

Review

Repertoires of Autophagy in the Pathogenesis of Ocular Diseases

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Key Words

Autophagy • Age-related macular degeneration • Glaucoma • Cataract • Diabetic retinopathy • Photoreceptor degeneration

Abstract

Autophagy is an important intracellular degradative process that delivers cytoplasmic proteins to lysosome for degradation. Dysfunction of autophagy is implicated in several human diseases, such as neurodegenerative diseases, infectious diseases, and cancers. Autophagy-related proteins are constitutively expressed in the eye. Increasing studies have revealed that abnormal autophagy is an important pathological feature of several ocular diseases. Pharmacological manipulation of autophagy may provide an alternative therapeutic target for some ocular diseases. In this manuscript, we reviewed the relevant progress about the role of autophagy in the pathogenesis of ocular diseases.

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Introduction

Cellular homeostasis requires a constant balance between biosynthetic and catabolic processes. Eukaryotic cells possess two major mechanisms for large-scale degradation, including proteasome and autophagy [1]. Autophagy is an evolutionarily conserved, genetically controlled cell pathway. Under normal physiological condition, autophagy regulates cellular homeostasis by eliminating damaged proteins/organelles for cellular component quality [2, 3]. Under adverse condition, autophagy serves as an adaptive mechanism to protect

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organisms against various disorders, such as cancer, aging, neurodegeneration, and cardiovascular disease [2, 4].

Aging and oxidative stress are recognized as the key pathological features in many ocular diseases. They lead to an increased amount of intracellular organelles and defective autophagic flux. Autophagy plays an important role in cellular homeostasis through removing abnormal organelles and proteins [5, 6]. Autophagy-related proteins are strongly expressed in all retinal cells from those comprising the cornea in the front of the eye to the retinal pigment epithelium (RPE). Defective autophagy is tightly associated with the occurrence of ocular diseases. Thus, pharmacological manipulation of autophagy may offer an alternative therapeutic target [7]. In this review, we summarized the progress on the role of autophagy in ocular diseases, and the ongoing efforts for autophagy modulation for treating ocular diseases.

Introduction of autophagy process

Autophagy is a lysosomal process used by eukaryotes for degrading and recycling cellular constituents, such as long-lived proteins and entire organelles. There are three major forms of autophagy, including microautophagy, chaperone-mediated autophagy (CMA), and macroautophagy. Microautophagy and CMA directly involve the lysosome, which either engulfs a small part of cytosol or receives chaperone-associated cargoes, respectively [8]. Macroautophagy is a vacuolar degradative pathway terminating in the lysosomal compartment after forming autophagosome that engulfs macromolecules and organelles (Fig. 1) [9].

Macroautophagy plays important roles in survival, development and tissue homeostasis [10]. CMA is activated by physiological stresses such as prolonged starvation, which is shown as the only autophagic pathway that allows selective degradation of soluble proteins in lysosomes [11]. The maintenance of organelle size, membrane homeostasis, and cell survival under nitrogen restriction are the main functions of microautophagy. Microautophagy is also coordinated with and complements macroautophagy, CMA, and other self-eating pathways [12].

Macroautophagy cascade is a highly complex process, dividing into several discrete steps, including signaling induction; cargo selection and packaging; nucleation of vesicle formation; docking and fusion of the completed vesicle with the lysosome/vacuole; and breakdown of the intraluminal vesicle and its cargo and recycling of the macromolecular constituents (Fig. 2) [13, 14]. Microautophagy involves the direct engulfment of cytoplasmic cargo at the boundary membrane by autophagic tubes, which mediates both invagination and vesicle scission into the lumen. During CMA, the substrate proteins are targeted to lysosomal membrane by the recognition of a targeting motif (a KFERQ-like motif) by chaperone complex, hsc70 and its cochaperones. Once at the lysosomal membrane, the protein interacts with lysosomal associated membrane protein type 2A (LAMP-2A), and is translocated across the membrane into the lysosomal lumen.

Signaling pathway involved in autophagy regulation

Currently, several signaling pathways have been implicated in autophagy regulation, such as mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), NRF2/KEAP1, and ER stress signaling (Fig. 3). mTOR signaling can be activated by growth factors, and inhibited by AMPK and p53. Inhibition of mTOR stimulates autophagy, while enhanced mTOR activity impairs autophagy. Activated mTOR can phosphorylate ULK1/2, thereby inhibiting the downstream autophagy cascade. In contrast, AMPK suppresses mTORC1 signaling, and stimulates autophagy through TSC1/2 phosphorylation [15-17]. NRF2/KEAP1 is the major signaling responsible for cell defense against oxidative stress [18,

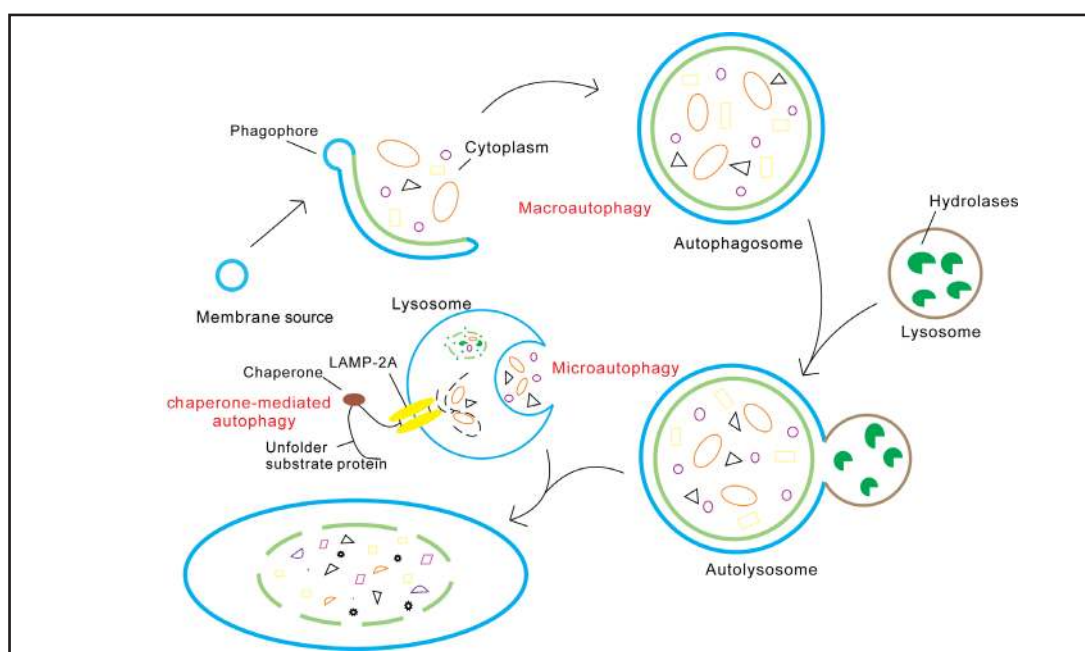


Fig. 1. Schematic model of different types of autophagy. During macroautophagy, the cargoes are sequestered within a unique double-membrane cytosolic vesicle, an autophagosome. Sequestration can be either nonspecific, involving the engulfment of bulk cytoplasm, or selective, targeting specific cargoes such as organelles or invasive microbes. Microautophagy is cytosolic components sequestration by lysosomes through invaginations in their limiting membrane. During CMA, the substrate proteins are targeted to the lysosomal membrane by a chaperone complex, hsc70 and its cochaperones. Once at the lysosomal membrane, the protein interacts with lysosomal associated membrane protein type 2A (LAMP-2A), translocated across the membrane into the lysosomal lumen assisted by chaperone.

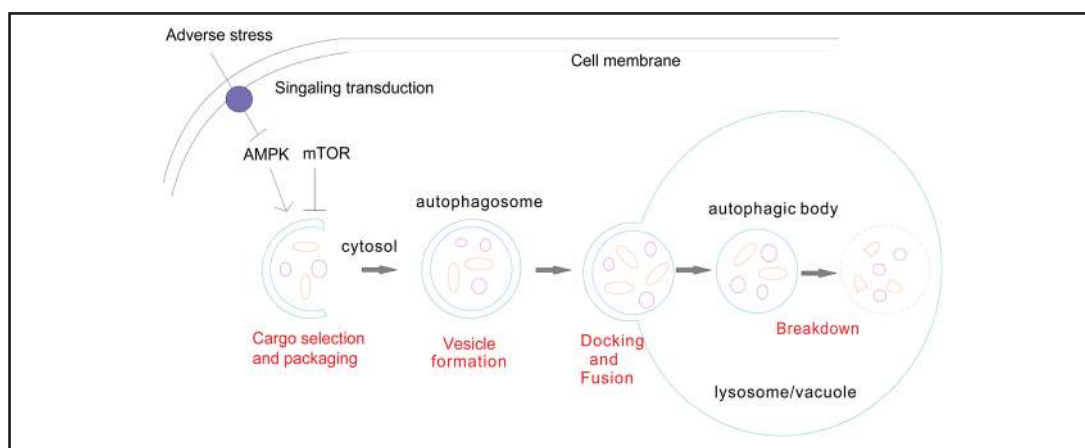
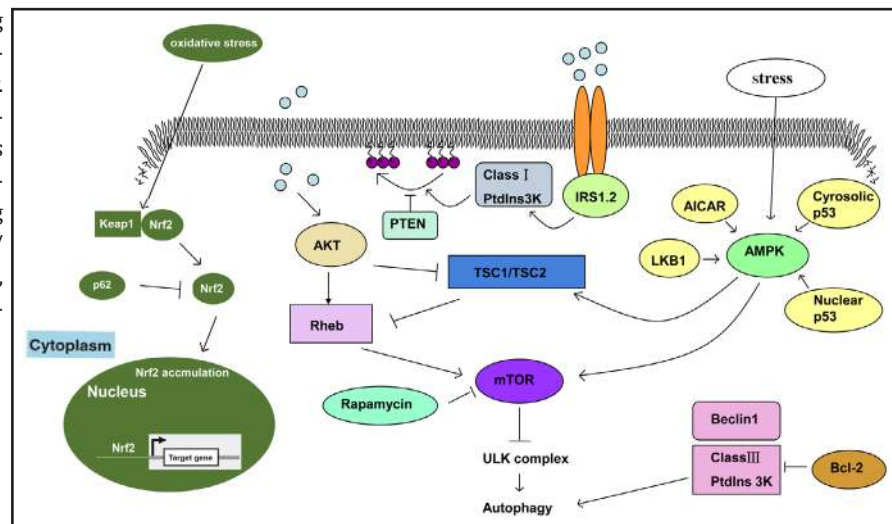


Fig. 2. Schematic depiction of autophagy pathway and its core molecular machinery. External stress leads to the inhibition of mTOR kinase, which in turn leads to autophagy activation. Membrane forms an unknown source which can nonspecifically sequester cytoplasm. The following double membrane autophagosome targets to and fuses with the lysosome. The fusion allows the release of the single-membrane autophagic body, which is degraded in the lumen allowing the recycling of cytoplasmic constituents.

19]. It enables cell adaptation to oxidative stress caused by various stimuli, such as chemical oxidative, electrophilic agents, or UV radiation. Autophagy-deficient mice show aberrant p62 accumulation. p62 accumulation could disrupt NRF2/KEAP1 association and provoke

Fig. 3. Signaling pathways involved in autophagy. Autophagy is regulated by a series of signaling cascades, including mTOR, NRF2/KEAP1, ER stress, and AMPK signaling pathway.



NRF2 stabilization and accumulation [20, 21]. In addition, p62 accumulation sequesters KEAP1 into aggregates, inhibiting KEAP1-mediated NRF2 ubiquitination [22]. ER stress can stimulate autophagy through PERK-eIF2 α pathway, IRE1-JNK1 pathway and Ca²⁺ release. Activation of eIF2 α by PERK contributes to the transcription of some autophagy genes [23].

Physiological role of autophagy

Autophagy is known as an adaptive process to defend against various metabolic stresses, such as hypoxia, nutrient deprivation and growth factor depletion [24]. It mobilizes intracellular energy to meet cellular demand [4]. Autophagy also functions as a cellular housekeeper in some biological processes, such as the elimination of defective proteins and organelles, the prevention of abnormal protein accumulation, and the removal of intracellular pathogens [24, 25]. Autophagy-lysosome system is critical for maintaining protein quality, preventing intracellular accumulation of mis-folded proteins. In addition, autophagy is shown as a potential genome guardian. Autophagy deficiency in the immortalized epithelial cells limits DNA damage and chromosomal instability [26].

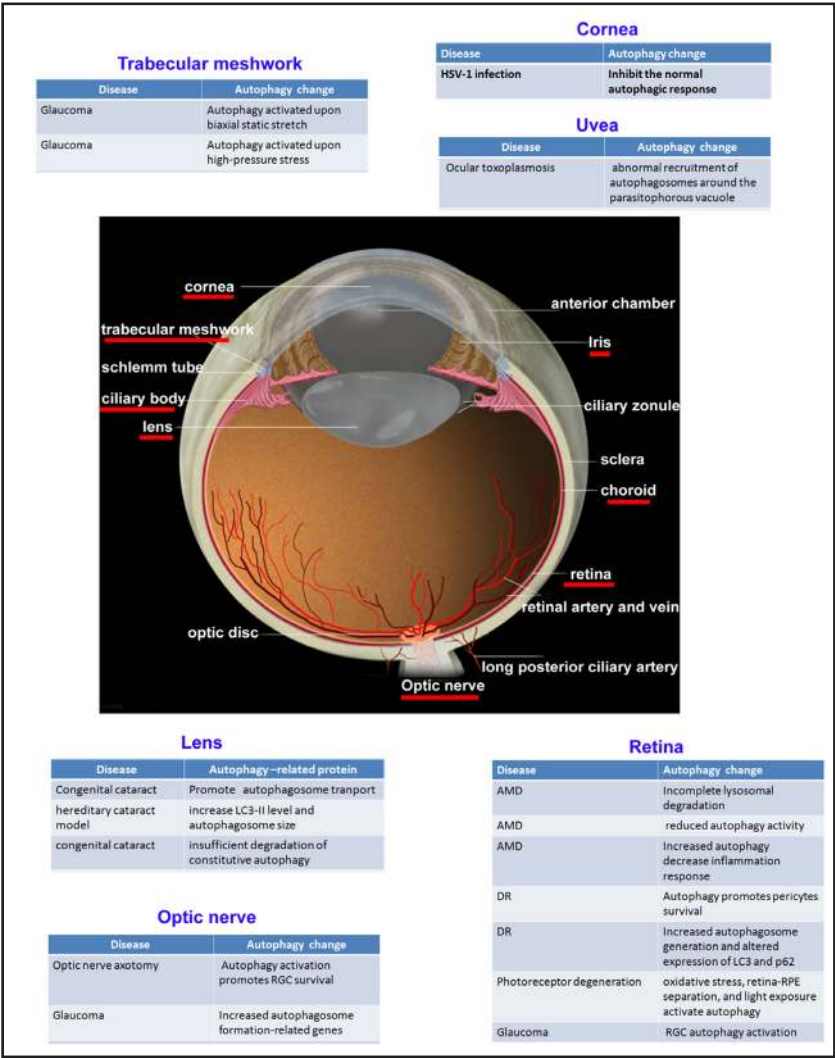
Pathological role of autophagy

Autophagy is essential for cell survival in many solid tumors. It coordinates the inactivation of apoptosis, and promotes necrosis and tumor progression [27, 28]. Tumor suppressor genes, such as PTEN, TSC1, and TSC2, inhibit mTOR signaling and stimulate autophagy. By contrast, mTOR-activating oncogenes, such as class I PI3K and Akt, inhibit autophagy [29]. Bcl-2 and Bcl-xL are frequently up-regulated in many human tumors. ER-localized Bcl-2 and Bcl-xL inhibits autophagy by binding to Beclin 1, an autophagy protein [30].

Inadequate or defective autophagy contributes to neuronal cell death in many neurodegenerative disorders, such as Parkinson's (PD), Huntington's, Alzheimer's disease (AD) [31]. Autophagy protects cells from cumulative oxidative damage to proteins and membranes in the aging nervous system [18, 32]. Autophagy also functions as a distinctive death mechanism. Obvious proliferation of autophagic vacuoles and progressive disappearance of organelles was observed in the dying neurons in chick embryo through an ultrastructural study [33].

Autophagy is used as a defense against microbes. Numerous medically important pathogens are degraded by autophagy, such as group A *Streptococcus*, *Mycobacterium*

Fig. 4. Autophagy change in different eye tissues. Schematic of the anatomy of the eye with tables displaying autophagy changes in different tissues leading to ocular diseases.



tuberculosis, *Shigella flexneri*, *Salmonella enterica*, *Listeria monocytogenes*, *Francisella tularensis*, herpes simplex virus type I (HSV-1), and *Toxoplasma gondii* [34-36].

Autophagy is shown as a response to cardiac stress such as ischemia or pressure overload [37]. In ischemia reperfusion liver injury, autophagy plays a pro-survival role against nutrient starvation and anoxia stress [38]. Upon hepatitis B or C infection, autophagy is used by some bacteria and viruses to invade host tissues [39, 40]. Autophagy is also an effector of Th1/Th2 polarization. It can fuel MHC II presentation of cytosolic antigens, shape central tolerance, and affect B and T cell homeostasis [41, 42].

Association between autophagy and ocular health or diseases

Autophagy-related proteins are strongly expressed in the ganglion cell layer, inner nuclear layer, outer nuclear layer, and RPE layer in retina. These cell layers have high metabolic demand and propensity for mitochondrial damage [6]. Under physiological condition, autophagy is a housekeeping process to remove damaged cytoplasmic proteins and cellular organelles [1]. They rely on one or more aspects of autophagy to maintain structure and/or normal physiological function. Autophagy dysregulation is involved in the occurrence of ocular disease (Table 1 and Fig. 4).

Table 1. Aberrant autophagy process in ocular diseases

Ocular disease	Description	Refs.
<i>T. gondii</i> infection	Autophagy dysregulation due to CD40 pathway defect	Subauste et al 1999; Subauste and Wessendarp, 2006
HSV-1 infection	inhibit normal autophagic response	Leib et al, 2009
AMD	Autophagy increase in the aged retina and the drusen of AMD donor eyes Increased autophagy during drusen formation	Wang et al, 2009b Wang et al, 2009a
Glaucoma	Inflammation regulation Regulation of oxidative stress Regulation of TM function Autophagy is activated after IOP elevation and traumatic injury Autophagy activation in the injured neuronal cells	Kauppinen et al, 2013 Karlsson et al, 2013; Wang et al, 2014 Porter et al, 2013, 2014 Piras et al, 2011; Park et al, 2012; Rodríguez-Muela et al, 2012 Kim et al, 2008
Cataract	Deletion of autophagy-related 5 (Atg5) and Pik3c3 Mutations in FYCO1 α B-crystallin R120G mutation	Morishita et al, 2013 Abouzeid et al, 2012 Wignes et al, 2013
DR	Autophagy induction in pericytes exposed to HOG-LDL High glucose-induced autophagy in RPE	Fu et al, 2012 Yao et al, 2014
Photoreceptor degeneration	Autophagy is activated in the rd/rd mouse during light-damage Autophagy is activated during oxidative stress Autophagy is increased in the retinas of Abca4 ^{-/-} Rdh8 ^{-/-} mice after light exposure	Melén et al, 2008 Kunchithapautham and Rohrer, 2007b Chen et al, 2013

Ocular infectious disease

Autophagy is critical for the degradation of invading microorganisms. The human cornea is a primary target for *T. gondii* and HSV-1, which enters endothelial cells through endocytosis. *T. gondii* survives within the host cells preventing the endosomal-lysosomal compartments from fusing with the vacuoles. It causes ocular toxoplasmosis and/or cerebral toxoplasmosis in adults. Ocular toxoplasmosis is the most common form of posterior uveitis [43]. It occurs in immunocompromised patients or in immunocompetent. CD40 activates macrophages to kill *T. gondii* through the recruitment of autophagosomes around the parasitophorous vacuole. Defects in CD40 pathway in patients develop cerebral and/or ocular toxoplasmosis, including patients with X-linked Hyper IgM syndrome who lack functional CD154 [44]. CD40-induced autophagic killing of *T. gondii* may be an important contributor for the control of *T. gondii* [45, 46]. HSV-1 is a double-stranded DNA virus in the herpesvirus family. PKR- and eIF2 α -dependent autophagy mediates the degradation of HSV-1. This virus produces ICP34.5, a neurovirulence factor that inhibits autophagy by the reversal of PKR-mediated eIF2 α phosphorylation and antagonizing Beclin 1 [47, 48]. Corneal HSV-1 infection could subvert cornea's response to infection by inhibiting autophagic response [5]. Collectively,

these studies reveal that the role of autophagy in controlling microorganism infection is via a rapid induction of the innate immune response.

Age-related macular degeneration (AMD)

Aging, hypercholesterolaemia, hypertension, obesity, arteriosclerosis, and smoking are risk factors to develop AMD. The pathology of AMD associates with increased oxidative stress, inflammation, and impaired proteasomal or lysosomal function that causes the formation of intra- and extracellular deposits. Autophagy is a cellular housekeeping process that removes damaged organelles and protein aggregates. A breakdown in the recycling capacity of autophagy is strongly linked to AMD pathogenesis [49]. AMD-related stress, such as caloric restriction, hypoxia, oxidative stress, can impair autophagy, increase protein aggregation, and cause inflammasome activation involved in AMD pathogenesis [50, 51].

A hallmark of AMD is the detrimental accumulation of lysosomal lipofuscin in RPE cells. The capacity of RPE to modulate diverse pathways of AMD pathogenesis makes it as the fulcrum [52]. Abnormally increased lipofuscin accumulation in RPE cells is observed in early- and late-stage AMD. Lipofuscin exerts phototoxic effects on RPE cells *in vitro*, resulting in free radical generation and cell apoptosis [53]. Incomplete lysosomal degradation is the underlying mechanism of lipofuscinogenesis [54]. Given the critical role of autophagy in lipofuscin accumulation, it is not surprise that pharmacological manipulation of autophagy may offer an alternative therapeutic target.

In addition to lipofuscin accumulation, reduced autophagy activity has been implicated in RPE dysfunction [55]. Decreased autophagy renders RPE cells susceptible to apoptosis induced by various stress including nutritional depletion and mitochondrial photooxidative damage [56, 57]. Preservation of autophagic activity could improve RPE function and retard disease progression [58, 59]. Protein aggregates induce the inflammasome activation in RPE cells. Increased autophagy activates the intracellular cleaning systems, and decreases the generation of inflammasomes, which could prevent inflammation response in AMD [60].

Glaucoma

Autophagy is an important recycling pathway implicated in neurodegeneration either as a pro-survival or a pro-death mechanism. Progressive RGC death involves novel non-apoptotic programmed cell death (paraptosis) at the early stage of glaucoma, which is accompanied by apoptosis and/or autophagy in the moderate and severe stages [61]. Pharmacological induction of autophagy *in vivo* increases the number of surviving cells after traumatic injury, suggesting that autophagy has a cytoprotective role in RGCs. Modulation of autophagy may provide a new therapeutic strategy to ameliorate retinal nerve diseases [62]. However, autophagy sometimes plays a detrimental role. The inhibition of autophagy attenuates axonal degeneration and ultrastructural alterations [63]. Elevated IOP could also activate autophagy, and up-regulate the levels of autophagy markers, LC3-II/LC3-I and beclin-1 [63, 64]. Autophagosome formation-related genes, including Atg5, Atg7, Atg12, Beclin-1, and LC3, are significantly activated during neuronal cell injury [65].

Trabecular meshwork (TM) plays important roles in the normal outflow of aqueous. Its abnormality affects the outflow and increases the intraocular pressure, thereby causing glaucoma. Chronic exposure of TM cells to oxidative stress causes the accumulation of non-degradable materials within the lysosomal compartment leading to diminished lysosomal activity. Autophagy in TM cells is also obviously activated upon biaxial static stretch or high-pressure stress. This activation allows TM cells to cope with the external stress. Reduced autophagic flux is recognized as a factor of progressive TM dysfunction [66, 67].

Optineurin (OPTN) was identified as an autophagy receptor involved in the elimination of cytosolic bacteria [10]. Mutations in OPTN gene are associated with normal-tension

glaucoma [12]. OPTN E50K is the most common disease causing mutation of optineurin, and overexpression of OPTN E50K mutation in mice lead to a loss of RGCs and other retinal cell types [11, 68].

Cataract

The lens of the eye is composed of fiber cells, which differentiate from epithelial cells and undergo programmed organelle degradation during terminal differentiation. Upon maturation, these differentiating fiber cells lose their organelles to produce the organelle free zone (OFZ) thus contributing to lens transparency. Cataract is the loss of transparency of the lens. The presence of autophagic vesicles was identified in embryonic and adult lens. Autophagy is involved in lens fiber cell maturation and formation of OFZ [69].

Congenital cataracts can be caused by improper clearance of proteins and organelles. FYCO1 is a PI (3) P, Rab7 and LC3 binding protein that mediates microtubule plus end-directed vesicle transport of autophagosomes. Mutation in FYCO1 gene was identified as the cause of autosomal recessive congenital cataract [70]. In hereditary cataract model, α B-crystallin R120G mutation increases LC3-II level and autophagosome size, and up-regulates p62 level in mouse lens epithelial and fiber cells [71]. Vsp34, a class III phosphatidylinositol 3-kinase, is involved in Atg5-independent autophagy. Vsp34 loss leads to congenital cataract and defective lens development [72]. Connexins form gap junctions, and their short half-life suggests that the degradation and renewal is important for cell-cell contact. CX50 P88S mutant is associated with inherited congenital cataracts. Autophagy can regulate the level of wild-type connexins. The persistence of accumulations of CX50P88S may result from the insufficient degradation of constitutive autophagy [70]. Collectively, these studies provide evidence for the role of autophagy in lens function. Disruption of autophagy causes the loss of lens resistance to stress and/or lens differentiation resulting in cataract formation.

Diabetic retinopathy (DR)

DR is a serious complication of diabetes mellitus characterized by microvascular dysfunction. Pericytes are essential for retinal capillary structure and function, and the loss is an early feature of DR. Autophagy promotes pericytes survival under mild stress, but lead to their death under extended stress [73]. The outer BRB is comprised of tight junctions between RPE cells. During DR, extra-vascular modified LDL may promote RPE injury through oxidative stress, ER stress, autophagy and apoptosis [74]. High glucose causes a marked increase in autophagosome generation and altered expression of LC3 and p62 in RPE cells [75]. In the scenario of high glucose-induced oxidative stress, autophagy is involved in the removal of damaged proteins, providing a default mechanism to prevent high glucose-induced injury in RPE cells. Metabolic stress such as growth factor and nutrient deprivation participate in cell death and the accumulation of damaged proteins in diabetic retinas. Autophagy is a major catabolic pathway involved in degrading and recycling damaged organelles and macromolecules to maintain intracellular homeostasis. It contributes to cell energy homeostasis and repair during basal and nutrient stress conditions. Autophagy is altered in diabetic retinopathy in response to the metabolic stress. Thus, autophagy modulation provides a novel avenue for the treatment of diabetes-related diseases.

Photoreceptor degeneration

The retina provides exquisitely sensitive vision that relies on the integrity of a uniquely vulnerable cell, the photoreceptor (PR). The genetic and mechanistic causes of retinal degeneration due to PR cell death, which occurs in the conditions such as retinitis pigmentosa

Table 2. Potential autophagy-based therapeutics for the treatment of ocular diseases

Drug	Ocular pathological conditions	Description	Refs.
Rapamycin	AMD	Autophagy induction	Kaarniranta et al, 2013
AMPK activator	AMD	Autophagy induction	Hyttinen et al, 2011
EGCG	Light-induced retinal damage	Regulator of mTOR signaling	Li et al, 2013
Chloroquine and hydroxychloroquine	AMD	Autophagy inhibition	Nylander, 1966; Shinjo et al, 2007
HNE, MDA	AMD	Reduced autophagy activity in RPE	Krohne et al, 2010
Calorie mimetics	Age-related eye disorders	AMPK signaling regulation	Kawashima et al, 2013
Resveratrol, RAP and MG-132	AMD	Autophagy induction in RPE	Petrovski et al, 2011

and age-related macular degeneration. Exposure to light damage causes oxidative stress and altered metabolism, which may induce caspase-dependent and caspase-independent rod and cone photoreceptor cell death through the activation of cysteine-proteases, lysosomal proteases and autophagy to overcome damaged protein overload [76-79].

Autophagy and apoptosis occur in parallel in photoreceptor degeneration in the rd/rd mouse during light-damage [76]. Upon oxidative stress, autophagy is activated to induce photoreceptor cell death both *in vivo* and in a photoreceptor cell line [77]. Autophagy activation also occurs in the photoreceptors after retina-RPE separation. The activation could prevent Fas-mediated apoptosis [78]. Expression of autophagosome marker and mitochondria-specific autophagy regulator is markedly increased in the retinas of *Abca4*^{-/-} *Rdh8*^{-/-} mice after light exposure. Autophagy could protect these retinas from light-induced degeneration [79].

Autophagy and ocular disease therapy

Recently, several studies have revealed that autophagy is a potential target for ocular disease treatment (Table 2). Rapamycin, a regulator of autophagy, is shown as a potential drug for AMD therapy [80, 81]. AMPK is an inhibitor of mTOR signaling, which evokes autophagy induction. AMPK-mTOR axis may also become a target for AMD treatment [82]. Calorie restriction (CR) and its mimetics reverse or slow age-related functional declines in the eye. The involvement of this pathway through which sirtuin 1 (SIRT1) and/or its upstream AMPK acts is a well-known mechanism underlying CR benefits [32]. Chinese medicine acts via a modulation of autophagy [83, 84]. Epigallocatechin-gallate (EGCG) plays a regulatory role in UVB irradiation-induced autophagy in RPE cells [85].

The induction of lysosomal dysfunction by lipid peroxidation-derived protein modifications, such as 4-hydroxynonenal (HNE) and malondialdehyde (MDA), results in increased lipofuscinogenesis and reduced autophagy activity in RPE, which may contribute to RPE cell dysfunction and degeneration in AMD [86]. Resveratrol at lower concentrations, RAP and MG-132 can provide a pro-survival stimulus to RPE cells through autophagy induction. This property can possibly be used for prolonging RPE lifespan in AMD [87].

Autophagy has the potential to either induce cell death or promote cell survival, suggesting a paradoxical role of autophagy. Chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) have been approved by the FDA due to the effectiveness *in vivo* and safety in clinical trials. They can suppress autophagy by blocking autophagosome fusion and degradation. Sometimes, both agents bind to the melanin in RPE cells, and this binding may serve to concentrate the agents and prolong their toxic effects. Thus, the incidence of irreversible retinal toxicity may also increase when patients were treated with CQ or HCQ [88, 89].

In the future, it is still required to develop novel regulators that specifically target autophagy machinery [90]. These drugs can be developed for targeting kinases (e.g., class III PI3K), proteases (e.g., Atg4B and C), and E1 or E2-like enzymes (Atg7 and Atg10) [91]. In addition, the existing less-specific autophagy activators (rapamycin analogues) and inhibitors (chloroquine and omeprazole) that are reasonably well-tolerated may enlighten the efficacy of autophagy regulation in the treatment of ocular diseases [92].

Concluding remarks

In this review, we summarized current knowledge about the role of autophagy in ophthalmic research. We know that functional autophagy is critical for retinal cell survival, development, and homeostasis [2]. Autophagy dysregulation could lead to the occurrence of several ocular diseases. Under most circumstances, autophagy functions as homeostatic mechanism for intracellular recycling and metabolic regulation [3]. Autophagy is critical for the removal of damaged proteins and organelles. Continuous autophagy activation may cause non-apoptotic programmed cell death. Thus, it is required to control the balance between too little and too much autophagy [4].

Autophagy is a double-edged sword in health and disease. Cells exposed to growth factor deprivation or glucose and oxygen shortage can lose the majority of their mass through autophagy. By contrast, it fully recovers when placed in optimal culture conditions [28, 93], implying that autophagy-mediated cell death is not a simple matter of crossing a quantitative threshold of self-digestion. Thus, it is critical for understanding how autophagy executes or protects against external stress before developing effective therapeutic or preventive interventions for ocular diseases. In addition, it is still required to determine whether altered autophagy is causative or secondary to the pathological processes of ocular diseases.

As a conserved cellular pathway, the process of autophagy should be tightly regulated. Signaling pathways, including mTOR, AMPK, oxidative stress, and ER stress signaling, are involved in autophagy regulation. Whether these signaling pathways crosstalk between each other or whether there is other signaling pathway involved in autophagy regulation is still unknown. Thus, further understanding autophagy regulation may allow us to develop therapeutic strategy to enhance chemotherapy effect and improve clinical outcomes during ocular disease treatment.

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Disclosure Statement

None declared.

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