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REVIEW

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The interplay of autophagy and oxidative stress in the pathogenesis and therapy of retinal degenerative diseases

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Abstract

Oxidative stress is mainly caused by intracellular reactive oxygen species (ROS) production, which is highly associated with normal physiological homeostasis and the pathogenesis of diseases, particularly ocular diseases. Autophagy is a self-clearance pathway that removes oxidized cellular components and regulates cellular ROS levels. ROS can modulate autophagy activity through transcriptional and posttranslational mechanisms. Autophagy further triggers transcription factor activation and degrades impaired organelles and proteins to eliminate excessive ROS in cells. Thus, autophagy may play an antioxidant role in protecting ocular cells from oxidative stress. Nevertheless, excessive autophagy may cause autophagic cell death. In this review, we summarize the mechanisms of interaction between ROS and autophagy and their roles in the pathogenesis of several ocular diseases, including glaucoma, age-related macular degeneration (AMD), diabetic retinopathy (DR), and optic nerve atrophy, which are major causes of blindness. The autophagy modulators used to treat ocular diseases are further discussed. The findings of the studies reviewed here might shed light on the development and use of autophagy modulators for the future treatment of ocular diseases.

Keywords: Autophagy, Reactive oxygen species, Glaucoma, Age-related macular degeneration, Diabetic retinopathy, Optic nerve atrophy

Background

Christian de Duve, a Nobel Prize winner in 1974, observed cellular autophagic structures by electron microscopy sixty years ago due to the discovery of peroxisomes and lysosomes [1, 2]. In the early 1990s, the Japanese scientist Yoshinori Ohsumi identified the autophagy-related (ATG) genes required for autophagosome formation and explained how eukaryotic cells recycle their components [3–6]. Autophagy can recruit damaged proteins/organelles to lysosomes through selective adaptors or non-selective bulk degradation to generate different substrates, such as nucleotides, sugars, fatty acids, and amino acids, for new synthesis [6, 7]. Oshumi's findings opened up research on the role of autophagy in the physiology of normal cells and the pathogenesis of various diseases and conditions, including neurodegenerative diseases, infections, and cancer. Therefore, Yoshinori Ohsumi was awarded the Nobel Prize in Physiology or Medicine in 2016.

There are three major types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). Although crosstalk may occur among the three pathways, and all three pathways deliver components to lysosomes for degradation, the mechanisms of delivery are quite different among them.

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Macroautophagy

Since macroautophagy is the most common form of autophagy, autophagy usually means macroautophagy. Macroautophagy requires autophagosome formation to pack abnormal proteins and organelles into autophagosomes and fusion with lysosomes to digest the contents [8]. Most forms of macroautophagy are selective because specific cargos or adaptors are essential for the recruitment of targets to autophagosomes, such as in mitophagy and pexophagy for the degradation of mitochondria and peroxisomes, respectively [8–11]. Several adapters for selective autophagy, such as squestome (SQSTM1, also known as p62) and NBR1, associate with ubiquitinated cargo proteins and autophagosomal protein LC3 via ubiquitin-associated (UBA) and LC3-interacting region (LIR) motif, respectively [12].

CMA

CMA is a chaperone (HSC70)-dependent degradation pathway. HSC70 recognizes cytosolic unfolded proteins containing KFERQ pentapeptide and delivers it to lysosomes by binding with the transmembrane receptor LAMP-2A [13, 14]. HSP90 then associates with the LAMP-2A complex to assist translocated substrate proteins into lysosomes for degradation [15]. The LAMP-2A complex is further disassembled to a monomer and eventually degraded by cathepsin A and a metalloproteinase in the lipid microdomain [16].

Microautophagy

Microautophagy was defined as micro portion of lysosomal membrane to engulf autophagic cargos, including proteins and organelles, in cells [17]. Microautophagy can be classified into three types according to the morphology of membrane deformation: type 1, lysosomal protrusion; type 2, lysosomal invagination; and type 3, endosomal invagination [18]. Some ATG proteins or HSC70 or ESCRT proteins are involved in the membrane deformation process [19, 20]. Therefore, crosstalk may occur among microautophagy and macroautophagy, CMA and endocytosis. Thus, further studies are required to elucidate the potential mechanisms through which this crosstalk would occur.

Autophagy-related proteins

There are more than 40 Atg proteins involved in macroautophagy signaling in yeast cells. Most of the proteins have been found to have ATG homologous proteins in mammalian cells, in which about 20 ATG proteins play crucial roles in autophagy progression, including preautophagosomal structure (PAS) formation, autophagosome maturation and fusion with lysosomes. The ATG proteins can be clustered into four complexes as listed in Table 1 [21–25] and their functions are described as below. The involvement of these complexes in autophagy machinery is also shown in Fig. 1.

i) ULK1/2-containing complex- ULK1/2 is the only ATG kinase that binds and phosphorylates FIP200 (mammalian Atg17 homologous), ATG13 and ATG101 for autophagosome nucleation and formation [26, 27]. ULK1/2 also phosphorylates several ATG proteins, such as ATG9 at Ser14, ATG4B at Ser316, BECN1 at Ser14 and ATG14L at Ser29 [28]. Moreover, AMPK directly phosphorylates ULK1, particularly in S317 and S777, to activate its kinase activity, whereas MTORC1 directly phosphorylates ULK1 at S757 to block the binding between AMPK and ULK1 [29]. Interestingly, ULK1 can phosphorylate and negatively regulate both AMPK and MTORC1 activity, suggesting the regulation loop of AMPK-MTORC1-ULK1 are important to control autophagic activity for maintaining energy homeostasis.
ii) BECN1-containing complex- BECN1 attaches to VPS15 and VPS34, which is a lipid kinase class III phosphatidylinositol 3 kinase (PI3K) that triggers the phosphorylation of phosphatidylinositol and results in phosphatidylinositol 3-phosphate (PI3P) formation [30, 31]. ATG14L/Barkor (mammalian Atg14 homologous) recruits the complex to the PAS site. UV radiation resistance-associated (UVRAG) protein associates with the BECN1 complex for autophagosome formation and maturation [32, 33]. In addition, AMPK phosphorylates BECN1 to activate VPS34 activity and induce autophagy [34], whereas Run domain Beclin-1 interacting and cysteine-rich containing (Rubicon) binds to BECN1 and inactivate class III PI3K complex 2 for blocking fusion step between autophagosome and lysosome [35].
iii) ATG9-containing complex- ATG9 is only one transmembrane protein among ATG proteins. ATG9A forms a homotrimer to form a pore to translocate ATG2-delivered phospholipids for PAS formation and phagophore nucleation [36]. ATG9 also coordinates with the ATG9 receptor and ATG11 to recruit ATG2, WIPI1/2 (mammalian Atg18 homologous) and LC3 for lipid transfer, which is important for autophagosome expansion [37, 38].
iv) ATG12 and LC3 ubiquitin-like conjugation complexes- ATG12 conjugated to ATG5 and LC3/GABARAP conjugated to phosphatidylethanolamine (PE) (LC3-II/GABARAP-II) are two ubiquitin-like complexes are essential for autophagosome elongation and maturation in mammalian cells [39, 40].

Table 1 The functions of each component in the autophagy complex involved in the autophagy machinery

Complex	Components		Functions
	Yeast	Mammals	
Atg1/ULK1/2 complex	Atg1	ULK1/2	It is the only ATG protein with kinase activity and phosphorylates several other ATG proteins (ATG9, BECN1, ATG14L) for the PAS, autophagosome elongation and maturation
	Atg13	ATG13	It serves as a linker among ULK1/2, FIP200 and ATG101
	Atg17	RB1CC1/FIP200	It is a scaffold protein for ULK1/2 and ATG13 and serves as a scaffold protein for the ULK1/2 complex
	–	ATG101	It interacts with ATG13
BECN1 complex	Atg6	Beclin1	It is a core component in class III PI3KI/II and binds lipids. It also associates with UVRAG for autophagosome elongation and maturation
		VPS34	It is a catalytic subunit of class III PI3K to generate PI3P
		VPS15	It is a protein kinase involved in the PI3P pathway
	Atg14	ATG14L (Barkor)	It associates with the BECN1 complex for membrane targeting
ATG9A complex		ATG9A	It is the only transmembrane protein among ATG proteins and forms homotrimer for the PAS, nucleation and autophagosome formation
	Atg18	WIPI1/2	It attaches to PI3P for the transportation of ATG9
	Atg2	ATG2A	It attaches to WIPW1/2
Ubiquitin-like complex	Atg8	LC3A-C, GABARAP	It is a ubiquitin-like protein and ligates with PE for autophagosome elongation and sealing
	Atg12	ATG12	It is another ubiquitin-like protein and ligates with ATG5 to form an E3-like ligase with ATG16
	Atg4	ATG4A-D	It is a protease required for the cleavage and activation of proLC3/GABARAP at the C-terminus for conjugation and further deconjugation of LC3/GABARAP-PE
	Atg7	ATG7	It serves as an E1-like enzyme for LC3 and ATG12 conjugation
	Atg3	ATG3	It serves as an E2-like enzyme for LC3/GABARAP conjugation with PE
	Atg10	ATG10	It serves as an E2-like enzyme for ATG12 conjugation with Atg5
	Atg5	ATG5	It covalently binds to ATG12 and associates with ATG16 to form the E3-like enzyme complex
	Atg16	ATG16L1	It is a part of the E3-like enzyme complex along with ATG12 and ATG5

LC3 and GABARAP are activated by ATG4 family proteases (including ATG4A, ATG4B, ATG4C and ATG4D) before conjugation [41]. All the conjugation requires the E1-like enzyme ATG7 and the E2-like enzyme ATG10 (for ATG12-ATG5) or ATG3 (for LC3-II/GABARAP-II) [42]. ATG16L stabilizes ATG12-ATG5 conjugates to form a complex of approximately 800 kDa and serves as an E3-like enzyme for the conjugation.

In addition to autophagosome maturation, LC3 and ATG12 ubiquitin-like proteins are also involved in the tethering complex. The tethering complex for the fusion step between autophagosomes and lysosomes consists of the homotypic fusion and protein sorting (HOPS) complex, Rab7, adaptors and receptors (LC3-II/ATG12-ATG5) [43]. The HOPS complex consists of Vps16, Vps18, Vps33, Vps39, and Vps41 and connects to syntaxin 17 by binding with oligomeric ATG14L to mediate fusion [44, 45]. PLEKHM1 and TECPR1 are adaptor proteins that connect autophagosomal LC3-II and ATG12-ATG5 with lysosomal Rab7 to ensure fusion specificity [43].

Reactive oxygen species (ROS) and autophagy

Oxidative stress is highly associated with elevated intracellular reactive oxygen species (ROS), which are involved in cellular physiological regulation and the pathogenesis of diseases, such as neuronal, ocular and cardiovascular diseases [46–48]. Intracellular ROS are mainly (approximately 90%) generated by the electron transport chain in the inner membrane of mitochondria and consist of H_2O_2, superoxide ($O_2.-$) and hydroxyl radicals ($OH.$) [49, 50]. ROS can oxidize organelles, nucleic acids, proteins and lipids, which results in cellular damage [51]. ROS not only trigger the autophagy pathway to maintain redox homeostasis and remove oxidized organelles and other components [52] but also inhibit autophagy, likely directly oxidizes ATG proteins (ATG7 and ATG10) or inactivating autophagy modulators (TFEB and PTEN) [53–55]. Conversely, autophagy can modulate ROS levels through several mechanisms. The reciprocal regulation of ROS and autophagy are discussed below.

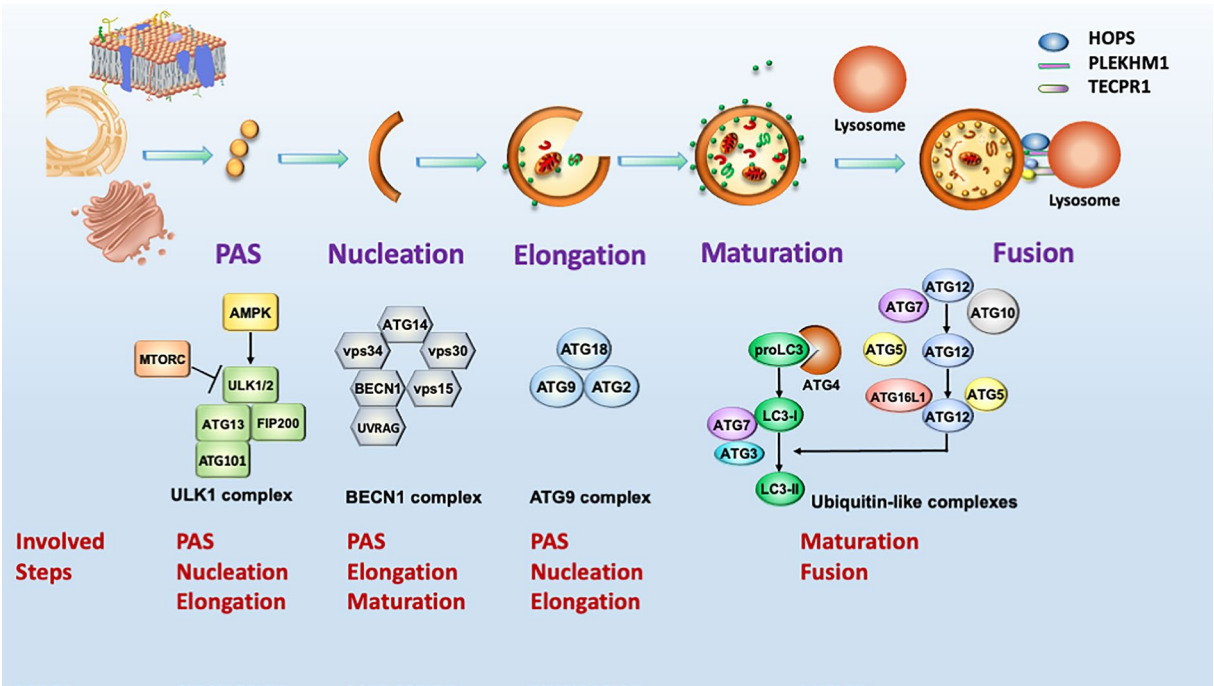

Fig. 1 Schematic diagram for components of each ATG-mediated complex and their involvement in autophagy steps. ULK1/2, BECN1, ATG9 and ubiquitin-like (LC3 and ATG12)-mediated complexes are the four major complexes involved in the core machinery of autophagy, from the PAS to autophagosome maturation/fusion. Many complexes are involved in several stages of autophagy, such as the ULK1/2-mediated complex involved in the PAS, autophagosome nucleation and elongation, since ULK1/2 can phosphorylate and activate many components of the other complexes. AMPK and MTORC are positive and negative regulators of ULK1/2, respectively. Moreover, LC3 and ATG12 are also involved in tethering complexes for the specificity of autophagosomal fusion with lysosomes

The regulation of autophagy by ROS

ROS induce autophagy

Autophagy can be induced by ROS through transcriptional (HIF-1α, NRF2, p53 and FOXO3) and posttranslational regulation (oxidation and phosphorylation) (Fig. 2).

ROS production has been reported to activate hypoxia-inducible factor-1α (HIF-1α), nuclear factor erythroid 2–related factor 2 (NRF2), p53 and forkhead box O-3 (FoxO3). These transcription factors drive the expression of the genes required for autophagy induction, including *BECN1, LC3, SQSTM1* and the mitophagy-associated genes *BNIP3* and *NIX* [56, 57].

Sestrins (SESNs) are another antioxidant cytoplasmic protein and consist of three members, SESN1, SESN2, and SESN3, in mammalian cells. ROS oxidize nucleic acids and cause DNA damage. The severe DNA damage may increase p53 transcriptional activity. The *SESN1* and *SESN2* genes are targets of p53; therefore, SESNs are induced in cells under oxidative stress [58]. Several other transcription factors are also reported to drive *SESNs* gene expression, such as NRF2 [59], HIF-1α [60], and the NH(2)-terminal kinase (JNK)/c-Jun pathway [61]. SESNs contain motifs required for the removal of ROS, including an N-terminal cysteine (C125) with an active site for oxidoreductase activity to reduce alkyl hydroperoxide radicals and a C-terminal aspartate-aspartate motif for mTORC1 suppression [62, 63]. Moreover, SESN2 interacts with KEAP1 to mediate its degradation with autophagy for further NRF2 activation and antioxidant gene expression, as mentioned above [64].

In terms of the effects of posttranslational modification of ROS on autophagy, SESN2 also binds to ULK1 and SQSTM1 to increase SQSTM1 phosphorylation at the UBA domain (S405/409), indicating that SESN2 recruits ULK1 to phosphorylate SQSTM1 and promotes autophagy [65]. In addition, SESN2 sustains AMPK activation to inhibit mTORC1 [66]. These observations provide links to the role of SESNs in autophagy in response to oxidative stress. In addition, starvation-induced H_2O_2 oxidizes ATG4 at Cys78 to spatiotemporally inactivate ATG4 and ensure that lipidated LC3-II can facilitate autophagosome formation before deconjugation [67]. In addition, ROS elevate AMPK phosphorylation and activity to inhibit mTORC1 [68]. Alternatively, ROS downregulate PI3K-AKT signaling to reduce mTORC1 activity for autophagy induction [69, 70]. As mentioned above, AMPK and mTORC1 are positive and negative regulators

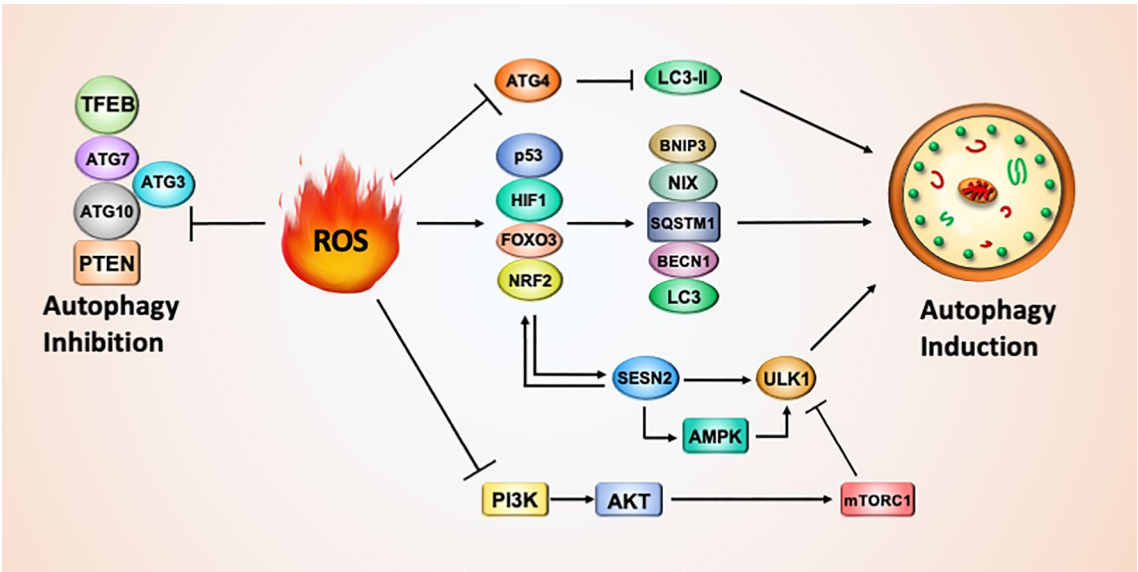

Fig. 2 Dual role of ROS in autophagy induction and inhibition. ROS trigger the activation of transcription factors, such as p53, HIF1A and NRF2, to induce the expression of autophagy-related genes. ROS spatiotemporally oxidize and inactivate ATG4 to maintain lipidated LC3-II and autophagosome formation. ROS also block PI3K-AKT-MTORC1 signaling to initiate autophagy signaling. In contrast, ROS oxidize ATG proteins and PTEN to suppress autophagy

of ULK1, respectively. Thus, ROS can initiate autophagy through AMPK activation and mTORC1 inactivation.

ROS inhibit autophagy

In contrast, the autophagy core protein E1-like enzyme ATG7 and E2-like enzymes ATG10 and ATG3 consist of sulfhydryl groups, which are sensitive to ROS oxidation and inactivate enzyme activity (Fig. 2) [53]. The inactivation of these core enzymes of autophagy leads to autophagy reduction. ROS also inactivate PTEN, a phosphatase that negatively regulates PI3K-AKT-mTORC1, to diminish autophagy [54]. Moreover, Transcription Factor EB (TFEB) is a mater regulator to drive gene expression required for biogenesis of autophagosome and lysosome [71]. Low concentration (100 or 200 μM) of H_2O_2 activates TFEB and has no effects on cell viability, whereas high concentration (400 or 800 μM) of H_2O_2 inactivates TFEB and leads to neuron cell death [55]. Thus, ROS may initially oxidize and inactivate essential autophagy genes and then induce several pathways to reactivate autophagy and compensate for the redox status. Alternatively, ROS-modulated autophagy might rely on the context of cell types and the timing or conditions of stress for ROS generation.

Regulation of ROS by autophagy

ROS stimulation accumulates impaired organelles and enhances cellular ROS in autophagy-deficient cells lacking BECN1, ATG5 or ATG7 [72, 73]. ROS-oxidized organelles and proteins can be removed by autophagy to protect cells [74, 75]. Autophagy is a form of quality control for cellular components, particularly for mitochondria, peroxisomes and proteins that are involved in ROS generation [10, 76]. Thus, although autophagy is modulated by ROS, autophagy also has a feedback loop to regulate ROS levels through transcription factor (NRF2, p53) activation or the degradation of damaged components, such as mitochondria, peroxisomes and unfolded proteins, as discussed below (Fig. 3).

Clearance of impaired organelles

Mitochondria and peroxisome are major ROS-producing organelles in cells. Mitophagy and pexophagy are types of selective autophagy to degrade impaired mitochondria and peroxisome, respectively. As mentioned above, cellular ROS are mainly produced from mitochondria, which are so-called mitoROS. MitoROS can be limited to regular oxidative phosphorylation reactions in the inner membrane of mitochondria in cells under normal conditions. In contrast, mitochondria also contain ROS scavenger systems, such as the superoxide dismutase (SOD) family of proteins [77], to convert $O2^-$ into H_2O_2 to maintain redox homeostasis and GSH (glutathione) redox systems to decompose H_2O_2 into O_2 and H_2O [78]. Mitochondrial dysfunction leads to cellular ROS elevation [79]. Mitophagy is a selective autophagy pathway that degrades impaired mitochondria. Mitophagy defects result in the accumulation of impaired mitochondria

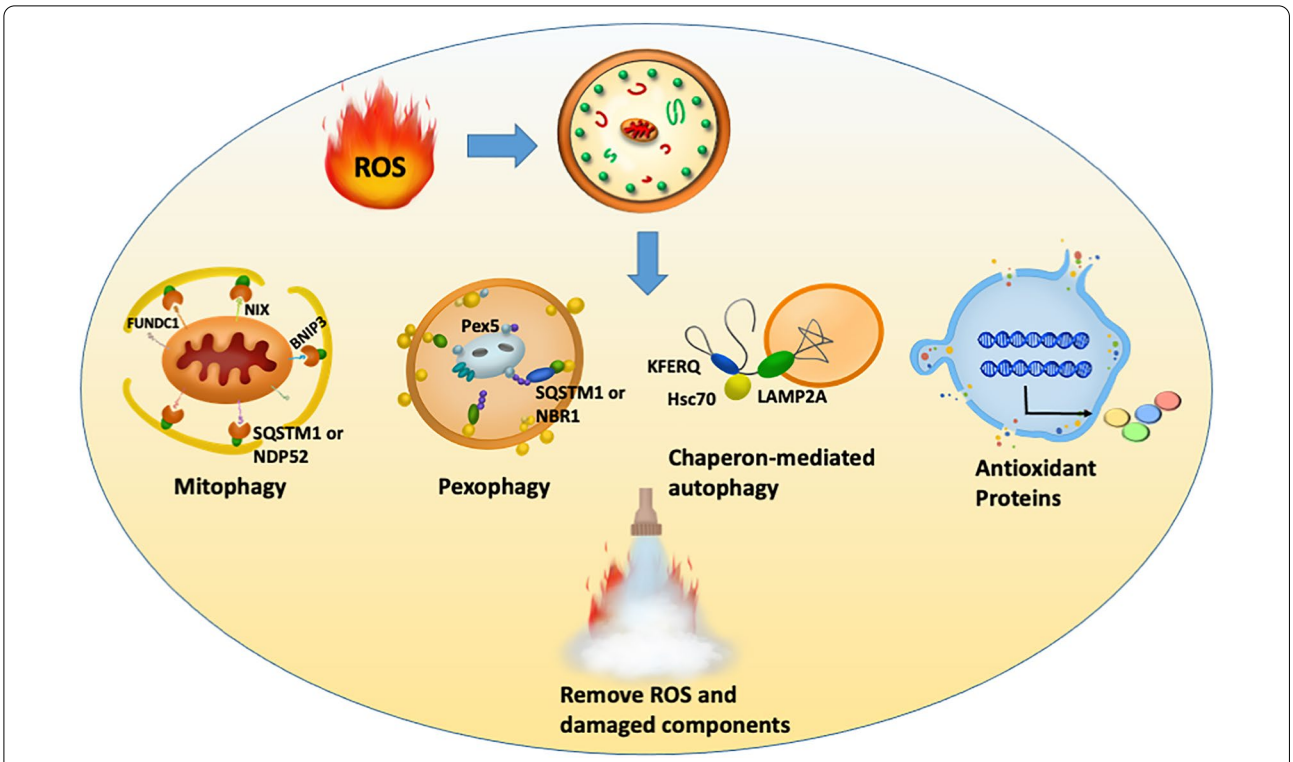

Fig. 3 Pathways involved in ROS elimination by autophagy in cells under oxidative stress. Autophagy can degrade ROS-generating organelles, including mitochondria (mitophagy) and peroxisomes (pexophagy), by binding ubiquitinated proteins to autophagy receptors (SQSTM1, NBR1 and NDP52). Autophagy also removes unfolded proteins through chaperone-mediated autophagy. In addition, autophagy activates NRF2 to induce antioxidant gene expression to eliminate excessive ROS in cells

and the elevation of cellular ROS and damage [80, 81]. Mitophagy is processed mainly via Parkin ubiquitination and BNIP3-NIX-FUNDC1 mitochondrial adaptor pathways.

Parkin is an E3 ubiquitin ligase and is phosphorylated at S65 by PTEN-putative kinase 1 (PINK1) [82]. The phosphorylation of Parkin is fully activated due to conformational changes to (i) eliminate autoinhibitory effects and (ii) bind charged E2 ligases [83]. Active Parkin ubiquitinates many mitochondrial proteins located in the outer membrane, matrix and inner membrane, such as voltage-dependent anion channel 1 and mitofusins (Mfn1 and Mfn2) [84, 85]. Ubiquitinated mitochondrial proteins associate with autophagy cargo receptors, such as SQSTM1, NDP52 and optineurin, to recruit damaged mitochondria to autophagosomes. The Rab signaling proteins RABGEF1, RAB5, and RAB7A, located on the mitochondrial surface, are also involved in the mitophagy recruitment process [86, 87]. Interestingly, Parkin translocates to mitochondria in cells under oxidative stress, indicating that Parkin is important for oxidative-stress-mediated mitophagy [88, 89].

Moreover, several other cargo adaptors are induced by oxidative stress to facilitate mitophagy, such as FUNDC1, NIX and BNIP3. These mitochondrial cargo adaptors include the LC3-interacting region, which connects mitochondria and autophagosomes to promote mitophagy [90]. FUNDC1-mediated mitophagy is positively and negatively regulated by ULK1 and Src kinase, respectively [90, 91].

Peroxisomes are organelles that undergo many metabolic pathways in cells, particularly pathways involved in lipid metabolism, such as the α- and β-oxidation of fatty acids, ketogenesis, and the metabolism of isoprenoids and cholesterol [92]. In addition to mitochondria, peroxisomes are another main organelle that produces intracellular ROS by releasing free electrons from several oxidases [93, 94]. Peroxisomes also contain many antioxidant enzymes to remove excessive ROS, including GPX, catalase, and SOD [95]. Defects or damage to peroxisomes may lead to intracellular ROS elevation, while damaged peroxisomes can be eliminated by pexophagy. Pexophagy starts with ataxia-telangiectasia mutated kinase (ATM) activation through ROS-mediated disulfide bond formation of ATM to dimerize and become its active form [96–98]. Active ATM promotes AMPK activation, which in turn phosphorylates ULK1 kinase for autophagy initiation [99, 100]. Additionally,

ATM phosphorylates peroxisomal protein Pex5 at Ser141 to trigger Pex5 ubiquitination [101]. Ubiquitinated Pex5 then interacts with the autophagy receptors SQSTM1 and NBR1 to degrade damaged peroxisomes through pexophagy [7]. In addition, ROS are elevated in patients with ATM mutations and ATM-deficient mice [102, 103], supporting the notion that pexophagy can eliminate excessive ROS to maintain redox homeostasis and keep cells healthy.

Clearance of unfolded proteins by CMA

CMA is a specific type of autophagy that delivers unfolded proteins into lysosomes and degrades them in a chaperone-dependent manner. In contrast to proteasomal degradation, CMA requires a KFERQ pentapeptide sequence as a degradation signal in substrate proteins (approximately 30% soluble proteins) instead of ubiquitination [104]. When cells are under oxidative stress, proteins containing the pentapeptide sequence are unfolded to expose the sequence for binding with constitutive heat shock protein 70 (HSC70) [105]. A recent study also showed that some of pentapeptide non-existing proteins may create a KFERQ-like structure for HSC70 recognition in cells under oxidative stress [106]. The chaperone-associated complex is then translocated to lysosomes and imported by LAMP-2A for degradation. Moreover, *LAMP-2A* gene expression is induced in cells during oxidative stress [105, 107]. Silencing LAMP-2A impairs CMA and increases ROS-induced ferroptosis in retinal pigment epithelial ARPE-19 cells, while cysteine and glutamine supplementation rescue ROS-induced cell death [108]. Interestingly, increased macroautophagy is not able to restore ROS-induced damage in CMA-defective cells [109], suggesting that CMA is essential for cytoprotection in response to ROS.

Expression of antioxidant and autophagic pathways

NRF2 is the major transcription factor involved in autophagy-mediated antioxidant mechanisms. NRF2 is normally ubiquitinated by the E3 ligase Kelch-like ECH-associated protein 1 (KEAP1) and results in degradation [110]. KEAP1 can be eliminated by autophagy, specifically through interruption by SQSTM1 (Fig. 4).

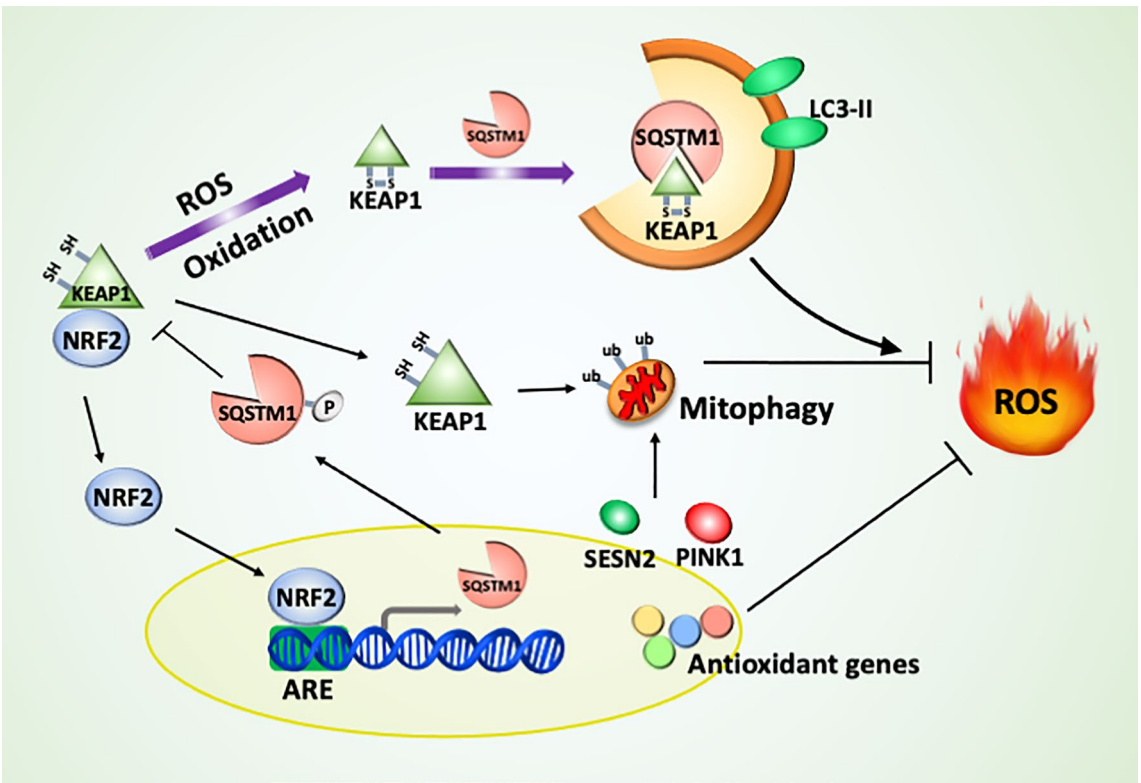

Fig. 4 The mechanisms of NRF2 activation and antioxidation. KEAP1, an E3 ligase of NRF2, can be directly oxidized and recruited by SQSTM1 to autophagosomes for degradation. Liberated NRF2 can induce the gene expression of the antioxidant genes Sqstm1, Sesn2 and Pink. The induced SQSTM1 is phosphorylated to interrupt the binding between KEAP1 and NRF2 for further positive feedback activation of NRF2. The released KEAP1 and induced SESN2 and PINK promote mitophagy to remove damaged mitochondria

Cysteine residues of KEAP1 are oxidized to form disulfide bonds and lead to conformational changes to release NRF2 [111]. NRF2 can enter the nucleus and bind to the promoter with an antioxidant-response element (ARE, 5′-TGACXXXGC-3′) to turn on the expression of several antioxidant, detoxification enzymes and autophagy genes, including NADPH quinone dehydrogenase 1 (*NQO1*), glutathione S-transferase (*GST*) genes and *SQSTM1* [110, 112–117]. SQSTM1 is phosphorylated by mTORC1 to compete for the interaction between KEAP1 and NRF2, thereby preventing NRF2 degradation [118, 119]. ATG8-defective mice accumulate SQSTM1, resulting in the hyperactivation of NRF2 and limiting oxidative stress [119], whereas Nrf2-knockout mice exhibit elevated oxidative stress [120]. Thus, NRF2 and SQSTM1 are parts of a positive feedback loop to reduce oxidative stress. Moreover, NRF2 induces the gene expression of *SESN2* and *PINK1* to promote macroautophagy and mitophagy in the cell response to oxidative stress, respectively [121, 122]. In addition to the Parkin E3 ubiquitin ligase, SQSTM1 triggers the translocation of KEAP1, an E3 ubiquitin ligase, to mitochondria for mitophagy activation [123].

The effects of ROS-mediated autophagy on survival and death

Autophagy acts as a recycling pathway to eliminate impaired proteins, organelles or pathogens to maintain cell health. Intracellular oxidative stress significantly regulates autophagy. In addition, autophagy regulates ROS levels in cells via mitophagy, pexophagy, proteasomal, and CMA pathways. Furthermore, autophagy can directly regulate antioxidant pathways (i.e., NRF2 and SESN molecules) to modulate redox homeostasis and cell survival. Thus, autophagy is thought to be a cytoprotective mechanism in cells under starvation or stressed conditions. However, excessive stress-induced autophagy may lead to cell death, which is called autophagic cell death [124]. Autophagic cell death meets the criteria that i) autophagic flux is increased and ii) the ablation of autophagy inhibits cell death to ensure that cell death is caused by autophagy rather than dying cells with protective autophagy. Autophagic cell death is observed under certain stresses, particularly oxidative stress. Hydrogen peroxide (H_2O_2) exposure or reactive oxygen species (ROS) generation through the disruption of mitochondrial function induces autophagic cell death [125, 126]. Genetic or pharmacological ablation of autophagy diminishes cell death, whereas the apoptosis inhibitor Z-VAD has no effects on cell death. The mechanisms of autophagic cell death can depend on certain cells in response to different conditions. For example, glycogen synthase kinase 3-beta, ryanodine receptor 3, and PARKIN are involved in mitophagy and autophagic cell death in hippocampal neural stem cells during insulin withdrawal [127]. Notably, the ryanodine receptor, which controls calcium release from the ER, is activated and leads to autophagic cell death in a variety of apoptosis-resistant cancer cells when exposed to neferine [128]. These observations suggest that excess autophagy may require lots of autophagy components, such as lipids, ATG proteins and signaling factors, and cause cellular burden/stress and death.

Autophagy and oxidative stress in the pathogenesis of retinal diseases

The roles of autophagy and oxidative stress in different ocular diseases are shown as schematic diagram (Fig. 5) and described below:

Glaucoma and optic neuropathies

Glaucoma is the second leading cause of blindness worldwide and was estimated to affect ~ 80 million people in 2020 [129]. Retinal ganglion cell (RGC) loss and extensive axon degeneration are the main signs of glaucoma. The elevation of intraocular pressure (IOP), one of the main causes of glaucoma, induces axonal degradation and RGC death, and this phenomenon is exacerbated with aging [130]. RGCs have long axons with a high density of mitochondria, which makes them more sensitive to oxidative stress [131]. In addition, growing evidence indicates that reactive oxygen species (ROS) play a key role in the pathogenesis of primary open angle glaucoma (POAG) by attacking trabecular meshwork (TM) cells [132, 133]. A recent study demonstrated that autophagy activation can be triggered by IOP elevation and mechanical stretch in TM cells, and primary cilia are critical for IOP homeostasis and autophagy activation [134].

In the optic nerve, oxidative stress is elevated after nerve crush injury [135], which triggers autophagy in RGCs, Müller cells [131, 136] and the primary visual cortex [137]. In addition, retinal hypoxia and axonal damage of the optic nerve also induce autophagy [138, 139]. Pharmacological induction of autophagy by rapamycin promotes RGC survival and after optic nerve axotomy in a mouse model [140]. The dysregulation of autophagy contributes to neurodegeneration in glaucoma [141]. SIRT1 activation enhances axonal protection in TNF-α-induced optic nerve degradation by elevating the autophagy pathway [142]. In addition, BNIP3L-mediated mitophagy is required for optic nerve oligodendrocyte differentiation [143]. Autophagy is enhanced after optic nerve crush (ONC) damage in zebrafish RGC axons, somas, and growth cones [144].

In a transgenic animal model, *Atg4b*-/- mice were more susceptible to stress, as optic nerve axotomy resulted in

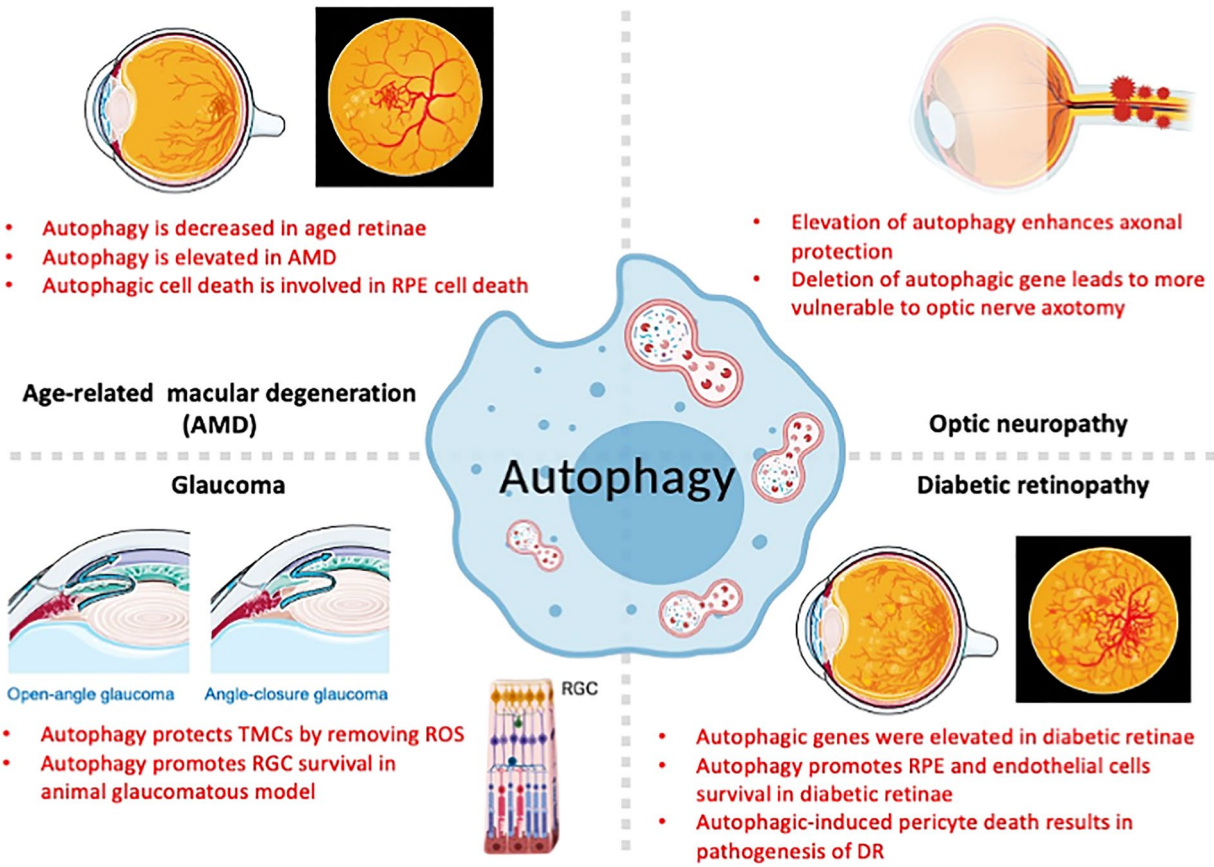

Fig. 5 The potential involvement of autophagy in different ocular diseases. Autophagy is involved in several ocular diseases, including age-related macular degeneration (AMD), glaucoma, optic neuropathy, and diabetic retinopathy (DR). In general, autophagic flux protects retinal cells from oxidative-induced insult. However, excess autophagic flux may cause cell death and lead to retinal degeneration, such as in cells of the retinal pigment epithelium (RPE) in AMD and pericytes in DR. This figure was created partially with BioRender.com and Smart.Servier.com

reduced RGC survival in these animals compared with WT mice, suggesting that autophagy levels can alter the capability of RGCs to respond to axonal stress [145]. In a mouse model, retinae with *Atg5* deletion by intravitreally injected with adeno-associated virus (AAV)2-ATG5$^{fl/fl}$ were more vulnerable to optic nerve axotomy than control mice [140]. Cells from autophagy-deficient animals show increased levels of ROS [131]. In addition, mutations of optineurin (OPTN) were known to associated with normal tension glaucoma [146]. Genetic mutation of *OPTN* at residue E50K was reported to affect autophagy and cause the apoptosis of RGCs. The disruption of OPTN^{E50K} induced autophagy affected the degradation of TDP-43, which led to glaucomatous retinal neurodegeneration [147].

MTOR, the mammalian target of rapamycin, plays an important role in RGCs and glial cells for retinal development and axonal survival after ON injury [148]. Many studies have reported that the mTOR inhibitor rapamycin is used to induce autophagy and treat glaucoma in rodent models [149], showing the promotion of RGC survival in the ischemia/reperfusion injury model caused by IOP elevation [150]. Autophagy decreases with aging in the retina, and the induction of autophagy shows neuroprotective effects in a glaucoma animal model [151]. Although most evidence shows that autophagy is protective in glaucoma, an opposing result showed that the inhibition of autophagy by 3-methyladenine (MA) alleviates acute axonal degeneration in a rat model [139]. Another study in a zebrafish model showed that the inhibition of autophagy promotes axonal regrowth [144].

Age-related macular degeneration

There are two main types of age-related macular degeneration (AMD), dry AMD (geographic atrophy) and wet AMD (choroidal neovascularization, CNV). In dry AMD, patients develop yellow deposits, called drusen, in their macula. Without appropriate treatment, drusen become increasingly numerous, causing light-sensitive cell death in the macula and leading to

multiple blind spots in the central vision. Once AMD reaches an advanced stage, blood vessels grow from underneath the macula and leak blood and fluid into the retina, eventually forming a scar and leading to permanent loss of central vision [152]. Among various factors, oxidative stress is strongly implicated in AMD [153, 154]. Aging [155] and oxidative stress [156] were reported to be involved in retinal neovascularization, which is an advanced progression of AMD. However, a study reported that oxidative stress-induced nuclear factor kappa B (NF-κB) signaling promotes retinal pigmented epithelial (RPE) cell survival through increased autophagy [157]. In addition, the catalytic subunit of human telomerase (hTERT) is known to be associated with AMD by interacting with mTORC1 (mechanistic target of rapamycin complex 1) and PINK1 (PTEN-induced kinase 1), which activates macroautophagy and mitophagy, respectively [158]. A decrease in autophagic activity with age observed in many tissues has been proposed to contribute to the aggravation of age-related diseases [159].

The RPE is responsible for the phagocytosis of photoreceptor outer segments (POSs) [155] and is considered one of the most important retinal cells involved in AMD [160]. With increasing age, lipofuscin accumulates in the RPE and contributes to the pathogenesis of AMD [155]. Autophagy regulates the death of RPE cells in AMD [161]. Impairing autophagy in RPE leads to inflammasome activation and enhances macrophage-mediated angiogenesis. In vitro inhibition of rotenone-induced autophagy in RPE cells elicits caspase-3-mediated cell death [162]. The autophagy marker ATG5 was observed in the drusen of human normal old eyes and was even more in AMD eyes, suggesting that autophagy contributes to the formation of drusen in aged RPE [163]. The deletion of ATG5 leads to apoptosis in the outer nuclear layer (ONL) of the mouse retina [164]. Compared with normal eyes, the RPE from human donor AMD eyes shows more autophagosome expression and is more susceptible to oxidative stress [165], which suggests that dysfunctional autophagy contributes to the pathophysiology of AMD [166]. The dying RPE triggered by autophagic pathway would be engulfed by human macrophages and dendritic cells (DCs), and a failure of engulfment in the retina may result in the accumulation of debris and the progression of AMD [167]. Oxidative stress was reported to induces autophagy and cell death in RPE cells [167, 168]. Silencing autophagy essential genes (*ATG5/ATG7*) diminishes cell death in ARPE-19 cells treated with H_2O_2 [169], suggesting that autophagic cell death is involved in RPE cell death when cells are exposed to excessive oxidative stress.

Diabetic retinopathy

Diabetic retinopathy (DR) is a severe ocular complication of diabetes and accounts for ~ 5% of all cases of blindness worldwide. Hyperglycemia, the common symptom of diabetes, is known to induce oxidative stress in retinal cells [170]. The early stage of DR is usually termed nonproliferative diabetic retinopathy (NPDR). In NPDR, the blood vessels in the retina close off, and blood cannot reach the macula, which is also called macular ischemia. DR that progresses to an advanced stage is termed proliferative diabetic retinopathy (PDR). In eyes with PDR, the retina begins to grow new blood vessels, called neovascularization. These new vessels often cause blood leakage into the vitreous and block vision. To test the correlation between diabetes and autophagy, a study conducted using a RPE cell culture exposed to hyperglycemic conditions showed that high glucose (HG) induces the autophagosome formation regulated by ROS-mediated ER stress signaling [171]. In a diabetic mouse model, autophagosome and autophagic proteins (Beclin-1 and Atg5) were elevated in the diabetic retina, leading to a loss of rod photoreceptors and a reduction in the thickness of the outer and inner synaptic layers [172]. In addition, HG promotes advanced glycation end product (AGE) formation, causing oxidative stress and inflammatory responses that alter vascular function in the diabetic retina, resulting in diabetic complications [173, 174]. Strong evidence indicates that autophagy plays a protective role in suppressing inflammasome activation [175]. On the other hand, an increase in autophagy through the inhibition of mTOR signaling promotes endothelial cell survival in diabetic retinas, which can alleviate the progression of DR [176]. Conversely, a long-term increase in autophagy induces pericyte cell death, which may result in the pathogenesis of DR [177].

Current therapy for retinal degeneration

Glaucoma

IOP elevation is one of the main causes of glaucoma. In the clinic, glaucoma is often treated with prescription eyedrops. A variety of eyedrops are used, including prostaglandins [178], beta blockers [179], alpha-adrenergic agonists [180], carbonic anhydrase inhibitors [181], Rho kinase inhibitors [182] and cholinergic agents [183], all of which regulate glaucoma through different molecular mechanisms. These eyedrops function to decrease eye pressure by improving the drainage of fluid from the eye or by decreasing the amount of fluid that the eye makes. However, some patients complain of side effects unrelated to the eyes due to the molecular absorption of eyedrops into the bloodstream.

In certain patients with advanced glaucoma, eyedrops fail to reduce eye pressure to the desired level, whilst

patients with acute angle-closure glaucoma require surgical procedures or alternative treatments, including laser therapy [184], filtering surgery [185], drainage tubes [186], or minimally invasive glaucoma surgery [187].

RGCs degenerate in glaucoma, which leads to permanent vision loss. Thus, a cell replacement strategy was considered a potential therapy to treat RGC loss. In the past decade, scientists have been able to differentiate human stem cells into RGC-like cells [188–192]. However, how to scale up donor cells, promote long-term cell survival and enhance synaptic integration into the visual circuit remains a challenge for stem cell therapy [193].

Optic neuropathies

Optic neuropathies take various forms, including non-arteritic anterior ischemic optic neuropathy (NAION), which damages the optic nerve and results from a change in blood flow or optic nerve trauma due to acute injury to the optic nerve. However, to date, there is no effective treatment for NAION. To slow the progression of NAION, treatment focuses on controlling blood pressure, reducing the symptoms and preventing NAION from damaging the other eye.

On the other hand, arteritic ischemic optic neuropathy treatment also aims to prevent further damage to the other eye and typically involves the use of anti-inflammatory drugs. Treatment depends entirely on the underlying condition or problem that causes the neuropathy and requires a full evaluation from an eye specialist.

Glaucoma is another main cause of optic neuropathy. Axons of RGCs degenerate in optic nerve injury and do not regrow; thus, what regulates axon regeneration remains a field of interest to scientists. Many studies have shown the promotion of axon regeneration by molecular therapies [194–198]. However, the length of regenerative axons and synaptic reconnection are still limited [199].

Optic glioma, which usually occurs in childhood, also leads to optic neuropathy and vision loss [200, 201]. A recent study indicated that light plays an important role in glioma formation during eye development [202]. Since light exposure induces photooxidative stress [203], which could induce autophagy, it would be interesting to ask whether autophagy regulates the formation of glioma-induced optic neuropathy in future studies.

Age-related macular degeneration

To date, there is no cure for macular degeneration. However, several treatments, mainly anti-vascular endothelial growth factor A (VEGFA) class, may slow the progression of AMD or maintain existing vision. For example, the anti-angiogenesis drugs aflibercept (Eylea) [204] and bevacizumab (Avastin) [205] are used to block the creation of blood vessels and the subsequent leakage from these vessels that cause wet macular degeneration. A portion of the lost vision of many AMD patients who have taken these drugs has been improved [206]. If AMD is advanced, the patient might need to receive this treatment multiple times and such treatment is applied only in advanced AMD, which requires multiple injections.

In some patients, ophthalmologists recommend performing laser therapy by applying high-energy laser light to destroy abnormal blood vessels growing in the eye [207]. Alternatively, the doctor may perform photodynamic laser therapy by injecting the light-sensitive drug verteporfin (Visudyne) into the bloodstream, which is absorbed by abnormal blood vessels [208]. In addition, there are adjuvant devices such as special lenses or electronic systems for creating larger images of nearby things, which can help those who have vision loss due to macular degeneration and maximize their remaining vision [209].

Diabetic retinopathy

Neovascularization is the hallmark of DR. In the clinic, intravitreal injection of anti- VEGF agents such as bevacizumab, aflibercept, ranibizumab [210], which we described above in the AMD section, is the primary procedure to slow the progression of DR. To reduce the swelling of the retina, scatter laser surgery might be used to help block leaking blood vessels. In addition, laser surgery also helps shrink blood vessels and prevent them from proliferation. However, laser treatment is associated with a risk of peripheral (side), color, and night vision loss.

Once advanced proliferative DR (PDR) develops, an ophthalmologist may recommend an alternative surgery called vitrectomy [211], a procedure to remove vitreous gel containing blood from leaking vessels and scar tissue in the back of your eye. However, the procedure is associated with some risks, including ocular infection, cataract formation and retinal detachment.

In the development of a less invasive treatment, pharmaceutical DR treatment strategies have been explored in recent decades. Aldose reductase (AR), the enzyme that converts glucose to sorbitol, is involved in a variety of diabetic complications, including DR [212]. Many AR inhibitors have been developed to alleviate the progression of diabetic complications and ocular inflammation in animal models [213]. However, renal and liver toxicity remains a concern in clinical trials [214, 215].

Role of autophagy in current ocular degeneration therapy

In addition to operating the procedures or surgeries mentioned above, slowing the onset or progression of such diseases still a goal for ocular degeneration therapy. Since ROS is one of the main causes of many degenerative diseases in the eye and autophagic pathway could clean

the cells of all irreversibly oxidized biomolecules [74], developing topical drug based on mediating autophagic pathway would be a great of interest for scientists and clinicians. Many autophagic inducers were tested in animal models or have been used in the clinic. We next explore the detail of autophagic inducers or inhibitors in the next chapter.

Effects of autophagic inducers and inhibitors on retinal degenerative diseases

Steroids

In a rat glaucoma model, neurosteroids induced the autophagy pathway to protect retinal neurons via GABRs/GABAA receptors [216]. However, another study reported that steroid therapy in the eye leads to the dysregulation of TMCs and glaucoma pathologies by inhibiting the autophagosome biogenesis pathway [217]. More studies are needed to conclude the effect of steroids on retinal neurons.

Rho kinase inhibitor

Ripasudil is a rho-associated coiled-coil-containing protein kinase 1 (ROCK1) inhibitor. In the clinic, ripasudil is a key component in ophthalmic solutions for treating glaucoma by reducing IOP [218]. In a rodent model study, ripasudil was shown to enhance intraaxonal autophagy and promote axonal protection [219].

mTORC1 inhibitors

Rapamycin

The activation of autophagy, modulated by the rapamycin-induced inhibition of mTORC1 signaling, is able to prevent the harmful AMD-related aging of RPE cells [220]. The mTOR inhibitor rapamycin ameliorates the high glucose-induced inflammatory responses and ROS in the RPE [221]. Rapamycin plays a protective role in a rodent chronic hypertensive glaucoma model [222] and significantly increases RGC survival following optic nerve transection [140]. The heteroplasmic mtDNA G11778A mutation is the most common cause of Leber's hereditary optic neuropathy. An in vitro study showed that rapamycin treatment induces the colocalization of mitochondria with autophagosomes, resulting in less damage from the G11778A mutation [223]. The findings of this study suggest the potential of rapamycin as a therapeutic strategy to treat Leber's hereditary optic neuropathy.

Everolimus

Fibroblast-mediated scar formation is a common complication of glaucoma filtering surgery. A study showed that everolimus, another mTORC1 inhibitor, suppresses the proliferation of fibroblasts in the eye after surgery [224]. In addition, everolimus has been shown to suppress angiogenesis [225], which is the onset of wet AMD [226] and DR [227]. Everolimus is also a common therapy for kidney transplant recipients at a late post-transplant stage [228]. However, a clinical case study reported that long-term administration of immunosuppressant everolimus or tacrolimus (an analog of everolimus) in a transplant recipient might be a risk factor for the development of posterior reversible encephalopathy syndrome or optic neuropathy [229, 230].

Temsirolimus

Temsirolimus, an analog of everolimus, inhibits RPE and endothelial cell proliferation and migration, and decreases VEGF and PDGF expression [231], which can be used to alleviate AMD and DR. In addition, sirolimus is also considered an antiangiogenic drug for DR progression [232].

AMPK activator

Metformin is able to trigger autophagy through AMPK activation and the subsequent inhibition of mTORC1 signaling [233]. Metformin is used to control blood sugar and is considered to reduce the risk of the onset of AMD [234], glaucoma [235] and DR [236] in diabetic patients.

mTOR-independent autophagy inducer

Lithium (LiCl) induces autophagy through an mTOR-independent pathway [237]. In animal studies, LiCl was reported to be an autophagy inducer for alleviating the progression of glaucoma [238], DR [239] and optic neuropathy [240].

Inhibitors of autophagosomes and lysosomes

Chloroquine (CQ) and hydroxychloroquine (HCQ) are autophagic inhibitors popularly used as antitumor agents [241]. Both CQ and HCQ have been reported to cause RGC damage [242, 243]. In the clinic, the mean values of quantified fundus autofluorescence (QAF, an indirect approach to measuring lipofuscin in the RPE in vivo) were significantly higher in patients receiving CQ/HCQ than in healthy controls, indicating that CQ/HCQ treatment leads to retinal damage [244]. Another case study reported the incidence of blindness in a population of rheumatic patients treated with HCQ [245]. In addition, CQ completely abolished the antiapoptotic effect of the somatostatin analog octreotide in hyperglycemia-treated retinal tissue [246], suggesting that CQ might worsen the progression of DR.

On the basis of the literature reviewed above, the promotion of the autophagic pathway plays a protective role in retinal degenerative diseases. The application of autophagic inhibitors in the clinic requires more research

Table 2 Effects of FDA-approved autophagy-target drugs on retinal degenerative diseases

Drug	Mechanism	Role	Diseases	Physiologic effects	References
Chloroquine (CQ) & hydroxychloroquine (HCQ)	Autophagy inhibition to Autophagosome & Lysosome	Harmful	Glaucoma	Treatment of CQ and HCQ causes RGC and retinal damage	[244–246]
			Diabetic retinopathy	CQ worsens the progression of diabetic retinopathy	[248]
			Blindness	Rheumatic patients treated with HCQ leads to blindness	[247]
Rapamycin	Autophagy activation by mTORC1 inhibition	Protective	Glaucoma	Rapamycin is neuroprotective in a chronic hypertensive glaucoma model and increases RGC survival following optic nerve transection	[142, 224]
			AMD	Rapamycin prevents AMD-related aging of RPE cells	[222]
			Diabetic retinopathy	Rapamycin ameliorates the high glucose-induced ROC in the RPE	[223]
			Optic neuropathy	Rapamycin-induced autophagy results in less damage from G11778A mutation, the most common cause of Leber's hereditary optic neuropathy	[225]
Everolimus	Autophagy activation by mTORC1 inhibition	Protective	Glaucoma	Everolimus suppresses the scar formation in glaucoma filtering surgery in an animal model	[226]
			AMD	Everolimus suppresses angiogenesis molecular pathways in the onset of wet AMD	[228]
			Diabetic retinopathy	Everolimus suppresses angiogenesis molecular pathways in the onset of diabetic retinopathy	[229]
		Harmful	Optic neuropathy	Long-term administration of everolimus may cause reversible encephalopathy syndrome and bilateral optic neuropathy after kidney transplantation	[231, 232]
Temsirolimus	Autophagy activation by mTORC1 inhibition	Protective	AMD	Temsirolimus inhibits RPE and endothelial cell proliferation and decreases VEGF and PDGF expression	[233]
			Diabetic retinopathy	Temsirolimus is considered as an antiangiogenic drug for diabetic retinopathy progression	[234]
Metformin	Autophagy activation by AMPK activation and subsequent inhibition of mTORC1 signaling	Protective	Glaucoma AMD Diabetic retinopathy	Metformin is used to control blood sugar and is considered to reduce the risk of the onset of glaucoma, AMD, and diabetic retinopathy in diabetic patients	[236–238]
Lithium (LiCl)	Autophagy activation by mTOR-independent pathway	Protective	Glaucoma Diabetic retinopathy Optic neuropathy	In animal studies, LiCl was reported as an autophagy inducer, which could alleviate the progression of glaucoma, diabetic retinopathy, and optic neuropathy	[240–242]
Ripasudil	Autophagy activation by inhibition of rho-associated coiled-coil containing protein kinase 1 (ROCK1)	Protective	Glaucoma	Ripasudil is the key component in ophthalmic solutions for treating glaucoma by reducing IOP Ripasudil promotes axonal protection in an animal model	[220, 221]
Steroids	Autophagy activation by $GABA_A$ receptor	Protective	Retinal degeneration	Neurosteroids induces the autophagy pathway to protect retinal neurons	[218]
	Inhibiting autophagosome biogenesis pathway	Harmful	Glaucoma	Steroid therapy in the eye leads to the dysregulation of TMCs and develop glaucoma pathology	[219]

RGC: Retinal ganglion cell; AMD: age-related macular degeneration; mTORC1: mammalian target of rapamycin complex 1; RPE: retinal pigment epithelium; VEGF: vascular endothelial growth factor; PDGF: platelet-derived growth factor; AMPK: AMP-activated protein kinase; IOP: intraocular pressure; TMC: trabecular meshwork cell

and assessments of the risk of their unfavorable side effects, especially in the eyes.

Conclusion

ROS-mediated damage to cellular components is highly associated with the pathogenesis of several ocular diseases, as mentioned above. Autophagy is one of the main routes to eliminate damaged components in cells in response to oxidative stresses. ROS may initially oxidize several enzymes, including ATG proteins, to inhibit autophagy. ROS then trigger signaling pathways to activate autophagy to form a negative feedback loop to suppress ROS. Though the role of autophagy in the pathogenesis of ocular diseases might vary, autophagy should be a beneficial pathway for ocular cell survival under short-term oxidative stress. As aforementioned (Table 2), several autophagy inducers, particularly the AMPK inducer and mTORC1 inhibitors, have been shown to diminish the severity of ocular diseases in preclinical and clinical studies. In contrast, autophagy inhibitors CQ or HCQ are harmful in ocular diseases. Additionally, Neurofibromatosis 1 (NF1) mutation was reported to develop optic pathway gliomas [202], which leads to permeant blindness. Studies showed that activation of the mTOR pathway has been identified in benign and malignant NF1 tumors [247, 248], suggesting that activation of autophagy by inhibiting mTOR pathway could be a potential therapeutic strategy for optic neuropathy in patients with glioblastoma. However, metformin inhibits mitochondrial enzymes to activate AMPK, and the effects on cell protection could be AMPK- or autophagy-dependent and autophagy-independent [249, 250]. mTORC1 not only regulates autophagy signaling but also modulates cell differentiation, cell proliferation, angiogenesis and inflammation [251]. Therefore, more research on the role of autophagy in ocular diseases is required, particularly in clinical settings. The limitations of research on the role of autophagy in clinical ocular diseases are mainly due to the following: (i) the ocular structure of animals cannot completely reflect that in patients, (ii) a precise assay for autophagic flux in patients is lacking, (iii) specific autophagy modulators as clinical drugs are lacking, and (iv) the role of autophagy in different ocular disease types and stages might vary. Nevertheless, this review sheds light on autophagy modulation as an intervention for ocular diseases.

Abbreviations

AGE: Advanced glycation end product; AMD: Age-related macular degeneration; AR: Aldose reductase; ATM: Ataxia-telangiectasia mutated; CMA: Chaperone-mediated autophagy; FoxO3: Forkhead box O-3; HIF-1*α*: Hypoxia-inducible factor-1*α*; HOPS: Homotypic fusion and protein sorting; IOP: Intraocular pressure; KEAP1: Kelch-like ECH-associated protein 1; LIR: LC3-interacting region; mTORC1: Mechanistic target of rapamycin complex 1; NPDR: Nonproliferative diabetic retinopathy; NQO1: NADPH quinone dehydrogenase 1; NRF2: Nuclear factor erythroid 2–related factor 2; ONC: Optic nerve crush; ONL: Outer nuclear layer; PAS: Pre-autophagosomal structure; PDR: Proliferative diabetic retinopathy; PI3K: Phosphatidylinositol 3 kinase; PI3P: Phosphatidylinositol 3-phosphate; PINK1: PTEN-putative kinase 1; POAG: Primary open angle glaucoma; POSs: Photoreceptor outer segments; RGC: Retinal ganglion cell; RPE: Retinal pigmented epithelial; ROCK1: Rho-associated coiled-coil-containing protein kinase 1; ROS: Reactive oxygen species; SOD: Superoxide dismutase; TFEB: Transcription Factor EB; TM: Trabecular meshwork; UBA: Ubiquitin-associated; UVRAG: UV radiation resistance-associated; VEGFA: Vascular endothelial growth factor A.

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Authors' contributions

KCC, PFL, YCL, YJC and CWS wrote the manuscript. CHC generated the figures and table. All authors read and approved the final manuscript.

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