abnormal autophagy is closely related to neurodegenerative diseases, and many studies have attempted to alleviate or treat neurodegenerative diseases by regulating the level of autophagy. Studies found that regulating the level of autophagy can alleviate or treat neurodegenerative diseases such as PD, AD, and HD.[6] In cell or animal models of HD, drug-induced autophagy reduces huntingtin accumulation and alleviates HD symptoms in mice and *Drosophila*.[92] In the APP transgenic mouse model of AD, it was found that injection of the lentivirus expressing Beclin1 into the brain significantly reduced the accumulation of amyloid in the brain of mouse models of early AD.[93] At the same time, *Becn1* with F121A mutation attenuated the inhibition of beclin1 by BCL-2, which reduced amyloid deposition and improved survival rate and cognitive function in *APP*/*PS1* transgenic mice.[94] Moreover, upregulation of *ATG7* expression in α-syn-overexpressing transgenic mice can decrease α-syn levels.[93]

Neuroprotection can be achieved by increasing the level of autophagy without causing autophagy stress. TFEB is involved in the regulation of autophagosome synthesis, transport, fusion, and lysosomal functions within the autophagy process, and may play an important role in the neuroprotective effects of autophagy. Therefore, TFEB is an ideal target for the treatment of neurodegenerative diseases.[39] Studies have found that upregulation of *TFEB* expression in tau-overexpressing rTg4510 model mice can reduce nerve fiber tangling and synaptic injury, and ameliorate neural behavior abnormalities.[94] In the human neuroblastoma cell BE-M17, upregulation of *TFEB* attenuates lysosomal collapse in the cytoplasm and reduces autophagic vesicles and α-syn accumulation simultaneously.[40] In vitro and in some rodent models, the therapeutic effect of TFEB on various neurodegenerative diseases such as PD and AD has attracted increasing attention. However, the protective effect of TFEB has not been confirmed in non-human primates. Thus, further research on TFEB is needed on the therapeutic effects of neurodegenerative diseases.

7 | CONCLUSION

Autophagy homeostasis is essential for the maintenance of normal cell function and is closely associated with the development of neurodegenerative diseases. As an important autophagy-regulatory

protein, TFEB is of great interest. More research on TFEB-related pathways and drug targets is needed.

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AUTHOR CONTRIBUTIONS

Changsong Dou wrote the paper. Professor Chuan Qin, Yu Zhang and Ling Zhang reviewed and edited the manuscript.

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