Progress of Autophagy Related Research in the Treatment of Ophthalmic Diseases

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Abstract: Autophagy is a process in which some organelles and proteins are wrapped by cells into specific membranes and then transported to lysosomes to degrade these membranes, ultimately degrading small molecules and energy. Autophagy can make cells have a certain tolerance to starvation, and remove damaged organelles and protein structure dislocation caused by cell aging, so as to balance the intracellular environment. Autophagy includes autophagy molecules, microactive autophagy and macrophage autophagy. The mechanism characteristics of autophagy itself have aroused the upsurge of relevant application research, and more and more diseases are related to it. This paper reviews the research progress of autophagy in novel clinical application of autophagy.

Keywords: Autophagy; Keratopathy; Retinal Diseases; RPE Degeneration; Glaucoma; RGCs Apoptosis

1. Instruction

Cell autophagy process mainly occurs in eukaryotic cells, make the cell without ribosome connected ER generate bilayer membrane, and these membrane structures will be to be cleared proteins, organelles to form autophagomes [1], these autophagy experience to lysosome, make the autophagy material to degradation, and then generate autophysosomes, complete the intracellular organelle update and cell metabolism process [2], is essential for maintaining cellular homeostasis under stressful conditions [3].

2. Discovery and application of autophagy characteristics in multiple domains

IL-13 in chronic inflammatory airway disease activates autophagy in epithelial cells of respiratory system and directly induces the cellular secretion of mucin and oxidative stress in chronic asthma and COPD. This finding is particularly important when analyzing an defined state of autophagy viability in epithelial cells of airway of asthma. The association of autophagy with AMPK and MTOR [4], the crucial molecules in the process of immune metabolism, serves as a promoting factor or inhibitor of inflammation of tumor and act on tumor developing, vascular growth, grade malignancy, and the likelihood of metastasis. Autopophagy-associated secretion can affect the tumor microenvironment, and plasma and possible monitoring of proteins that mediate autophagy in tumors can be treated as surrogate indicators of autophagy activity within tumor cells. In the field of neurodegeneration, although plenty of number of studies linking autophagy to neurodegenerative diseases[5], lacks convincing clues to link inflammation through autophagy[6]. Furthermore, Atg5-induced epithelial

autophagy prevents renal fibrosis by blocking G2/M resistance, which is an important host defense mechanism [7].

3. Discovery and application of autophagy in keratopathy

To effectively maintain the stability of corneal epithelial cells, the cilia generation and autophagy process play an unnegligible role and coordinate molecular involvement through E phA2. In order to strengthen the autophagy effect, rapamycin suppresses the negative regulator rapamycin target protein, thus alleviating the degree of TGFβI mutation, which shows that if the autophagy is insufficient, it is easy to cause the problem of corneal undernutrition. Some substances with toxic toxicity such as lithium metal and rapamycin can promote cellular autophagy in the form of substrate, which have significant effect in relieving and healing degenerative neurological diseases (8). In herpeskeratitis, autophagy is controlled by the rapid induction of HSV-1 infection through an innate immune response. In echanthamoeba keratitis, it was found that low concentrations (0.00125%) autophagy inhibitors can fully remove echanthamoeba cells while ensuring the relatively safe state of epithelial cells, which also provides a new way in the fields related to treating eye diseases.

4. Discovery and application of autophagy in retinal diseases

In treating retinal diseases, cell autophagy is important,and the regulation of autophagy is able to create an alternative therapeutic strategy for retinoid disorders. Targeted autophagy can prevent retinal cell death by inhibiting the process of apoptosis, to recover denatured proteins and organelles to rebuild the retina, increased clearance of denatured mitochondria, decreased oxidative stress induced by ROS, and decreased activity of retinal microglia has found that in diabetic retinal (DR) lesions, The density of RGCs decreased gradually with the prolongation of the disease. High glucose can cause autophagy in RPE. Age-related dysfunction in RPEs is noted to be a cause of retinal diseases. The inflammatory response to amyloid B induced RPE dysfunction may be mediated by SIRT6. Autopophagy regulated by SIRT6 may be a pro-inflammatory mechanism of amyloid-b induced RPE dysfunction. SIRT6 causes inflammation mainly by promoting macrophage.

Studies have shown that a significant number of mirnas targeting autophagy, small RNA molecules and epigenetic regulators have been found in AMD patients and in experiments. It opens up prospects for the application of autophagy targets in AMD therapy. The results also showed that autophagy was involved in the protective effect of H2S on apoptosis of retinal ARPE-19 cells induced by oxidative stress. These findings led us to discover the possibility of exogenous H_2S in treating AMD.

In addition, studies that upregulate basal autophagy by targeting the protein factor Rubicon could help to prevent RPE damage caused by aging and inflammation caused by photoinduced cell stress, oxidative stress under intermittent high-glucose conditions, induced RPE damage, and autophagy could be important in mitigating this process. Protein HMGB1 mediates signaling in both ways.

5. Progress of autophagy in the trabecular meshwork

Autopophagy promotes the antioxidant process of trabecular mesh cells and opens new ideas for the treatment of open-angle glaucoma. Autophagy functions in regulating fibroblast formation in TM cells through BAMBI and Smad2/3 signaling. The significance of autophagy in inducing fibrotic responses opens up a new field for studying therapeutic targets to improve TM fibrosis. Dysregulates the autophagy in trabecular mesh sheets and retinal structure as the old, and suggests that this abnormal autophagy regulation helps with nerve damage in glaucoma.

RGCs death has been related with a variety of visual disease. Oxidative stress damages mitochondria through a variety of mechanismsand induce cell apoptosis. The structural functional features of long axons and long lives of RGC make them sensitive to lack of energy, they are more susceptible to dysmitochondria and more sensitive to oxidative stress. When undernutrition, hypoxia, ischemia and other stress reactions occur,oxidative stress and intracellular ROS accumulation is

very important in stimulating autophagy. Other studies have shown that apoptosis in RGC cells caused by the E50K mutation (OPTNE50KNTG) of the OPTN gene also has some therapeutic basis.

6. Role of autophagy in RGCs

Long axonal neurons with myelinated structures within the central nervous system constitute retinal ganglion cells, the axon through which the optic nerve can deliver retinal captured signals to the CNS of the brain. Compared to other neurons, the blood supply to the cell body and to the RGC axons is different, resulting in neurons being extremely sensitive to differential stress damage. Autopagy is an adaptive response to various stress conditions. It has been found that autophagy within the dendrites with gradually increasing IOP in RGCs is activated in the first time, starting to exert its protective role on the cells. Immediately thereafter, partial autophagy occurs in the cytoplasm that ultimately causes apoptosis. Relevant studies speculate that neuronal axons are rich in mitochondria, which can therefore detect the body's chronic ischemia in time, thus first triggering autophagy to maintain cellular homeostasis, and terminating apoptosis by eliminating damaged mitochondria and releasing energy to prevent cell necrosis by catabolism. However, as IOP increases gradually, autophagy in neurons is also activated, homeostasis is disrupted, and cell viability may be reduced. If the intraocular pressure increases dramatically,the autophagy of the retina is unbalanced, and the autophagy activity in the retinal ganglion cell layer (retinal ganglion cell, GCL) increases immediately, mainly in the cell body and in a short time. The progression of various optic neuropathy is influenced by individual differences and environmental factors, making the degree of oxidative stress and autophagy vary in the RGC. If we increase autophagy in the early stages of neuropathy,the death of RGCs might be reduced in axons, pending further investigation.

7. Enhanced autophagy to reduce RGC apoptosis due to mutations in the OPTN gene-associated glaucoma

OPTN (Optiineurin) is involved in cell signal transduction, vesicle transport and autophagy. The E50K mutation (OPTNE50KNTG) in OPTN gene leads to the increase of Optineurin (OPTN) in pluripotent stem cells in normal intraocular glaucoma (NTG) patients. NTG induces OPTNE50K cell aggregation, astrocyte activation, decreased RGC number, and increased apoptotic cell death. Timolol reduces OPTNE50K-positive regions and reduces insoluble OPTNE50K, so we predict that timolol has the potential to reduce OPTNE50K increasing. It can also increase ath5-positive cells, resulting in a reduced number of tunel-positive cells, and increased LC3B-II/LC3B-I values, and thus reduced p62 expression levels. These results suggest that timolol may increase autophagy intensity and decrease OPTNE50K. It is a potential therapeutic agent for OPTNE50KNTG because it can reduce the increase of OPTNE50K in RGC by enhancing autophagy and neural protection. TBK1 protein kinase may be used in the treatment of e50K-OPTN and M98K-OPTN-induced glaucoma in the future because TBK1 inhibitors strongly inhibit M98K-OPTN apoptosis induced in retinal cells. Given the role of OPTN in the immune signaling pathway, the immune effect of OPTN in glaucoma needs further study.

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