· Review ·

Study of progress of autophagy in glaucoma and retinal degeneration

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自噬在青光眼和视网膜退行性病变中的研究进展

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摘要

自噬是细胞的管家程序,是细胞维持内环境稳定的必需途径。主要通过移除错误折叠的蛋白和损伤的细胞器来实现目的。自噬途径涉及到人体多种疾病,包括肿瘤、神经退行性疾病以及传染性疾病。神经退行性疾病与许多眼部疾病的病理机制密切相关,比如青光眼以及年龄相关性黄斑病变。此外,眼内细胞持续暴露于各种应激因子中,可导致自噬的发生,自噬通过回收利用代谢前体细胞,或者促进受损细胞的死亡来提高整体存活率。自噬与凋亡也被证实在不同的实验环境中存在协同和拮抗作用,而这一切与许多疾病的病理机制息息相关。本文对自噬的机制及调控进行了回顾,并总结了较新的有关青光眼中视网膜神经元自噬的理论以及运用自噬的治疗手段。

关键词:自噬;青光眼;视网膜退行性病变

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Abstract

• Autophagy, a cellular housekeeping process, is indispensable to controlling the homeostasis of cytoplasm by removing unused proteins and damaged cell organelles. This process involves different types of human diseases, including cancers, neurodegenerative diseases and infectious diseases. Neurodegeneration is a critical pathological process of many eye diseases, such as glaucoma and age-related macular degeneration. The retina and all intraocular cells are constantly exposed to environmental stress and injuries, including oxidative stress and starvation, which lead to autophagy. Autophagy promotes cell survival through the recycling of metabolic precursors, or promotes cell death if autophagy is over-active. Additionally, autophagy and apoptosis have been shown to be harmonious or contrasting, depending on different experimental contexts. All of this contributes to the pathogenesis of many diseases. This paper reviews the mechanisms and regulation involved in autophagy, current understandings of neuronal autophagy in glaucoma and retina and strategies for therapeutic modulation.

• KEYWORDS: autophagy; glaucoma; retinal degeneration

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INTRODUCTION

Glaucoma is an optic neuropathy characterized by the progressive degeneration of retina ganglion cells (RGCs) and the optic nerve head, it leads to a restricted visual field, which is usually related to increased intraocular pressure (IOP), and subsequent retinal ischemia and neuronal death[1]. However, the mechanism of RGC death in glaucoma is not fully understood. Several recent studies indicate that autophagy is activated in RGCs and plays a crucial role in cell death in glaucoma[2-5].

Autophagy was previously reported to play an important role in both the regulation of autophagic cell death and neurodegeneration. It is a basal catabolic process that involves cytoplasmic homeostasis and controls the turnover and, removal of unused proteins, damaged cell organelles and molecules that produce amino acids when nutrients become limited[6]. Among the multitudinous types of autophagy, macroautophagy (hereafter referred to as autophagy) involves the rearrangement of subcellular membranes to form autophagosomes, which are then delivered to lysosomes through microtubules and form autophagolysosomes that degraded and recycle metabolic material[7]. Autophagy can be activated in response to different stressors, such as starvation, oxidative stress, the accumulation of misfolded proteins and hormonal signaling[8-9]. In some cells, over-active autophagy

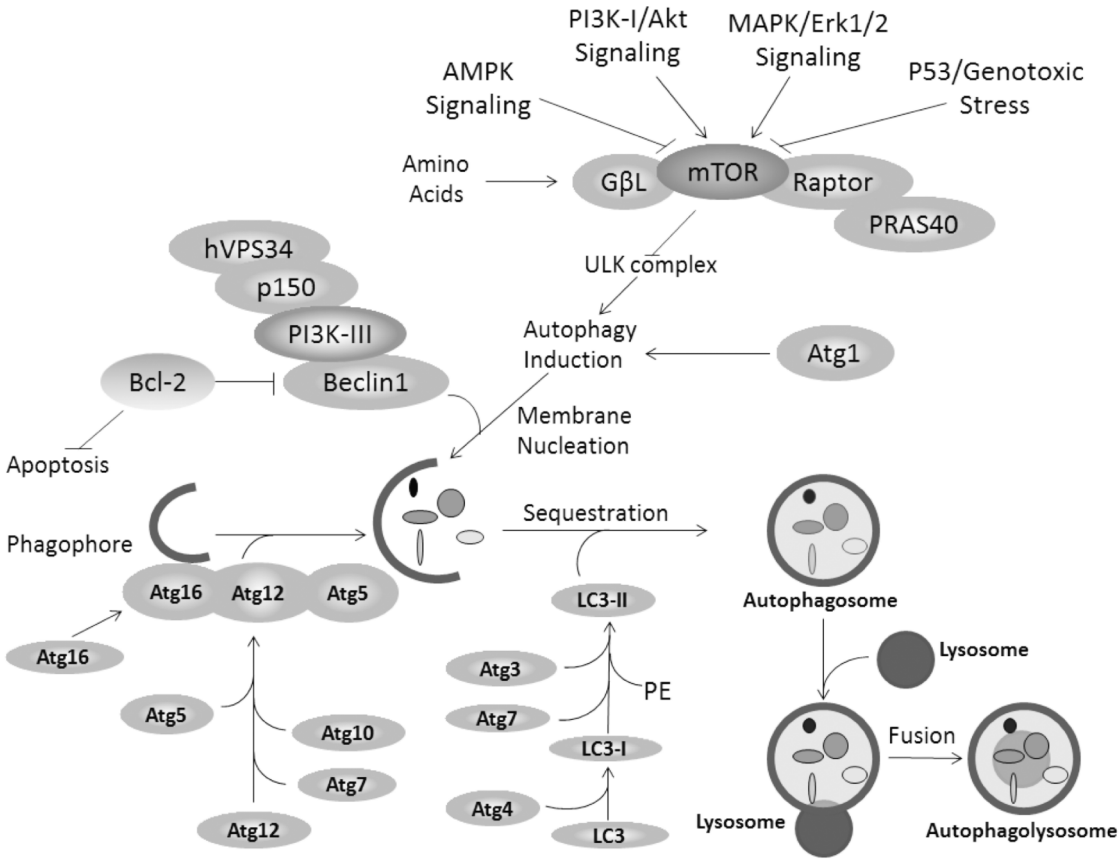

Figure 1 Autophagy is negatively regulated by the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway, which activates mammalian target of rapamycin (mTOR) in response to growth factors and also phosphorylates Beclin 1. The adenosine 5'-monophosphate-activated protein kinase (AMPK) negatively regulates mTOR thereby acting as a positive regulator of autophagy in response to AMP levels. mTOR resides in the mTOR signaling complex, which regulates the mammalian uncoordinated-51-like protein kinase (ULK1) complex. Atg1-ULK1 kinase complex is required for the induction of autophagy. Autophagy is also regulated by the Beclin 1 complex, consisting of Beclin1, class III phosphatidylinositol-3-kinase (hVPS34 or PI3K-3) and p150. Interaction of Beclin1 with the antiapoptotic Bcl-2 family proteins is also a critical aspect of autophagy regulation, resulting in inhibition of autophagy. Stimulation of the Beclin 1 complex triggers membrane nucleation. Autophagosome expansion, an early step in autophagy, involves insertion of LC3-II into vacuole membrane. This requires the ATG5-ATG12-ATG16 and LC3-PE conjugation systems, Atg7 (E1-like ubiquitin-activating enzyme), Atg3 (E2-like ubiquitin-conjugation enzymes), and other Atgs to work in concert to conjugate phosphatidylethanolamine to LC3-I, thus forming LC3-II. Atg12 binds to Atg5 followed by Atg16 binding to form the Atg5-Atg12-Atg16 complex. LC3-PE complex formation is initiated by cleavage of LC3 by Atg4, followed by coordinated interactions with the Atg7, Atg3. Lipid conjugation of LC3-I occurs from the action of Atg7 and Atg3 activities. The conversion of LC3-I (free form) to LC3-II (lipid-conjugated form) is a major step in autophagosome formation. The tumor suppressor protein p53 potentially interact with the autophagy machinery at the indicated sites.

due to stressors leads to cell death, which is called autophagic cell death or type II programmed cell death[10]. Autophagy is highly regulated by a number of evolutionarily conserved autophagy-related genes (Atg) and ubiquitin-like conjugation systems[7].

Here, we reviewed current understandings of autophagy in glaucoma and retinal degeneration induced by stressors, and focused on recent findings involving the role of autophagy in retinal tissues. These have allowed us to consider how autophagy contributes to glaucoma and retinal degeneration, both of the two items are correlative.

Signaling Mechanisms and Gene Regulation in Autophagy

The mammalian target of rapamycin (mTOR) pathway (Figure 1) has been widely studied as a critical signaling pathway of autophagy[11-12]. In nutrient-poor conditions, mTOR is inactive and autophagy is induced by alleviating mTOR phosphorylation of uncoordinated-51-like protein kinase 1 (ULK1) and Atg13[13]. Beclin-1 is a class Ⅲ phosphatidylinositol-3-kinase (PI3K) complex that participates in the early steps of the formation of autophagic vesicles and is essential to the recruitment of other Atg proteins to the preautophagosomal structure[14]. The interaction between Beclin-1 and antiapoptotic BH3 proteins, such as Bcl-XL and Bcl-2, is also a critical aspect of autophagy regulation that can influence autophagy and even mTOR independence[15].

Subsequent to the identification as part of the research of yeast, a number of critical Atg whose gene products regulate distinct steps in the induction or progression of autophagy have been identified[16-17]. The elongation of the autophagosome membrane requires the action of two ubiquitin-like conjugation systems, the Atg5-Atg12 conjugation system and microtubule-associated protein-1 light chain 3 (LC3, Atg8) conjugation system[18-19]. Atg4B converts the proform of LC3B

into its cytosolic free form (LC3-Ⅰ). In mammals, the conversion of LC3-Ⅰ (and other Atg8 homologues) into its phosphatidylethanolamine-conjugated and autophagosome-membrane associated form (*i. e.* LC3-Ⅱ) is an initiating step in autophagy[19].

Autophagy and Cell Survival in Retina Piras *et al* showed that autophagic retinal cell death increased in the ischemia/reperfusion (I/R) injury rat model as a result of acute IOP elevation, which had previously been proven to be involved apoptotic cell death[3-20]. An earlier study showed that retinal I/R increased both autophagic[21] and apoptotic cell death[22]. However, it has yet to be proven whether the autophagic response to ischemia is protective or detrimental to neurons. An experiment by Park *et al*[4] showed a marked accumulation of autophagosomes (APs) in the dendrites and cytoplasm of RGCs following IOP elevation. They then analyzed autophagosomes in the cytoplasm of RGCs in the ganglion cell layer (GCL) and in the dendrites of RGCs in the inner plexiform layer (IPL) separately. They also found that autophagosomes occasionally appeared in the cytoplasm of RGCs in the GCL prior to IOP elevation and the number of RGCs displaying APs in the GCL increased after IOP elevation. The different distribution of autophagosomes is not clear, but they represent cell layers with high metabolic demand and a propensity for mitochondrial damage[23]. Autophagy exists in normal cells and is vital to maintaining cytoplasmic homeostasis. Moreover it is rapidly upregulated in response to cellular stress. Some experiments have shown that autophagy protects cell survival. Research by Young *et al*[24] has demonstrated that apoptosis increases in starved circulation during the knockdown of the autophagy-related gene. Kim *et al*[2] induced autophagy in RGC-5 cells in vitro through serum starvation and assayed cell viability showed that autophagy promoted the survival of these cells. Rodríguez-Muela *et al*[5] demonstrated that autophagy in mice is activated a short time after optic nerve axotomy and serves a cytoprotective function. They also demonstrated that genetic downregulation of autophagy increased RGC death, whereas pharmacological upregulation of autophagy reduced RGC loss in vivo. The results of Park *et al*[4] demonstrate that autophagy is involved in RGC apoptosis and the inhibition of autophagy reduced RGC death after chronic IOP elevation in vivo. Mice deficient in the autophagy protein Atg5 are susceptible to the lethal effects of starvation[25]. Research by Russo *et al*[26] verified that Beclin-1 silencing reduces RGC-5 viability under starvation. They also showed that the inhibition of autophagy by pharmacological inhibitors or Beclin-1 silencing in RGC-5 increased cell death[26]. Sternberg *et al*[27] proved that 3-Methyladenine (3-MA), a type of autophagy inhibitor, also increased the rate of death of retina cells in the GCL in vitro. These studies suggest that autophagy promotes cell survival under stress.

The structure of the lamina cribrosa (LC) of the optic nerve head is disrupted in response to elevated IOP inprimary open angle glaucoma (POAG)[28]. Lipofuscin formation is related to reactive oxygen species (ROS)[29]. LC cells accumulated lipofuscin in eyes with glaucoma[30], which may alter autophagy activity in cells. In glaucomatous LC cells, autophagy markers are elevated[31]. In the future, anti-glaucoma strategies may aim to reduce oxidative stress and/or stimulate cellular degradation systems at the LC level.

Research has not only shown the positive effects of autophagy on retinal cells, but also demonstrated the negative effects of autophagy on inducing apoptosis in retinal cells. However, the tipping point between autophagy and apoptosis is unclear. Whereas basal levels of autophagy ensure the physiological turnover of old and damaged proteins and cell organelles, the massive accumulation of autophagic vacuoles may represent either an alternative pathway to cell death or an ultimate attempt by cells to survive by adapting to stress[32].

Autophagy and Apoptosis in the Retina Cell death is reliant, at least in part, on components of autophagic-lysosomal machinery[33]. Experimental evidence suggests that, once apoptosis has been activated, the effector molecules may restrain autophagy. For example, Beclin-1 may be cleaved and inactivated by caspases during the activation of apoptosis[34]. It has been observed that Atg12 and Atg4D play dual roles in autophagy/apoptosis regulation[35-36]. Piras *et al*[3] also observed that autophagy and apoptosis occurred in the same retinal cells. The fusion of autophagosomes and lysosomes, which are related to apoptosis, could be detected under a high magnification electron microscopy. Autophagy and apoptosis may not necessarily overlap and can occur independently or at disparate times. He also used 3-MA treatment to inhibit autophagy, thus preventing neuronal death following injury. Yet, 3-MA itself may affect cell death, so it is not enough to only use 3-MA to determine whether autophagy can induce apoptosis in cells. Park *et al*[4] demonstrated that autophagy is involved in RGC apoptosis and restraining autophagy reduced RGC death after chronic IOP elevation in vivo. Gorski *et al*[37] showed that multiple genes involved in apoptotic cell death also appeared to be regulated in autophagic cell death, upholding the view that these two processes can utilize common pathways or components of pathways. Certainly, autophagic and apoptotic pathways display common upstream signals and their functional relationship is complex[38]. An interesting finding from an experiment by Produit-Zengaffine *et al*[39] was that LC3BII, which presents autophagy, was first seen to increase in the early stages of recovery but did not persist until the late stages of recovery after retinal ischemia. Post-ischemic induction of autophagy as a result of intravitreal rapamycin treatment did not provide protection against the lesion induced by ischemic stress. On the contrary, the number of apoptotic cells increased following I/R in the retinas treated with rapamycin. This could mean autophagy plays a protective role in the earlier stages of stress, but then turn into an accelerator of apoptosis in later stages. It is generally recognized that, as a basal pathway, autophagy acts as a housekeeper to maintain the normal physiologic conditions. However, this process could spiral out of control and accelerate apoptosis by phagocytosing important organs, such as mitochondria.

RGCs areresponsible for transmitting visual information from the retina to the visual cortex of the brain. Because of the distance between the retina and brain, the long axons of RGCs must transport metabolites and organelles *via* axonal transport, a process that requires high energy. There are ample mitochondria in unmyelinated parts of axons that produce adenosine triphosphate (ATP), which is needed to generate the action potential of the brain. Therefore, interferences in axonal transport or mitochondrial function can have severe consequences for RGC function and viability[40-41]. It is generally recognized that IOP elevation may obstruct axonal transport, thus triggering apoptosis. Chronic IOP elevation results in the activation of autophagy, which is sustained after chronic IOP elevation. Autophagy increased soon after IOP elevation, which precedes significant RGC loss, and was sustained throughout the experimental period[4]. Other stressors may induce similar procedures.

Due to known molecular crosstalk between autophagy and apoptosis, it is still unclear if autophagy and apoptosis are cooperative or mutually exclusive processes. The distinctions between autophagy and apoptosis require additional research, as the two processes are not always mutually exclusive and may take place simultaneously.

Autophagy in Trabecular Meshwork Aqueous humor dynamics is a conventional outflow pathway gated by the trabecular meshwork (TM), which provides resistance to aqueous outflow. TM failling to maintain normal levels of aqueous humor outflow resistance could cause intraocular pressure to rise, and thus increasing the risk of developing glaucoma. Porter *et al*[42] hypothesized that TM cells would activate autophagy to allows cells to cope with and adapt to mechanical forces. Normal metabolism often generates ROS, which subjects TM cells to chronic oxidative stress. Liton *et al*[43] improved on this by showing that TM cells respond quickly to the accumulation of oxidized cross-linked materials by activating the degradation pathway of autophagy. The accumulation of mutated myocilin protein in the TM and Schlemm's canal, is thought to be related to POAG[44]. The point mutations of the myocilin gene tend to cause the protein misfold[45] which would normally trigger autophagy, and then restore balance to the outflow pathway. Autophagic clearance mechanisms may be dysfunctional in the TM tissue of glaucoma patients. All of these theories contribute to the reasonable argument that autophagy contributes to progression of glaucoma.

CONCLUSION AND PERSPECTIVE

At present, there are no effective treatments for most retinal degenerations. One approach to alleviate retinal cell death is to manipulate the mTOR signaling pathway and stimulate autophagy. An emerging consensus is that autophagy represents a double-edged sword, an alternatively protective and pro-survival mechanism, or is part of a pathway that leads to cell death. On the one hand, deficiencies or absences in the functions of autophagy may play a pathogenic role in human neurodegenerative diseases[46-48]. On the other hand, there is considerable cross-talk between the molecular regulation of autophagy and other regulated forms of cell death[32,49-50]. Therefore, it is important to decide whether to induce or inhibit autophagy during the treatment. Perhaps autophagy could be induced in earlier stages and inhibit autophagy in the later stages of the pathological process.

Higher resistance to aqueous humor (AH) outflow through the TM generates elevated IOP in POAG. Recent research indicated dysregulation of the autophagic pathway and autophagic response to oxidative stress in TM cells[51]. And dysregulated autophagic capacity could detrimental to outflow pathway tissue[42]. However, an insufficient amount of research has covered this, so it may be possible to discover the pathogenesis of glaucoma by studying autophagy in outflow pathway tissue.

Although numerous articles have focused on using drugs to modulate autophagy, it should be noted that there may be other ways, some of which could also be beneficial to health, such as gene therapy. Thus, future research, should focus on finding more genes closely related to autophagy and effective ways to control these genes.

Nevertheless, a number of questions remain to be answered: What is the origin of the autophagosomal membrane? What are the autophagy substrates in axon terminals, dendrites and synapses? How can autophagy be controlled at the appropriate time? With the progress that has been made in the last few years, it is likely that these and other important problems in the field of autophagy will be solved in the near future. Additional studies are needed to define the dynamic equilibrium between autophagy, apoptosis, necrosis, and other modes of cell death in the context of retinal disease pathogenesis[52]. Achieving this would lead to new and valuable therapeutic strategies for the prevention of glaucoma and other neurodegenerative diseases.

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