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Mitophagy in the retina: Viewing mitochondrial homeostasis through a new lens

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ABSTRACT

Mitochondrial function is key to support metabolism and homeostasis in the retina, an organ that has one of the highest metabolic rates body-wide and is constantly exposed to photooxidative damage and external stressors. Mitophagy is the selective autophagic degradation of mitochondria within lysosomes, and can be triggered by distinct stimuli such as mitochondrial damage or hypoxia. Here, we review the importance of mitophagy in retinal physiology and pathology. In the developing retina, mitophagy is essential for metabolic reprogramming and differentiation of retina ganglion cells (RGCs). In basal conditions, mitophagy acts as a quality control mechanism, maintaining a healthy mitochondrial pool to meet cellular demands. We summarize the different autophagy- and mitophagy-deficient mouse models described in the literature, and discuss the potential role of mitophagy dysregulation in retinal diseases such as glaucoma, diabetic retinopathy, retinitis pigmentosa, and age-related macular degeneration. Finally, we provide an overview of methods used to monitor mitophagy *in vitro*, *ex vivo,* and *in vivo*. This review highlights the important role of mitophagy in sustaining visual function, and its potential as a putative therapeutic target for retinal and other diseases.

1. Introduction

1.1. Autophagy

Autophagy is one of the main intracellular recycling pathways, in which the material to be degraded is delivered to the lysosome for digestion by acid hydrolases. Intrinsically a catabolic process, autophagy was long associated with cell death until the discovery of its crucial pro-survival role during starvation in mammalian cells (Boya et al., 2005). Autophagy is responsible for preserving homeostasis by degrading damaged or superfluous intracellular components of a wide range of sizes, from specific proteins to whole organelles, including mitochondria (Aman et al., 2021). Three main types of autophagy are described, each differing in the manner in which the cargo is delivered to the lysosome (Fig. 1).

Macroautophagy (henceforth referred to simply as "autophagy") is characterized by the formation of autophagosomes, a double-membrane vesicle containing the engulfed cargo, which is degraded within the acidic lumen of the lysosome following fusion. Autophagy initiation is mediated by the Atg/Ulk1 complex, which cooperates with the membrane-bound lipid scramblase Atg9 to trigger autophagosome formation. Simultaneously, the Atg/Ulk1 complex recruits and stimulates the class III PI3K complex, which promotes the generation of phosphatidyl inositol 3-phosphate (PI3P). PI3P accumulation at the initial phagophore initiation site recruits proteins from the PI3P-binding WIPI family, thereby promoting phagophore elongation. Finally, two ubiquitin-like conjugation complexes (Atg12 module and LC3 lipidation module) mediate cargo recognition and autophagosome formation. Lipidation of LC3 (or other Atg8-family proteins) through conjugation to phosphatidylethanolamine leads to recognition by autophagic substrates or by adaptors such as SQSTM1/p62, which contain a LC3-interacting region (LIR) motif. Once the cargo is fully enclosed, autophagosomes mature through fusion with endosomes and lysosomes (Levine and Kroemer, 2019; Nakatogawa, 2020).

Chaperone-mediated autophagy (CMA) is a highly selective pathway

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Abbreviations

ΔΨm	mitochondrial membrane potential
A2E	bis-retinoid N-retinyl-N-retinylidene ethanolamine
ADOA	Autosomal dominant optic atrophy
AGEs	advanced-glycation end products
AMD	age-related macular degeneration
ASM	autophagic secretion of mitochondria
BBB	blood-brain barrier
BRB	blood-retina barrier
CE	ceramide
CL	cardiolipin
CMA	chaperone-mediated autophagy
CNS	central nervous system
CSE	cystathionine-γ lyase
DAMPs	damage-associated molecular patterns
DMF	Dimethyl fumarate
DM	diabetes mellitus
DR	Diabetic retinopathy
ECs	endothelial cells
EM	electron microscopy
eMI	endosomal microautophagy
ER	endoplasmic reticulum
ERG	electroretinography
GCL	ganglion cell layer
GSH	glutathione
HDACs	histone deacetylases
IMCLAM	intramitochondrial CLICK to asses mitophagy
IMM	inner mitochondrial membrane
INL	inner nuclear layer
IOP	intraocular pressure
IPL	inner plexiform layer
IS	inner segments
KG	α-ketoglutarate
LDL	low-density lipoproteins
LHON	Leber's hereditary optic neuropathy
LIR	LC3-interacting region
LMP	lysosomal membrane permeabilization
MDVs	mitochondria-derived vesicles
MMS	methyl methanesulfonate
MTHFR	methylenetetrahydrofolate reductase
MTS	mitochondria-targeting sequence
OLM	outer limiting membrane
OMM	outer mitochondrial membrane
ONC	optic nerve crush
ONL	outer nuclear layer
OPL	outer plexiform layer
OS	outer segment
OxPhos	oxidative phosphorylation
PAMPs	pathogen-associated molecular patterns
PHDs	prolyl-4-hydroxylases
PI3P	phosphatidyl inositol 3-phosphate
POS	Photoreceptor outer segment
RGC	retina ganglion cell
ROS	reactive oxygen species
RP	retinitis pigmentosa
RPE	retinal pigment epithelium
SI	sodium iodate
TIM	translocase of the inner membrane
TOLLES	TOLerance of Lysosomal EnvironmentS
TOM	translocase of the outer membrane
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labelling
TXNIP	Thioredoxin-interacting protein
VLDLR	very low-density lipoprotein receptor

in which proteins containing a KFERQ-related motif are recognized by the chaperone Hsc70 and delivered to the lysosomal membrane, where it interacts with the lysosomal receptor LAMP2A, triggering its multimerization. The protein to be degraded is denaturalized, internalized via the LAMP2A multimer channel, and released into the lysosome for subsequent degradation (Gómez-Sintes and Arias, 2021). Long thought to be a pathway exclusive to mammals, a recent study described the presence of CMA in medaka fish (Lescat et al., 2020). Microautophagy is a less studied pathway, in which material to be degraded enters the lysosome directly though invagination of the lysosomal or late endosomal membrane (Fleming et al., 2022). While the underlying mechanisms are not fully understood, a subset of KFERQ-containing proteins can also be recognized by Hsc70 and delivered into late endosomes via this pathway, a process termed selective endosomal microautophagy (eMI) (Fleming et al., 2022). The recently described age-associated decline in eMI is compensated for through increased exocytic secretion of superfluous or damaged proteins to maintain proteostasis (Krause et al., 2022). These three distinct pathways share a common endpoint: degradation of the cargo inside the lysosome by acid hydrolases and release of its essential components (amino acids, nucleotides, lipids) back into the cytoplasm.

While autophagy is essential to maintain homeostasis in physiological conditions, it also plays an important role in responding to internal and external stressors such as starvation and bacterial infection. In the retina, which has a high metabolic rate and contains post-mitotic neurons, autophagy plays a crucial role as a housekeeping system, ensuring neuronal survival throughout the organism's lifetime, avoiding the accumulation of toxic cellular byproducts (Boya et al., 2016; Klionsky et al., 2021b). Our group has demonstrated a progressive age-associated decline in autophagy in the retina, starting at middle age, that leads to the accumulation of undigested cargo within lysosomes (Rodriguez-Muela et al., 2013). Interestingly, we have also described simultaneous upregulation of CMA in aged animals, indicating that distinct autophagic pathways can compensate for one another to maintain retinal proteostasis (Rodriguez-Muela et al., 2013). A similar upregulation of CMA has been described in the retina of *Atg5$^{flox/flox}$;Nestin-Cre* mice, which selectively exhibit impairment of autophagy in neurons, leading to severe retinal degeneration (Hara et al., 2006; Rodriguez-Muela et al., 2013).

The specificity of autophagy has also been revealed in recent years. While bulk autophagy describes the degradation of non-specific cytoplasmic material, several different subtypes of selective autophagy have been also observed, including lipophagy (lipid droplets), lysophagy (lysosomes), pexophagy (peroxisomes), and ribophagy (ribosomes) (Johansen and Lamark, 2020; Villarejo-Zori et al., 2021). Selective autophagy is usually regulated by specific receptors and adaptors and can act as a response to selective organelle damage or nutritional cues. For example, lysosomal membrane permeabilization (LMP) triggers specific degradation of the subset of permeabilized lysosomes through lysophagy (Maejima et al., 2013), and lipid droplet degradation supports fatty acid-fueled mitochondrial beta-oxidation in rapidly proliferating cells (Singh et al., 2009).

1.2. Mitophagy

Mitophagy is a subtype of selective autophagy that leads to the degradation and recycling of whole mitochondria and can be triggered by mitochondrial damage. Mitophagy can also degrade mitochondria

during development and differentiation and is called programmed mitophagy, this has been observed during erythrocyte and RGC differentiation (Esteban-Martinez and Boya, 2018; Fivenson et al., 2017). Mitophagy can be divided into three main subtypes: PINK1/Parkin-dependent, receptor-mediated, and lipid-mediated mitophagy (Fig. 2).

1.2.1. PINK1/Parkin-dependent mitophagy

PINK1/Parkin-dependent mitophagy is triggered by mitochondrial membrane depolarization. In steady-state conditions, newly-translated PINK1 is recruited by the translocase of the outer membrane (TOM) complex in the outer mitochondrial membrane (OMM) and transported to the translocase of the inner membrane (TIM) complex. PINK1 mitochondria-targeting sequence (MTS) is then processed by mitochondrial peptidases (MPP, PARL) and cleaved PINK1 is finally degraded by the proteasome (Greene et al., 2012). Upon mitochondrial depolarization, triggered by oxidative damage (e.g. OxPhos uncoupling or protonophore treatment), loss of mitochondrial membrane potential ($\Delta\Psi m$) inhibits PINK1 transport by TOM and PINK1 accumulates in the OMM. PINK1 then phosphorylates ubiquitin^{Ser65} and the homologous residue found in the ubiquitin-like domain of Parkin, an E3 ubiquitin ligase that further conjugates ubiquitin to other mitochondrial substrates in the OMM. These events lead to a positive feedback loop that amplifies the mitophagy-triggering signals. Different adaptor proteins with ubiquitin-binding domains, such as NDP52, OPTN, and SQSTM1/p62, bind to phospho-ubiquitin residues and recruit autophagy initiation machinery (Nguyen et al., 2016). Even though several different adaptors are recruited to the OMM by PINK1, only NDP52 and OPTN are essential to link upstream autophagy effectors (Lazarou et al., 2015). Recently, it has been described that OPTN is able to drive mitophagy initiation independently of ULK1/2, utilizing TBK1 as an alternative kinase to activate the PI3K complex (Nguyen et al., 2023).

1.2.2. Receptor-mediated mitophagy

Receptor-mediated mitophagy is ubiquitin-independent, and can also be triggered by hypoxia or developmental cues (Teresak et al., 2022). It is mediated by adaptor proteins that contain both a MTS and a LIR, namely BNIP3, BNIP3L/NIX, AMBRA1, FUNDC1, BCL2L13, PHB2, and FKBP8 (Teresak et al., 2022). Each receptor shows differential affinity toward distinct members of the LC3/GABARAP family such is the case of BNIP3L/NIX for GABARAPL1 or FUNDC1 for LC3B (Liu et al., 2012; Novak et al., 2010; Teresak et al., 2022). Receptor-mediated mitophagy is usually regulated at the transcriptional level and is the most physiologically important pathway in basal conditions in highly metabolic tissues (McWilliams et al., 2018).

1.2.3. Lipid-mediated mitophagy

Finally, mitophagy can also be modulated by certain lipid species such as cardiolipin (CL) and ceramide (CE), leading to direct cargo recognition. In basal conditions CL is found in the inner mitochondrial membrane (IMM), but can be translocated to the OMM by the scramblase PLSCR3 upon induction of mitochondrial damage. OMM-anchored CL can interact directly with DNM1L, favoring mitochondrial fission, or BECN1 and LC3B, favoring mitophagy (Chu et al., 2013; Huang et al., 2012; Stepanyants et al., 2015). Long-chain CE generated by the enzyme CERS1 (C_{18}-ceramide) accumulates preferentially in the OMM and can also interact directly with LC3B, triggering mitophagy (Teresak et al., 2022). More recently, defects in mitochondrial protein import machinery, such as those caused by aberrant protein misfolding, have been shown to trigger mitophagy independently of $\Delta\Psi m$ loss (Michaelis et al., 2022). An alternative mitophagy pathway that involves Rab9-associated autophagosomes and is triggered by nutrient starvation has also been described (Saito et al., 2019). Mitochondrial components can also be recycled through the formation of autophagy-independent mitochondria-derived vesicles (MDVs) that are delivered directly to the lysosome

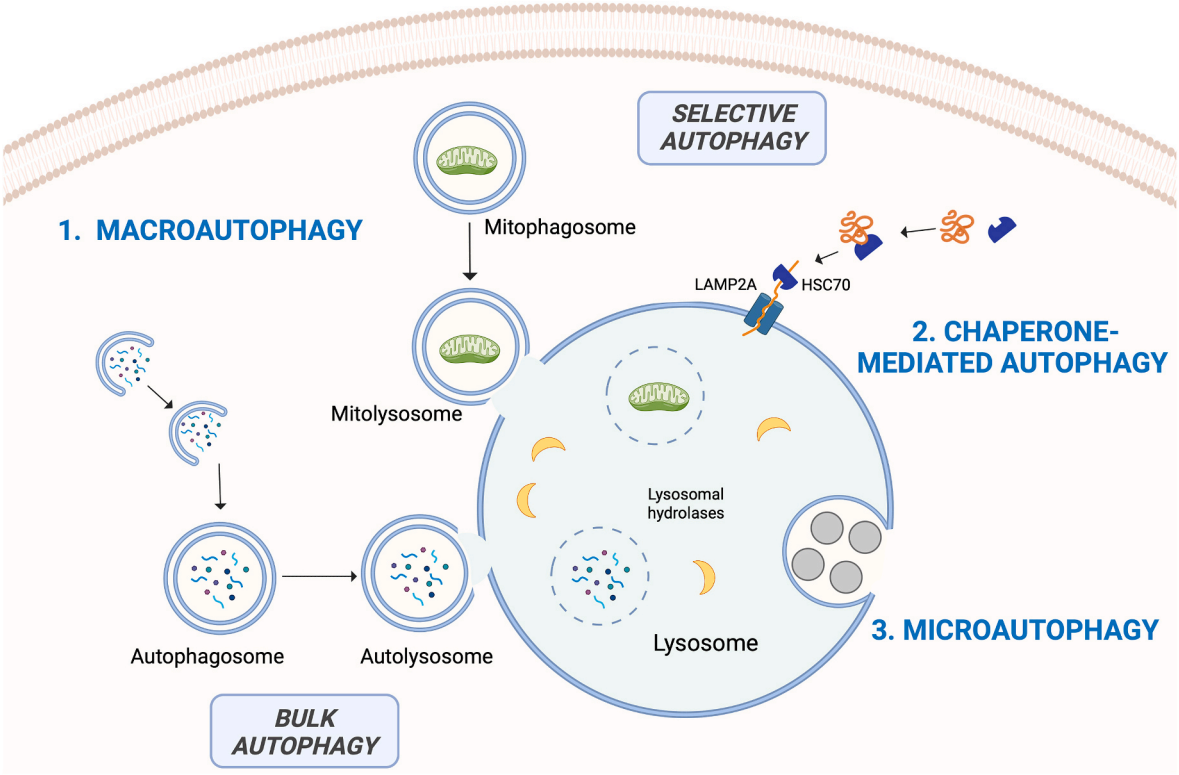

Fig. 1. *Autophagy pathways*. Macroautophagy ("autophagy") is characterized by the engulfment of cargo inside a double-membrane organelle, the autophagosome. It can be further classified as bulk or selective macroautophagy. CMA degrades KFERQ-containing proteins, which are recognized in the cytoplasm by Hsc70 and imported into the lysosome through LAMP2A multimer channels. Microautophagy is characterized by direct cargo mediated by lysosomal membrane invagination. All pathways result in the degradation of autophagic cargo by lysosomal hydrolases.

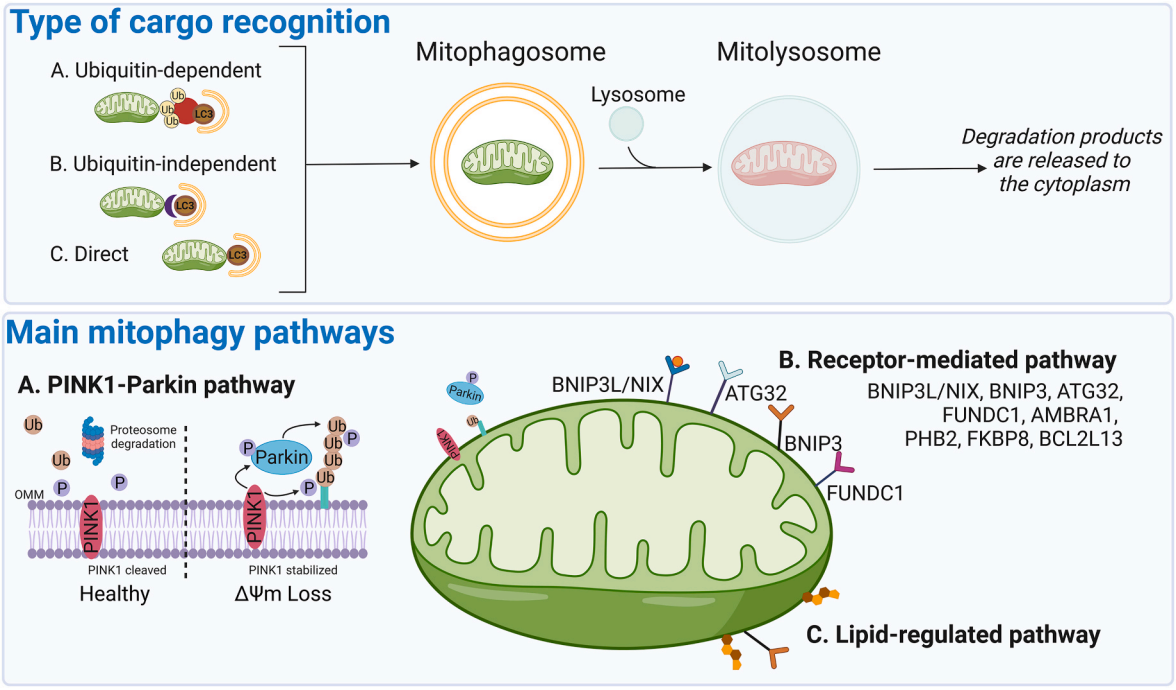

Fig. 2. *Main mitophagy pathways*. Mitochondria degradation through selective autophagy can be classified depending on how the cargo is recognized. Ubiquitin-dependent (PINK1/Parkin pathway), ubiquitin-independent (receptor-mediated pathway) or direct lipid-mediated pathway.

(König et al., 2021), lysosome-dependent autophagic secretion of mitochondria (ASM) (Tan et al., 2022), or transcellular degradation in phagocytic cells (Davis et al., 2014; Nicolás-Ávila et al., 2020). Whether these alternative pathways play a role in the retina in physiological conditions remains to be elucidated.

1.3. Retinal phenotype of autophagy- and mitophagy-deficient mice

The retina is a highly organized tissue located in the posterior region of the eye that converts light stimuli into electrical impulses, which in turn are processed to generate visual images. The neural component of the retina is organized into 5 layers: 3 nuclear layers and 2 synaptic layers. The main light-sensitive cells in the outer part of the retina are photoreceptors (rods and cones), the nuclei of which form the outer nuclear layer (ONL). Rods mediate black and white vision and vision in low-light/dark conditions. Cones mediate color vision and vision in high light conditions, and can be stimulated by different light wavelengths. Both share a common cytoplasmic structure called the outer segment (OS), which encloses a stack of membranous structures called discs. These contain rhodopsin and other important proteins involved in phototransduction. The inner nuclear layer (INL) is composed of bipolar cells, horizontal cells, and amacrine cells. A dense network of synapses involving photoreceptors, bipolar cells and horizontal cells form the outer plexiform layer (OPL). Amacrine cells participate in the synapses between bipolar cells with RGCs in the inner plexiform layer (IPL). The innermost layer is mainly composed of RGCs that constitute the ganglion cell layer (GCL). The projecting axons of the RGCs merge to form the optic nerve, which connects the retina with the brain. Other important non-neuronal cells are retinal glia: Müller cells and astrocytes. Müller glia span the entire retina while astrocytes are mainly located within the GCL. Patrolling microglia also infiltrate the retina and are present in the subretinal space (Boya et al., 2016; Villarejo-Zori et al., 2021).

Located immediately outside the neuroretina, the retinal pigment epithelium (RPE) provides nutrients and trophic support to photoreceptors, and mediates recycling of photoreceptor OS, thereby eliminating toxic intermediates generated in the phototransduction process and providing new substrates for the visual cycle (Strauss, 2005).

Because the retina is a neural tissue it requires autophagy as a quality control mechanism to maintain cellular homeostasis in neurons: post-mitotic cells are incapable of redistributing altered proteins or damaged organelles in daughter cells. This was first demonstrated in autophagy-deficient mouse models in which Atg5 or Atg7 is specifically deleted in neuronal precursors (Hara et al., 2006; Komatsu et al., 2006). These mice exhibit early neurodegeneration and die before reaching 3 months of age, thus highlighting the essential role of basal autophagy in neuronal cells.

1.3.1. Systemic models of autophagy/mitophagy deficiency

Selective deletion of Atg5 in retinal neuronal precursors results in photoreceptor cell death and gliosis, and reduced visual function as measured by electroretinogram (ERGs) (Rodriguez-Muela et al., 2013). AMBRA1, activating molecule in BECN1-regulated autophagy protein 1, is a protein involved in the initiation phase of autophagy, and has also been recently linked to mitophagy modulation. In PINK1/Parkin-dependent mitophagy, AMBRA1 promotes PINK1 stabilization at the OMM, and also interacts with ATAD3A, a transmembrane protein that regulates PINK1 import and degradation (Di Rienzo et al., 2022). Furthermore, AMBRA1 has been detected in the OMM in steady-state conditions, where it can also initiate mitophagy upon mitochondrial depolarization by direct binding to LC3 via its LIR motif (Strappazzon et al., 2015). AMBRA1-mediated mitophagy is dependent on its phosphorylation by IKKα and HUWE1 E3 ubiquitin ligase activity (Di Rita et al., 2018). AMBRA1 haploinsufficiency in mice obtained by gene-trapped allele technique (*Ambra1*$^{+/gt}$ mice) results in an accelerated retinal aging phenotype, with increased photoreceptor loss and impaired visual function, coinciding with increased inflammation, protein aggregate accumulation, and metabolic alterations in the retina (Ramírez-Pardo et al., 2022). *Ambra1*$^{+/gt}$ mice also show reduced RGC survival after optic nerve injury and reduced photoreceptor survival after induction of RPE damage (Bell et al., 2020; Ramírez-Pardo et al., 2022). Mice lacking Atg4b protease also show increased RGC vulnerability to optic nerve axotomy (Rodriguez-Muela et al., 2012). Similarly, *Map1lc3b*$^{-/-}$ mice lacking LC3 exhibit an age-associated decrease in retinal thickness and function and increased gliosis, an effect linked to

deficits in OS processing, the visual cycle, and lipid homeostasis in the RPE (Dhingra et al., 2018). Despite an absence of retinal alterations in basal conditions, *Becn1*$^{+/-}$ and *Park2*$^{-/-}$ mice are more susceptible to light-induced damage (Chen et al., 2013). *Pink1*$^{-/-}$ mice show no neuroretinal alterations or changes in mitophagy (McWilliams et al., 2018). However, similarly to human AMD patients, the RPE of Pink1-deficient mice shows disrupted mitochondrial homeostasis and undergoes epithelial-mesenchymal transition. This phenomenon is abolished in the absence of the antioxidant master regulator Nrf2/Nfe2l2 (i.e. in *Pink1*$^{-/-}$*Nfe2l2*$^{-/-}$ mice), pointing to an as-yet unexplored crosstalk between the accumulation of damaged mitochondria, ROS signaling, and cellular reprogramming (Datta et al., 2022). BNIP3L/NIX-deficient animals also show lower numbers of differentiated RGCs due to deficient developmental mitophagy and the consequent effects on metabolism (Esteban-Martinez et al., 2017a).

Mice lacking the lysosomal hydrolase cathepsin D show outer and inner retina degeneration with decreases in retinal thickness of 50% by post-natal day 15 (P15) and 90% by P25. Degeneration is accompanied by inflammation markers such as astrogliosis and microgliosis and increased levels of structural lysosomal proteins as LAMP1 and LAMP2 (lysosomal associated membrane protein 1 and 2) and other cathepsins as cathepsin Z (Bassal et al., 2021). Interestingly, gene therapy consisting of intravitreal injection of cathepsin D rescues this degenerative effect (Liu et al., 2022). Similarly, LAMP2 deficiency leads to intracellular and extracellular accumulation of cell debris, thickening of Bruch's membrane and alterations in autophagic flux similar to those observed in AMD (Notomi et al., 2019).

1.3.2. Neuroretina-deficient models

Different mouse models have been generated to study the role of autophagy in specialized cell types in the retina. In cones, Atg5 deletion (*Atg5*$^{flox/flox}$*;HRGP-Cre*) leads to a reduction in cone number, starting at 2 months of age. Visual impairment is evident at 10 months, and these mice display increased sensitivity to light stress with a reduction in cone OS length and swelling of the inner segments (IS), where mitochondria accumulate (Zhou et al., 2015a). In rods, deletion of Atg5 (*Atg5*$^{flox/flox}$*; Rhodopsin-iCre75*) produces degeneration beginning at 20 weeks, characterized by decreased ONL thickness. By 44 weeks the ONL is severely affected, showing terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL), an apoptosis marker, and few remaining rods. Decreases in cone OS length and cone number are observed (He et al., 2019). Although this abnormal cone phenotype is not very severe, cone function is markedly impaired. Rod degeneration is also observed in dark conditions, but is not exacerbated by light exposure. Progressive degeneration is accompanied by the accumulation of transducin, one of the main proteins involved in phototransduction, suggesting that autophagy regulates the removal and recycling of this protein (Zhou et al., 2015b). In a proof-of-concept study, crossing of this *Atg5*$^{\Delta rod}$ model with the transducin-deficient *Gnat*$^{-/-}$ mouse model revealed less rod degeneration and preserved cone function, further supporting a role of transducin accumulation in the degeneration resulting from defective autophagy (Yao et al., 2016). In an autophagy-deficient mouse model with Atg7-deficient rods (*Atg7*$^{flox/flox}$*;LOMP-Cre*), no overt alterations were observed in normal light conditions, but exposure to intense illumination for 2 h resulted in retinal degeneration, including reduced photoreceptor number and increased cell death (Chen et al., 2013). RabGEF1, a protein implicated in endolysosomal function (Hargrove--Grimes et al., 2020), is also proposed to be essential for visual function. Rabgef1-deficient mice show autophagosome accumulation in the IS of photoreceptors (Hargrove-Grimes et al., 2020). Moreover, RabGEF1 has been recently linked to PINK1/Parkin-dependent mitophagy, where it is recruited to damaged mitochondria via its ubiquitin-binding domain and locally regulates Atg9a endosome formation (Yamano et al., 2018). Interestingly, selective knockout of the autophagy initiation protein Vps34 in rods leads to photoreceptor cell death, progressive retinal degeneration, and reduced visual function associated with inefficient autophagic flux (He et al., 2016a). Rod-driven retinal degeneration in Vps34-deficient mice is followed by cone atrophy and loss of function. Interestingly, selective knockout of Vps34 in cones also leads to decreased visual function without rod alterations (Rajala et al., 2020), a phenomenon that may be associated with the secretion of pro-survival rod-derived cone viability factor (RdCVF) (Ait-Ali et al., 2015). Finally, Vps34 deficiency in bipolar cells also leads to age-associated visual function loss and accumulation of autophagic cargo, highlighting the universal role of Vps34 in maintaining homeostasis in different cell types (He et al., 2019). In summary, defective autophagy in the retina leads to retinal degeneration and in most cases produces alteration of the visual function. These effects reveal a central role of autophagy in well-functioning retinal cells.

1.3.3. RPE-deficient models

Autophagy deficiency also has deleterious effects in the RPE. In the mouse model of Ambra1 deficiency described above, RPE degeneration is observed even at early time points, with morphological alterations and protein aggregate accumulation in the RPE. These mice also show increased RPE susceptibility to sodium iodate (SI)-induced oxidative damage (Ramírez-Pardo et al., 2022). In mouse models, RPE-specific autophagy deficiency usually results in accelerated aging or degeneration. Disrupted lysosomal processing has been described in a mouse model in which Atg5 is deleted in RPE cells (*Atg5*$^{flox/flox}$*;BEST1 (VMD2)-Cre*), together with deficient photoreceptor responses to light stimuli and consequent impairment of visual function (Kim et al., 2013). These effects are accompanied by decreased levels of 11-*cis*-retinal, which is part of the visual cycle and essential for phototransduction. Interestingly, administration of an exogenous analog of the chromophore restores electrophysiological responses of rods and cones. These findings suggest that non-canonical autophagy supports chromophore regeneration through the efficient processing of photoreceptor outer segments (POS) in the RPE (Kim et al., 2013). Other study used a similar approach to delete either Atg5 or Atg7 in a conditional manner (*Atg5*$^{flox/flox}$ or *Atg7*$^{flox/flox}$*;VMD2-tTA-Cre*;Tet-ON inducible), revealing accumulation of SQSTM1/p62, N-Tyr, and 8-OHdG, indicating concomitant protein and DNA oxidization (Zhang et al., 2017). This resulted in a degenerative condition that was more severe in Atg7-deficient versus Atg5-deficient RPE. Contrary to the aforementioned studies, a study of the same RPE Atg7-deficient mouse model revealed normal retinoid recycling, histology, and A2E (bis-retinoid N-retinyl-N-retinylidene ethanolamine, a major toxic fluorophore of lipofuscin) accumulation, and concluded that A2E accumulation and retinoid recycling do not rely on Atg7-mediated autophagy, and that Atg7 deficiency does not result in RPE degeneration in these mice (Perusek et al., 2015). Alterations reported in another mouse model based on FIP200 deficiency (*Rb1cc1*$^{flox/flox}$*;BEST1-Cre*) include decreased conversion of LC3-I to LC3-II, SQSTM1/p62 accumulation, decreased levels of cathepsin D and LAMP1, and increases in mitochondrial number and intracellular lipid levels (Yao et al., 2015). At 4 months, these mice display areas of patchy atrophy with subretinal hyper-reflective spots that evolve to disrupt the hexagonal structure of the RPE and lead to secondary loss of photoreceptors and retinal function at 8 months. It has been described that A2E induces autophagy impairment and the simultaneous upregulation of Rubicon, a negative regulator of autophagy, in human polarized RPE monolayers. Those authors demonstrated normal ERGs in mice with Rubicon deficiency (*Rubcn*$^{flox/flox}$*;BEST1-Cre*) and an attenuated effect of chronic blue light exposure on inflammation and debris accumulation. Based on their findings, they have proposed that Rubicon deletion may protect the RPE from induced or age-associated damage (Ando et al., 2021). More studies are needed to better understand the importance of autophagy/mitophagy in RPE.

In conclusion, the body of evidence described above highlights the essential role of mitophagy in maintaining retinal homeostasis, while the more severe phenotype observed in autophagy-deficient mice in the absence of upstream regulators (Vps34, Ambra1) suggests that other

components of the system can compensate for a lack of downstream autophagy modulators (LC3, PINK1, BNIP3L/NIX) (Table 1).

1.4. Mitochondrial dynamics

Degradation of mitochondria through mitophagy requires fission in order to generate piecemeal fragments small enough to be enclosed by the phagophore (Tilokani et al., 2018). Mitochondrial fission is initiated through pre-constriction by the ER and actin cytoskeleton, that generate a binding site for the master regulator Dynamin-related protein 1 (DRP1) (Smirnova et al., 2001). DRP1, recruited and bound to the OMM through protein adaptors MFF and FIS1, will oligomerize in a GTP-dependent manner eventually leading to full constriction and scission of a mitochondrial fragment, that will be sent for degradation or generate a new functional mitochondrion depending on its size and composition (Kleele et al., 2021). Pharmacological modulation of DRP1 is possible using the small molecule inhibitor Mdivi-1 (Cassidy-Stone et al., 2008), and has also been shown to reduce mitophagy in a fission-dependent manner (Mizumura et al., 2014). Mdivi-1 has been shown to be neuroprotective in a model of acute retinal ischemia (Park et al., 2011), and represents a therapeutical opportunity in contexts where mitophagy plays a detrimental role. Antagonistically, mitochondrial fusion promotes the formation of a complex tubular mitochondrial network and is mediated by GTP-dependent MFN1 and MFN2 dimerization at the connecting OMMs (Chen et al., 2003) and OPA1 within the IMM (Griparic et al., 2004). Mutations in OPA1 have been linked to a

Table 1
Summary of the retinal phenotype of autophagy- and mitophagy-deficient mice.

Cell type affected	Genotype	Function	Phenotype	Associated disease	Reference
Systemic	*Ambra1*$^{+/gt}$	Phagophore nucleation	Decreased RGCs survival after ONC, impaired antioxidant response	Glaucoma	Bell et al. (2020)
Systemic	*Ambra1*$^{+/gt}$	Phagophore nucleation	Accelerated neuroretina and RPE aging, metabolic impairment, increased susceptibility to RPE-targeted damage	Age-associated decline, AMD	Ramírez-Pardo et al. (2022)
Systemic	*Atg4b*$^{-/-}$	LC3 processing	Decreased RGCs survival after axotomy	Glaucoma	Rodriguez-Muela et al. (2012)
Systemic	*Becn1*$^{+/-}$	Phagophore nucleation	No basal alterations, increased susceptibility to light-induced damage	Light damage	Chen et al. (2013)
Systemic	*Pink1*$^{-/-}$	PINK1/Parkin-mediated mitophagy	No morphological alterations, no changes in mitophagy	–	McWilliams et al. (2018)
Systemic	*Park2*$^{-/-}$	PINK1/Parkin-mediated mitophagy	No basal alterations, increased susceptibility to light-induced damage	Light damage	Chen et al. (2013)
Systemic	*Bnip3l*$^{-/-}$	Receptor-mediated mitophagy	Decreased RGCs differentiation	Developmental defects	Esteban-Martinez et al. (2017a)
Systemic	*Ctsd*$^{-/-}$	Lysosomal degradation	Progressive retinal degeneration, gliosis	NCL	Bassal et al. (2021)
Systemic	*Ctsd*$^{-/-}$	Lysosomal degradation	Retinal degeneration, gliosis, restored with RPE-, Müller-targeted scAAVshH10-CTSD	NCL	Liu et al. (2022)
Systemic	*Rabgef1*$^{-/-}$	Endolysosome trafficking, PINK1-Parkin mediated mitophagy	PR degeneration, reduced visual function	–	Hargrove-Grimes et al. (2020)
Neuronal precursors	*Atg5*$^{flox/flox}$*;Nestin-Cre*	Phagophore elongation	Increased PR cell death, gliosis, reduced visual function	Neurodegeneration	Rodriguez-Muela et al. (2013)
RGCs	*Atg5*$^{flox/flox}$*;AAV2-Cre-GFP*	Phagophore elongation	Decreased RGCs survival after axotomy	Glaucoma	Rodriguez-Muela et al. (2012)
ON-Bipolar	*Vps34*$^{flox/flox}$*; Pcp2-Cre*	Phagophore nucleation	Age-associated decreased visual function	–	He et al. (2019)
Rods	*Vps34*$^{flox/flox}$*; Rhodopsin-iCre75*	Phagophore nucleation	Progressive retinal degeneration, reduced visual function	–	He et al. (2016b)
Rods	*Vps34*$^{flox/flox}$*; Rhodopsin-iCre75*	Phagophore nucleation	Progressive retinal degeneration, cone atrophy, reduced visual function	–	Rajala et al. (2020)
Rods	*Atg5*$^{flox/flox}$*; Rhodopsin-iCre75*	Phagophore elongation	PR degeneration, reduced visual function	–	Zhou et al. (2015b)
Rods	*Atg7*$^{flox/flox}$*;LMOP-Cre*	Phagophore elongation	No basal alterations, increased susceptibility to light-induced damage	Light damage	Chen et al. (2013)
Cones	*Vps34*$^{flox/flox}$*; HRGP-Cre*	Phagophore nucleation	Cone degeneration, reduced visual function	–	Rajala et al. (2020)
Cones	*Atg5*$^{flox/flox}$*;HRGP-Cre*	Phagophore elongation	Cone degeneration, reduced visual function, increased susceptibility to light-induced damage	Light damage	Zhou et al. (2015b)
RPE	Rb1cc1$^{flox/flox}$; BEST1-Cre	Autophagy initiation	Progressive RPE atrophy, reduced visual function	–	Yao et al. (2015)
RPE	*Atg5*$^{flox/flox}$*;BEST1 (VMD2)-Cre*	Phagophore elongation	Imapired visual cycle, reduced visual function	–	Kim et al. (2013)
RPE	*Atg5*$^{flox/flox}$*; VMD2-rtTA-Cre*	Phagophore elongation	RPE degeneration	AMD	Zhang et al. (2017)
RPE	*Atg7*$^{flox/flox}$*; VMD2-rtTA-Cre*	Phagophore elongation	Severe RPE degeneration	AMD	Zhang et al. (2017)
RPE	*Atg7*$^{flox/flox}$*; VMD2-rtTA-Cre*	Phagophore elongation	No morphological or functional alterations	–	Perusek et al. (2015)
RPE	*Map1lc3b*$^{-/-}$	Phagophore elongation	Progressive retinal degeneration, reduced visual function, gliosis	–	Dhingra et al. (2018)
RPE	Rubcn$^{flox/flox}$; BEST1-Cre	Negative autophagy regulator	No basal alterations, decreased impact of light-induced damage	Light damage	Ando et al. (2021)
RPE	*Pink1*$^{-/-}$	PINK1/Parkin-mediated mitophagy	RPE epithelial-mesenchymal transition	AMD	Datta et al. (2022)
RPE	*Lamp2*$^{-/-}$	Lysosomal membrane	RPE morphological alterations, thickened BrM, debris accumulation	AMD	Notomi et al. (2019)

rare retinal disease called dominant optic atrophy (ADOA) (Ito and Di Polo, 2017). Mitochondrial dynamics modulation might represent a new upstream pharmacological target to fine-tune mitophagy (Cassidy-Stone et al., 2008; Zacharioudakis et al., 2022).

1.5. Metabolism at the retina-RPE interface

The retina has one of the highest metabolic rates of any tissue in the body, a consequence of the demand for energy to support phototransduction, neurotransmission, and homeostasis (Ames, 1992). The metabolic interplay between the neuroretina and RPE reflects a complex and finely tuned symbiotic relationship. In physiological conditions, the outer neuroretina constitutes a semi-hypoxic niche that favors tumor-like Warburg metabolism, while the RPE is fueled mainly by mitochondrial oxidative metabolism (Fisher and Ferrington, 2018; Ng et al., 2015). This metabolic adaptation shared by cancer cells and the neuroretina may be a consequence of the latter's constant need to fuel cell growth and renew photoreceptor OS on a daily basis, despite its post-mitotic status (Casson et al., 2013). The lateral and apical membranes of the RPE are rich in GLUT1 glucose transporters, which shunt glucose from the choroidal blood flow straight to photoreceptors. Photoreceptors rely on anaerobic glycolysis, which produces lactate that can be shuttled back to the RPE and the neighboring Müller glia (Kanow et al., 2017). The neuroretina exhibits regional differences in metabolism, with more active glycolytic (and mitochondrial) metabolism observed in the cone-rich macular region (Li et al., 2020). Fatty acid β-oxidation has been recently described as a major pathway contributing to photoreceptor energetic homeostasis (Joyal et al., 2016). A study in which palmitate was added to retinal explants reported increased oxygen consumption and ATP production, and the authors identified Ffar1 as the modulator of fuel utilization in the retina (Joyal et al., 2016). Moreover, they showed that when circulating lipid levels increase, Ffar1 reduces glucose uptake through downregulation of Glut1 expression levels. In mice lacking the very low-density lipoprotein receptor (VLDLR), increased Ffar1 activity led to decreased glucose utilization, which was not compensated for by lipid uptake and β-oxidation, resulting in decreased levels of α-ketoglutarate (KG), followed by a consequent reduction in hypoxia inducible factor 1a (HIF-1α) stabilization and neoangiogenic events (Joyal et al., 2016). Ffar1 also appears to modulate autophagy in response to fatty acids, through downregulation of TFEB signaling, and to reduce mitochondrial respiration (Heckel et al., 2022). The crosstalk between nutrient sensing, fatty acid metabolism, and autophagy requires further exploration and is one possible avenue for the development of therapies for angiogenic and age-associated retinal diseases.

Lactate and lipids derived from photoreceptor OS can be oxidized and are the main substrates for mitochondrial metabolism in the RPE. In addition, lactate dehydrogenase activity in the RPE depletes the NAD + pool by reducing it to NADH, thereby decreasing levels of one of the key substrates for glycolysis and favoring glucose delivery to photoreceptors (Kanow et al., 2017). Reductive carboxylation is another major pathway in the RPE that sustains fatty acid synthesis and redox potential (Du et al., 2016). Mitochondrial dynamics and metabolism also vary throughout the light-dark cycle and in response to light stimuli (Giarmarco et al., 2020; Yako et al., 2021). In cones, mitochondrial populations undergo daily cycles: during day-time high mitochondrial activity supports phototransduction, leading to oxidative damage, and mitochondria associate with autophagosomes, presumably undergoing mitophagy; at night, mitochondrial biogenesis increases, leading to an increased number of smaller, more metabolically active mitochondria (Yako et al., 2021). Mitochondria have also been found in the extracellular space surrounding the outer limiting membrane (OLM), where they are extruded by cones (Yako et al., 2021).

Aged RPE cells show decreased basal mitochondrial function and loss of spare capacity as demonstrated by respirometry (Rohrer et al., 2016). Studies in animal models have also revealed an age-associated decline in mtDNA integrity and copy number, as well as concomitant alterations in fusion/fission dynamics that may further hinder mitochondria functionality (Wang et al., 2019b). However, only small alterations in glutamine metabolic capacity have been described in the aged RPE, in which neuroretinal metabolism remains stable, suggesting possible alterations in nutrient acquisition or RPE-retina communication rather than nutrient utilization (Tsantilas et al., 2021).

Alterations in either photoreceptor or RPE metabolism can trigger degeneration in the other cell type. For example, selective stimulation of glycolysis in the RPE in mice through genetic manipulation of the hypoxia response (HIF/VHL axis) leads to decreased glucose shuttling and subsequent photoreceptor degeneration (Kurihara et al., 2016). A similar phenotype is described in mice lacking Glut1 (Swarup et al., 2019). Mice lacking the metabolic regulator AMPK in photoreceptors show abnormal metabolism that leads to RPE degeneration (Xu et al., 2020). Similarly, deficits in enzymes involved in fatty acid β-oxidation, such as PPARα or HADHA, lead to photoreceptor degeneration and RPE alterations (Lawlor and Kalina, 1997; Pearsall et al., 2017). Mitochondrial biogenesis and removal of damaged mitochondria through mitophagy may therefore be essential to sustain metabolically-demanding visual function and preserve retinal homeostasis.

2. Methods to assess mitophagy in the retina

The retina is commonly used as a model in which to study the central nervous system (CNS), mainly owing to its accessibility and the fact that it can be cultured *ex vivo* in defined medium, providing researchers with complete control of the nutrient and growth factor exposure. Owing to the slightly higher permeability of the blood-retina barrier (BRB) compared with the blood-brain barrier (BBB), the retina is the only part of the CNS in which autophagic flux can be evaluated *in vivo* using the protease inhibitor leupeptin (Esteban-Martinez and Boya, 2015).

2.1. Autophagy assessment

Autophagic flux, defined as the difference between the number of autophagosomes/LC3-II in the presence and absence of lysosomal inhibitors, can be evaluated in *ex vivo* retinal explants by monitoring LC3-II levels or lipidation by Western blot and by fluorescence microscopy or flow cytometry in GFP-LC3 transgenic mice (Esteban-Martinez and Boya, 2015; Gomez-Sintes et al., 2017). Autophagy can also be evaluated by monitoring the dynamics of a tandem fluorescent-tagged LC3 vector containing both pH-sensitive and pH-insensitive fluorescent proteins such as GFP and mCherry, respectively (Klionsky et al., 2008). Using this method, autophagosomes are visualized as yellow puncta (GFP^+ $mCherry^+$) and autolysosomes as red puncta (GFP^- $mCherry^+$), due to the quenching of GFP signal by the intra-lysosomal acidic pH (Klionsky et al., 2008). Autophagy reporter mice (CAG-RFP-EGFP--MAP1LC3B, mCherry-GFP-MAP1LC3B (MAP)) have been recently developed following this principle, and a recent publication has summarized the pros and cons of this technique to assess retinal autophagy (McWilliams et al., 2019; Ramachandra Rao and Fliesler, 2022). Finally, autophagy can also be assessed by quantifying the levels of different autophagy regulators, such as LC3, Beclin-1, and Ambra1, as demonstrated by our group in chick (Mellén et al., 2008) and mouse retinas (Figueiredo-Pereira et al., 2023; Gomez-Sintes et al., 2017). To better explore the dynamics of autophagic flux, our group has developed an immunostaining procedure to assess autophagosome and autolysosome levels within retinal cell types using a cytoplasmic cell type-specific marker for cones, LC3, and LAMP1 (Samardzija et al., 2021).

2.2. Mitophagy assessment

While the tools and methods used to study autophagy have been refined over time (Klionsky et al., 2021a), the range of assays available

for mitophagy assessment remains limited.

2.2.1. Electron microscopy

Electron microscopy (EM) is one of the traditional approaches used to study mitophagy, and was first used to this end to examine the cones of hibernating ground squirrels undergoing metabolic re-adaptation (Reme and Young, 1977). This technique requires a high level of expertise: it is essential to correctly identify the autophagosomes and the mitochondria in different stages of degradation contained within them. Another drawback of this method is that in the absence of lysosomal inhibitors mitochondria are rapidly degraded inside autophagosomes, and therefore the number of mitophagosomes present at a given time-point is limited. Moreover, in contrast to optical microcopy, EM only visualizes a very thin section of the total cellular volume, further reducing the number of mitophagosomes observed. This limitation can be overcome by performing morphometric quantification in a large number of cells, although this makes the technique very laborious.

2.2.2. Fluorescence microscopy

While EM was once the gold standard, nowadays mitophagy is most commonly evaluated using fluorescence microscopy. One of the most widely used approaches to detect mitochondria undergoing autophagic degradation is to assess colocalization of mitochondrial markers with the autophagosomal marker LC3 or a lysosomal marker, using either a fluorescently-tagged protein chimera or antibodies against different targets in living or fixed cells, respectively (Dagda et al., 2009; Florey et al., 2011; Narendra et al., 2008; Rambold et al., 2011; Wang et al., 2012). The different stages of mitophagy can be further dissected and monitored using different combinations of tagged proteins: EGFP-LC3+Mito-DsRed to study the early phases of mitophagy and mitochondria-EGFP + LAMP1-RFP for later stages (Indira et al., 2018). Finally, an immunofluorescence method based on monitoring mitochondrial translocation of an autophagy receptor (NDP52) and the formation of initiation foci during PINK1/Parkin-dependent mitophagy has been described (Padman and Lazarou, 2022). These approaches may be somewhat imprecise, as it cannot be verified whether an increase in mitophagosome number is due to induction of mitophagy or altered mitophagosome degradation within lysosomes. In order to differentiate between these two phenomena, autophagic and mitophagic flux should be monitored by comparing autophagosome/mitophagosome numbers in the absence and presence of lysosomal inhibitors (Klionsky et al., 2021a).

Reporters such as MitoTimer, mt-Keima, and *mito*-QC can be used in tandem fluorescence assays to monitor and quantify mitophagy *in vitro*, *ex vivo,* and *in vivo* (Montava-Garriga et al., 2020; Rosignol et al., 2020; Williams et al., 2017). The mt-Keima mouse, the first *in vivo* mitophagy reporter model generated, expresses the pH-sensitive dual-excitation protein Keima targeted to the mitochondrial matrix (Katayama et al., 2011): within the acidic lysosome mt-Keima switches to its ionized state and is excited by long wavelengths. However, assessment of mitophagy in the retina of these mice is not possible due to their FVB background: these mice are homozygous for the *Pde6b*^{rd1} mutation, which leads to retinal degeneration (Sun et al., 2015). Another drawback of mt-Keima mice is that fixation of retinal tissue is not possible without losing the fluorescence, and the rapid and meticulous sample processing required for these mice largely precludes assessment of mitophagy within the retina.

In the more recently developed *mito*-QC reported mouse, which has a C57Bl6/J background, mitophagy is also monitored based on changes in pH (Fig. 3). *mito*-QC has a tandem mCherry-GFP tag fused to the mitochondria-targeting sequence of the OMM protein FIS1 (FIS1$_{101\text{-}152}$). Healthy mitochondria in *mito*-QC mouse tissue show green and red fluorescence (GFP^{+}mCherry^{+}). However, when mitophagy is activated and mitochondria are delivered to the lysosome, GFP is quenched by the acidic pH and mitolysosomes are visualized as red puncta (GFP^{-}mCherry^{+}) (McWilliams et al., 2016). Recent reports have discussed the differences between these two mitophagy reporters: while mt-Keima appears to detect mitophagy with higher sensitivity in certain settings, such as cardiac exhaustion (Liu et al., 2021), the background of this mouse model must be taken into account (FVB mice present

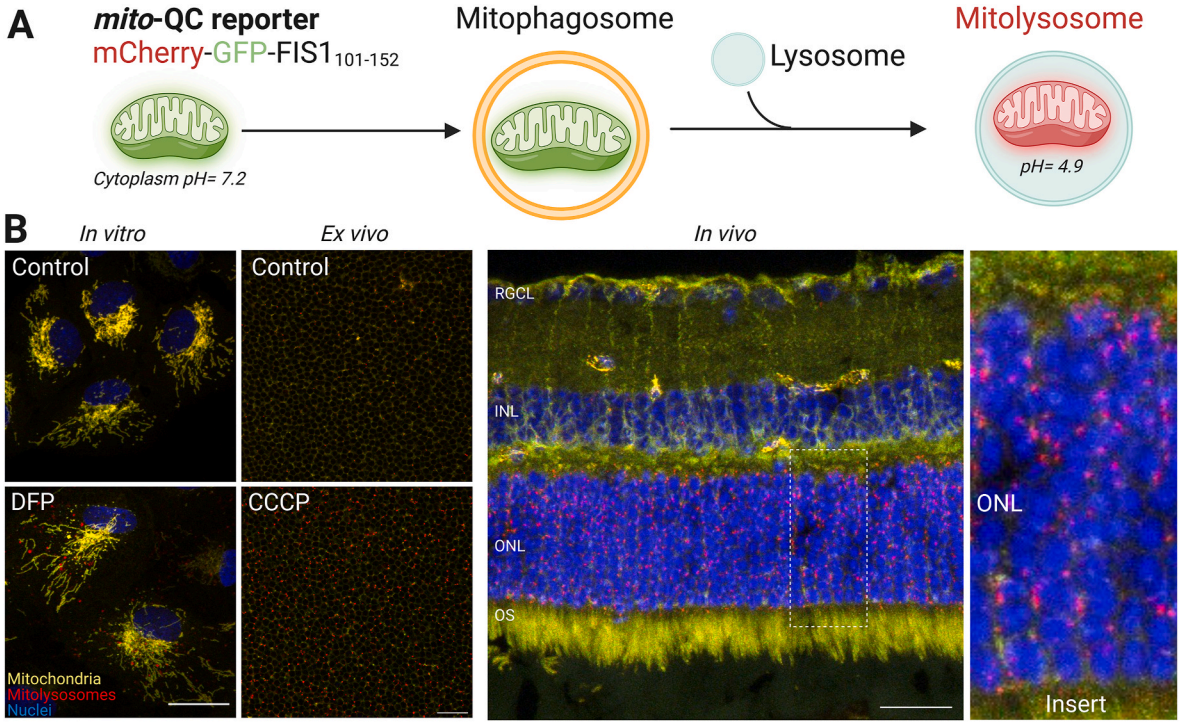

Fig. 3. *Assessment of mitophagy in the retina using mito-QC reporter.* (A) Scheme depicting the basis of *mito*-QC reporter. (B) (Left) ARPE-19 cells treated with 1 mM DFP for 24h. (Center) Flatmount of retinas cultured *ex vivo* in the presence of 25 μM CCCP for 6h. (Right) Whole retina cryosection, inset depicts high mitophagy levels present in the ONL. Nuclei are counterstained with DAPI. Scale bar 15 μm, 25 μm, 25 μm.

hyperactivity, altered circadian rhythms, and metabolic alterations) (Eltokhi et al., 2020; Enríquez, 2019). Differential targeting of the reporters (mt-Keima, mitochondrial matrix; *mito*-QC, OMM) may also contribute to the observed differences in sensitivity. Specifically, pH changes in the mitochondrial matrix and cytosol, respectively, may bias mitophagy readouts in specific contexts.

Using *mito*-QC mice, our group has demonstrated different levels of mitophagy in distinct retinal cell types during development and in adult mice (Figs. 4 and 5). In these studies, mitophagy assessment was performed in parallel with autophagy evaluation using the MAP reporter, which is based on the same principal as the *mito*-QC reporter, but the mCherry-GFP tandem is fused to the N-terminus of the MAP1LC3B protein (McWilliams et al., 2019). RGCs isolated from reporter mice are also a very reliable source of primary neurons for mitophagy assessment (Rosignol et al., 2020). Our laboratory recently developed a method to assess mitophagic flux in retinal explants from *mito*-QC mouse and performed *in vivo* studies after optic nerve crush (ONC) in these mice (Rosignol et al., 2020). While an increase in mitophagy in RGCs after optic nerve damage had been previously hypothesized, this was very difficult to detect and quantify. Other groups have also analyzed mitophagy levels using the *mito*-QC reporter in models of diabetic retinopathy, age-associated muscle disease, and chronic obstructive pulmonary disease (Hombrebueno et al., 2019; Maremanda et al., 2019; Mito et al., 2022). A Cre-inducible reporter called CMMR (conditional mitochondrial matrix-targeting mitophagy reporter) has also been developed using the MTS of the mitochondrial matrix protein COXIV fused to a mCherry-GFP tandem (Aoyagi et al., 2022). Combination of this approach with cell-type specific promoter Cre lines will help better understand the relevance of mitophagy in the different components of the retina.

Finally, certain reporters enable the monitoring of mitochondrial dynamics by examining their lifetime, remodeling, and biogenesis. On such example is MitoTimer, a mutant of dsRed that undergoes changes in fluorescence from green to red as the protein matures. Increased green fluorescence suggests alterations in mitochondrial dynamics or biogenesis. Changes in the expression of red fluorescent protein without changes in green fluorescence suggest alterations in mitochondrial degradation (Trudeau et al., 2014). This model has been used to investigate mitochondrial turnover in the heart (Stotland and Gottlieb, 2016).

Mito-SRAI is another fluorescent tandem YPet-afCFP (TOLLES: TOLerance of Lysosomal EnvironmentS) construct that has been used to assess mitophagy *in vivo* using AAV vectors. The acid sensitivity of YPet allows distinction of TOLLES-positive puncta in acidic compartments, revealing mitophagy in a similar manner to *mito*-QC, and can be evaluated using a ratiometric approach (Katayama et al., 2020). An intramitochondrial CLICK to assess mitophagy (IMCLAM) assay using an acidity-responsive ΔΨm probe and a pH-inert reference probe has been recently described. IMCLAM can detect the induction of mitophagy by measuring the levels of red fluorescence, generated upon delivery of mitochondria into acidic lysosomes (Shi et al., 2021).

2.2.3. Flow cytometry

The aforementioned methods to study mitophagy sometimes require expensive, time-consuming, and sophisticated image analysis techniques in order to distinguish between healthy cytosolic mitochondria and those delivered to acidic lysosomes. Therefore, a fast and quantitative method has been developed to evaluate mitophagy in cells by flow cytometry using mitochondrion-selective fluorescent probes like MitoTracker Deep Red FM (Mauro-Lizcano et al., 2015). This approach allows the determination of mitophagic flux when combined with

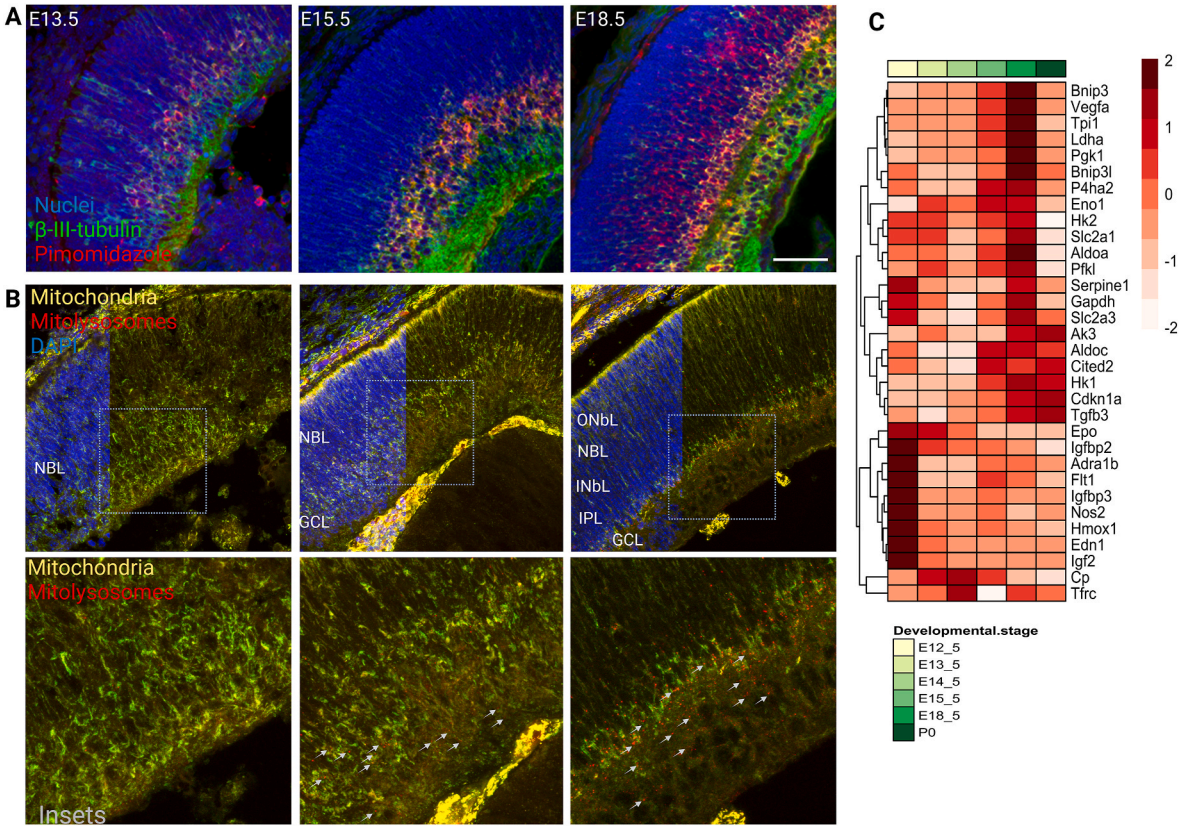

Fig. 4. *Hypoxia and mitophagy in the developing retina.* (A) Retina cryosections from embryos at E13.5, E15.5 or E18.5 immunostained with β–III–tubulin to label neurons and pimonidazole to label hypoxic regions (A) or from (B) *mito*-QC reporter mice (B), displaying mitochondria in yellow and mitolysosomes in red, where the GFP fluorescence has been quenched inside the acid environment of the lysosome. Nuclei are counterstained with DAPI. Gray arrows indicate mitophagosomes. Scale bar, 15 μm. (C) Heatmap of hypoxia-regulated genes throughout retina development (GSE84299).

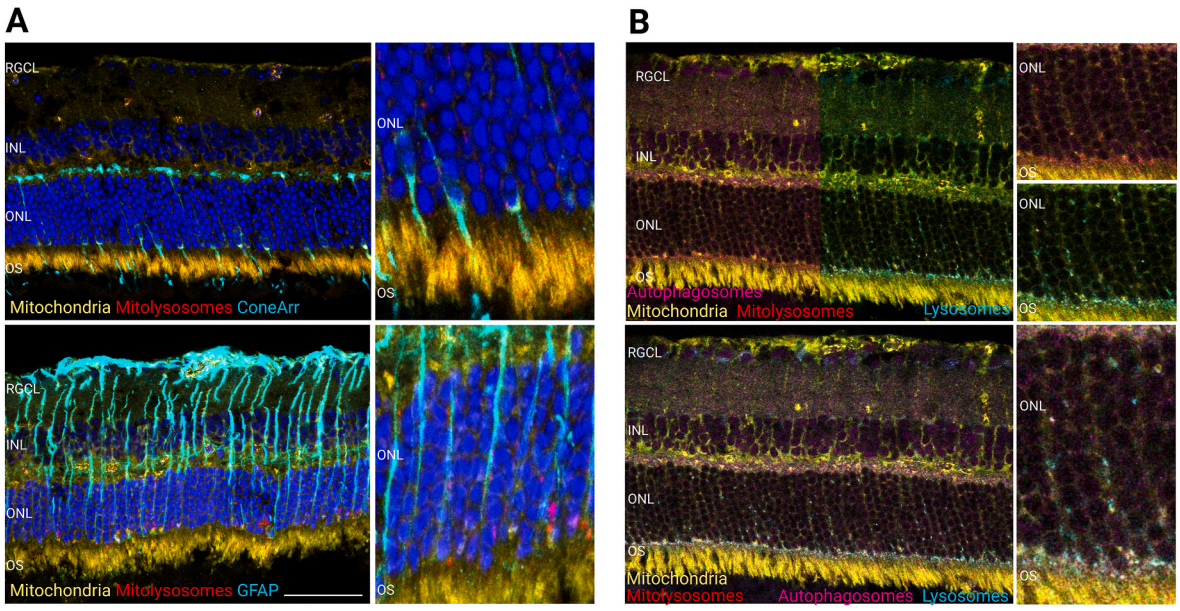

Fig. 5. *Co-localization of mito-QC with cell type-specific and autophagic markers.* Whole retina cryosections were immunostained with Cone Arrestin (cones), GFAP (astrocytes and Müller glia), LC3 (autophagosomes) and LAMP1 (lysosomes). Scale bar 25 μm.

Table 2
Methodology available for the study of mitophagy *in vitro, ex vivo and in vivo*.

Methodology	Application	Readout	Advantages	Disadvantages	Reference
Electron microscopy	*in vitro, in vivo*	TEM imaging, morphometry quantification	Reliability, ability to assess the different steps of mitophagy	Time-consuming, requires high expertise. Low mitophagosome numbers unless lysosomal degradation is blocked	Reme and Young (1977)
EGFP-LC3+Mito-DsRed	*in vitro*	Colocalization by fluorescence imaging, manual or automated quantification	Accessible, selectively reports mitophagosome generation	Requires confocal imaging to asess co-localization	Indira et al. (2018)
mito-EGFP + LAMP1-RFP	*in vitro*	Colocalization by fluorescence imaging, manual or automated quantification	Accessible, selectively reports mitolysosome formation	Requires confocal imaging to asess co-localization, GFP pH-sensitive quenching might lead to underestimation of results	Indira et al. (2018)
GFP-NDP52 foci formation	*in vitro*	Colocalization by fluorescence imaging, automated quantification	Accessible, fast	Requires confocal imaging, only measures NDP52-mediated mitophagy	Padman and Lazarou (2022)
mt-Keima	*in vitro, in vivo*	Fluorescence imaging, manual or automated quantification, flow cytometry	Accessible, high sensitivity, allows mitophagic flux assessment	Requires confocal imaging, cannot be fixed, requires live imaging and fast tissue isolation, prone to artifacts due to sample processing, RD background	Katayama et al. (2011)
mito-QC	*in vitro, ex vivo, in vivo*	Fluorescence imaging, manual or automated quantification, flow cytometry	High sensitivity, allows mitophagic flux assessment, fixable, can be multiplexed with cell type-specific markers	Requires confocal imaging, careful processing to ensure neutral pH 7.0 throughout sample processing	McWilliams et al. (2016)
CMMR-flox	*in vivo*	Fluorescence imaging, manual or automated quantification	Cell type-specific mitophagic flux assessment, fixable	Requires confocal imaging, careful processing to ensure neutral pH 7.0 throughout sample processing	Aoyagi et al. (2022)
MitoTimer	*in vitro, in vivo*	Fluorescence imaging, manual or automated quantification	Allows tracking of mitochondrial age and biogenesis assessment	Requires confocal imaging, co-localization with autophagosome and lysosome markers to detect mitophagy	(Stotland and Gottlieb, 2016; Trudeau et al., 2014)
mito-SRAI	*in vitro, in vivo*	Fluorescence imaging, manual or automated quantification, flow cytometry	Accessible, fixable	Requires confocal imaging, no constitutive reporter mice strain available	Katayama et al. (2020)
IMCLAM	*in vitro*	Fluorescence imaging, manual or automated quantification, flow cytometry	Allows tracking of mitochondria, fixable	Requires confocal imaging, time-consuming, limited availabilty, hinders cell proliferation, limited *in vivo* applicability	Shi et al. (2021)
MTDR	*in vitro, ex vivo*	Flow cytometry	Accessible, fast, reproducible results, low cost, can be multiplexed. Flux determination by using protease or lysosomal inhibitors	Requires a flow cytometer equipped with red/far red laser line and detectors, might be affected by drugs that severely disrupt ΔΨm	(Esteban-Martinez et al., 2017a; Mauro-Lizcano et al., 2015)
pUb^{Ser65} ELISA	*in vivo*	ELISA, enzyme immunoassay	Fast, translational approach for clinical use	Limited to PINK1-mediated mitophagy detection, no commercial kits available	Watzlawik et al. (2021)

lysosomal inhibitors and/or mitophagy inducers (Esteban-Martinez et al., 2017b). Our group has successfully used this approach to study mitophagy in the developing retina, in retinitis pigmentosa models, and in proliferating endothelial cells (Esteban-Martinez et al., 2017a; Mauro-Lizcano et al., 2015; Sahún-Español et al., 2022). Furthermore, thanks to its far-red emitting properties, combination of MitoTracker Deep Red FM with other dyes and probes allows the determination of other intracellular parameters such as viability, oxidative stress, and ΔΨm (Esteban-Martinez et al., 2017a).

An innovative new approach to measure mitophagy in mouse brain and human clinical and pathological samples involves the use of a sandwich ELISA targeting the mitophagy marker pUb^{Ser65}, which holds promise as a potential biomarker for neurodegenerative diseases in clinical practice (Watzlawik et al., 2021). In conclusion, the development of new tools and methods has been pivotal in furthering our knowledge of the basic functions of mitophagy in the retina, both *ex vivo* and *in vivo* (Table 2). While tandem fluorescence reporters allow us to monitor the dynamics of this process, there remains a need for efficient, fast, and reliable tools.

3. Physiological functions of mitophagy in the retina

3.1. Role of mitophagy in retina development

In mammals, retinal development occurs in the anterior region of the neural plate, and consists of the appearance of the optic pit and evagination of the optic primordium (Chow and Lang, 2001). In mice this process begins around embryonic day (E) 7.5, with development of the neuroretina beginning around E12.5 (Bharti et al., 2006). From this point, a dynamic spatiotemporal process begins in which the different retina cell types arise from the multipotent progenitors (Zagozewski et al., 2014). The mouse embryonic retina exhibits high levels of HIF-1α and pimonidazole staining (Kurihara et al., 2010), which are indicative of hypoxia, one of the main inducers of mitophagy (Zhang et al., 2008). Taking into account the energy-demanding proliferation-differentiation balance and its hypoxic environment, it is reasonable to speculate that mitophagy may play an important role in the developing retina. Indeed, our group has demonstrated that BNIP3L/NIX- and Atg5-dependent mitophagy contributes to the metabolic shift towards glycolysis that drives RGC differentiation (E15.5) during retinal development (Esteban-Martinez et al., 2017a) (Fig. 6). This switch to glycolysis for differentiation challenges the general paradigm, as differentiation is usually associated with increased mitochondrial activity (Agathocleous et al., 2012; Agostini et al., 2016; Cedikova et al., 2016; Ellen Kreipke et al., 2016; Wagatsuma and Sakuma, 2013). However, oxygen levels and the hypoxic niche surrounding the developing retina may play an essential role in the metabolic shift toward glycolysis or oxidative phosphorylation (OxPhos). If hypoxia is the driver of the differentiation process (oxygen levels decrease over time), mitophagy-dependent metabolic reprogramming towards glycolysis may regulate cell differentiation (Fig. 4). This could also explain the metabolic shift in the opposite direction (from glycolytic to a more OxPhos-dependent metabolism) observed in the *Xenopus* retina, in which differences in oxygen levels were observed between proliferating and fully differentiated retinae (Agathocleous et al., 2012). Another observation supporting this hypothesis is the increased mitophagy and decreased mitochondrial activity that accompanies the differentiation of mouse skin mesenchymal stem cells into chondrocytes (Forni et al., 2016), a hypoxia-regulated differentiation process (Araldi and Schipani, 2010). Together, these findings indicate that mitophagy-dependent metabolic reprogramming appears to regulate cell differentiation in hypoxic conditions.

Supporting the view that BNIP3L/NIX may participate in organelle degradation, BNIP3L/NIX-KO mice show accumulation of mitochondria, ER, and Golgi protein markers in the lens (Brennan et al., 2018). However, a recent study demonstrated that PLAAT phospholipases are the main players in organelle removal during lens development (Lastres-Becker et al., 2021; Morishita et al., 2021). In summary, the mechanism by which BNIP3L/NIX protein participates in lens degradation or whether said alternative mechanisms (PLAAT) are involved in neighboring neuroretina development remains unclear and requires further research.

Using the recently developed *mito*-QC reporter mouse, our group has generated a map of mitophagy and general macroautophagy in the E16.5 mouse retina (McWilliams et al., 2019). However, at this developmental stage mitophagy only accounts for around 25% of autophagic degradation within the retina, indicating that other substrates or organelles may need to be removed following the mitochondrial remodeling observed at E15.5 (Esteban-Martinez et al., 2017a; McWilliams et al., 2019). Other *in vitro* approaches highlight the importance of the

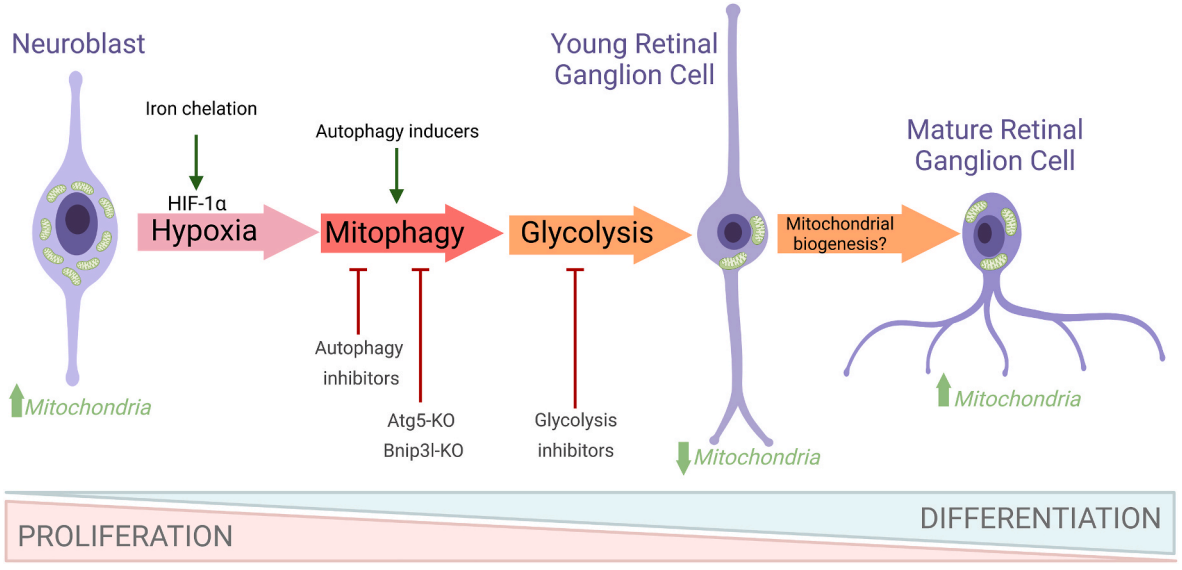

Fig. 6. *Mitophagy mediates RGC differentiation*. During retinal development neuroblasts undergo a metabolic switch from a predominant oxidative to a more glycolytic metabolism, mediated by BNIP3L/NIX-dependent mitophagy that regulates RGCs differentiation. Hypoxia triggers HIF-1α stabilization and transcriptional upregulation of BNIP3L/NIX, to eliminate mitochondria. Pharmacological or genetic inhibition of any of these steps hinders RGC differentiation while autophagy induction increases the number of differentiated RGCs.

autophagy pathway in differentiated cells versus progenitor cells (Das et al., 2020; Yazdankhah et al., 2021). Human retinal ganglion cells (hRGCs) rely more on the endo-lysosomal pathway for protein degradation while stem cells predominantly use the ubiquitin-proteasome system (Das et al., 2020). Moreover, autophagic and mitophagic flux are higher in differentiated versus undifferentiated rat oligodendrocytes (Yazdankhah et al., 2021). If mitochondria fission is inhibited, oligodendrocyte differentiation is also reduced, suggesting that mitophagy could also be implicated (Yazdankhah et al., 2021). In conclusion, mitophagy (and autophagy) seem to be essential for proper differentiation of the retina, with BNIP3L/NIX-mediated mitophagy playing a key role in RGC metabolic reprogramming and neurogenesis in the developing retina, and in certain situations driving changes in metabolic status.

3.2. Role of mitophagy in the adult retina

Although mitophagy has been generally described as a mechanism to respond to mitochondrial damage, several recent studies have demonstrated a basal level of mitophagy *in vivo* (Rodger et al., 2018). In our collaboration with Ian Ganley's research group, we performed an exhaustive comparison of autophagy and mitophagy levels in the main cell types in the E16.5 and adult eye using autophagy (MAP) and mitophagy (*mito*-QC) reporter mice respectively. We found that autophagy was present in all areas of the eye, both in development and adulthood (McWilliams et al., 2019). However, in the adult eye mitophagy accounted for most of the ongoing autophagic degradation in the cornea and the retina (McWilliams et al., 2019). The highest levels of mitophagy were found in the ONL, which is extensively populated by photoreceptors and Müller glia processes. Compared to other retinal cell types, adult photoreceptors have a higher metabolic demand and are very susceptible to light-induced damage. A high mitophagy activity may therefore be necessary to avoid the accumulation of damaged mitochondria. This hypothesis is supported by the lower levels of mitophagy observed during the later stages of embryonic retina development, a period during which phototransduction has not yet started and photo-oxidative damage is therefore absent. In stark contrast, we found very low levels of mitophagy during adulthood in regions such as the ciliary body and lens (McWilliams et al., 2019). While mitophagy in the RPE was observed in the *mito*-QC mice, further studies are required to determine its importance in this cell type, which relies on OxPhos and mitochondrial metabolism to sustain OS recycling (McWilliams et al., 2019). Retinal mitophagy has been proposed to rely primarily on PINK1-independent pathways in both light and dark conditions (McWilliams et al., 2018), although this hypothesis is yet to be proven.

In conclusion, high levels of mitophagy can be observed in the adult retina, particularly in photoreceptors. More studies are required to identify the mitophagy pathways involved in photoreceptor homeostasis and to unravel the physiological relevance of mitophagy in this mainly glycolytic cell type. While the phenotype of mitophagy-deficient animals is mild, the use of mitophagy reporter mice and breeding with different autophagy- and mitophagy-deficient strains (Table 1) will shed further light on these questions.

4. Alterations in mitophagy in retinal disease

4.1. Glaucoma

Glaucoma is a multifactorial, neurodegenerative disease associated with aging. It is the leading cause of irreversible blindness worldwide and will affect over 100 million people by 2040 (Tham et al., 2014). Glaucoma is frequently associated with elevated intraocular pressure (IOP) that leads to progressive optic nerve damage, culminating in vision loss caused by RGC death. Current treatments are mainly aimed at reducing IOP. However, glaucoma can progress even in patients receiving these therapies, and some patients develop glaucoma without showing an increase in IOP. Regardless of the origin of the insult, RGCs will die once their axons have been damaged, and currently there are no treatments capable of either halting this process or inducing axonal regrowth.

RGCs are very vulnerable to mitochondrial deficits, as evidenced in various rare inherited diseases caused by mutations in genes that regulate mitochondrial function, such as Leber's hereditary optic neuropathy (LHON; caused by mutations in the mitochondria-encoded subunits of NADH dehydrogenase MT-ND1, MT-ND4, MT-ND4L, and MT-ND6) and autosomal dominant optic atrophy (ADOA; caused by mutations in OPA1, which is involved in mitochondrial fusion). Furthermore, multiple studies have described mitochondrial dysfunction in glaucoma patients and in experimental models in which reduced ATP, increased ROS production, and mitochondria-dependent apoptosis contribute to RGC damage and cell death (Ito and Di Polo, 2017; Jassim et al., 2021a). High oxidative stress levels also lead to increased mitochondrial damage, triggering a pathogenic loop that could perpetuate and exacerbate damage caused by elevated IOP or other factors. Thus, the selective removal of mitochondria via mitophagy could represent a mechanism to stop this vicious cycle (Frank et al., 2012). Why RGCs are especially sensitive to mitochondrial damage is a focus of ongoing research, and may be linked to their unique morphology, i.e., very long axons and complex dendritic arbors that require highly-compartmentalized bioenergetic machinery and metabolism.

Using experimental models of severe axonal damage such as ONC or axotomy, several studies have highlighted how autophagy can play a protective role and promote RGC survival (Chang and Guarente, 2014; Kim et al., 2008; Lee et al., 2021; Rodriguez-Muela et al., 2012; Russo et al., 2013; Su et al., 2014). Supporting this cytoprotective role of autophagy in RGCs, animals with deficient autophagy such as the Atg4B–KO and the RGC-specific Atg5-KO mice, show increased susceptibility to axonal damage (Rodriguez-Muela et al., 2012).

Interestingly, in some autophagy-deficient models this susceptibility increases with age. The consequences of ONC on RGC survival in young (5–6 months) Ambra1 heterozygous animals (*Ambra1*$^{+/gt}$) are comparable to those in wild-type littermates (*Ambra1*$^{+/+}$), while in middle-aged animals (12–14 months) fewer RGCs survive after ONC (Bell et al., 2020). In physiological conditions, no changes in the number of RGCs are observed in young or middle-aged animals, while geriatric (22–26 months) mice show a tendency towards reduced RGC number (Ramírez-Pardo et al., 2022). Proteomic analysis of the retina of Ambra1-deficient animals also reveals lysosomal alterations, with decreases in the levels of the lysosomal proton pump subunit ATP6V1A and a massive reduction in the levels of crystallin molecular chaperones (CRYBB2, CRYAA, CRYAB), deficits which have been associated with impaired lysosomal function (Valapala et al., 2014). In the context of glaucoma, crystallins have been linked to neuroprotection of RGCs after ONC (Anders et al., 2017; Ying et al., 2008). Data from our and other research groups suggest that reduced autophagy renders RGCs more susceptible to external insult, and may therefore play an essential pro-survival role during glaucoma progression.

A prominent feature of autophagy dysfunction is the accumulation of damaged mitochondria (Komatsu et al., 2005). It has been suggested that defective removal of mitochondria via autophagy results in increased oxidative stress as well as activation of immune-activating damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), and can lead to cell death (Frank et al., 2012). For example, a recent study reported that the antiviral defense protein TRIM5α regulates Parkin-dependent and -independent mitophagy pathways, in which TRIM5α recruits upstream autophagy regulators to damaged mitochondria (Saha et al., 2022). Thus, defects in mitophagy can result in increased inflammation and glial activation. Indeed, we observed increased astrocytic gliosis and microglial activation in the retina of old Ambra1-deficient animals, together with increased oxidative stress in the neuroretina and RPE in middle-aged mice (Ramírez-Pardo et al., 2022). These data further

support a key pro-mitophagic function of Ambra1, preventing oxidative stress and inflammation and sustaining retinal homeostasis.

Evidence also supports a cytoprotective role of mitophagy in glaucoma. First, mitophagy increases after ONC in *mito*-QC mitophagy reporter mice, and a similar increase in mitophagy is observed in primary RGCs cultured *in vitro* under different stress conditions (Rosignol et al., 2020). Second, rapamycin has been shown to reduce oxidative stress *in vivo* after axotomy, after which EM revealed mitochondria inside autophagosomes and autolysosomes, suggesting mitophagic degradation (Rodriguez-Muela et al., 2012). In agreement, beneficial effects of rapamycin have been demonstrated in glaucoma rodent models (Harder et al., 2020; Wang et al., 2020), although a detrimental effect of mTOR (mammalian target of Rapamycin) inhibition has also been reported in similar models (Agostinone et al., 2018), and restoration of mTOR activity protects dendrites in injured RGCs (Belforte et al., 2021). One possible explanation for these conflicting findings is that the beneficial effects depend on the disease stage. For example, in a model of chronic hypertensive glaucoma in rats the number of mitophagosomes in the optic nerve decreased at 3 days, but increased at 2 weeks following IOP elevation (Dai et al., 2018). In that model, Parkin overexpression increased RGC survival and improved mitochondrial health (Dai et al., 2018). Taken together, these data suggest that mitophagy could be triggered to eliminate damaged mitochondria to cope with stress in early disease stages, but that cumulative damage over time causes the compensatory mechanisms to fail, resulting in impaired mitophagy and progressive RGC damage (Dai et al., 2018). Indeed, we have found that in basal conditions aged *Ambra1*$^{+/gt}$ mice show increased transcriptional activation of cytoprotective pathways (e.g. the oxidative stress response), which could result in exhaustion of the anti-oxidant enzymes and consequent impairment of the response in conditions of added stress (Bell et al., 2020). Alternatively, deficient mitophagy could be a primary defect in Ambra1 heterozygous mice, contributing to the accumulation of damaged mitochondria and increasing oxidative stress. This, together with the deficient anti-oxidant response, could explain the accelerated aging of the retina observed in Ambra1 heterozygous animals. In any of these scenarios, the pathogenic loop of impaired mitophagy–increased ROS would be further exacerbated in autophagy/mitophagy-deficient animals, thereby increasing cell death (Ramírez-Pardo et al., 2022).

IOP elevation can reduce oxygen supply to the retina, inducing hypoxia-triggered HIF-1α signaling (Ergorul et al., 2010). As mentioned above, the downstream target genes of HIF-1α include BNIP3 and BNIP3L/NIX, key regulators of Parkin-independent mitophagy (Teresak et al., 2022). Indeed, our group has described transcriptional upregulation of BNIP3 and BNIP3L/NIX in response to ONC, an effect that was attenuated in Ambra1-deficient mice (Bell et al., 2020). A recent study presented evidence of hypoxia and ROS accumulation in the retina of DBA/2J mice (a model of high IOP glaucoma), together with a decrease in mitochondrial mass and citrate synthase activity (Jassim et al., 2021b). Mitophagic flux was not evaluated, but increased levels of Rheb were observed in the glaucomatous retina, suggesting increased mitophagy in these experimental conditions, although this hypothesis needs to be confirmed. Additionally, an accumulation of mitochondria with altered morphology was observed in the optic nerve of DBA/2J mice, concomitant with increased number of autophagosomes and LC3-II/LC3-I ratio (Coughlin et al., 2015; Hirt et al., 2018). While no differences were observed in PINK1 or Parkin levels, the involvement of other mitophagy pathways and whether these alterations are subcellular localization-specific remains to be studied.

Maintenance of a fine balance between mitochondrial biogenesis and mitophagy is a key determinant of mitochondrial homeostasis. Excessive mitophagy in the absence of mitochondrial biogenesis could compromise the cell's ability to sustain metabolic demands, resulting in cell death (Doxaki and Palikaras, 2020). Thus, mitophagy triggers concomitant mitochondrial biogenesis, and this compensatory response allows them to survive under stress conditions (Palikaras et al., 2015). How mitochondrial biogenesis and mitophagy are coordinated in RGCs remains to be elucidated, as defects in mitochondrial biogenesis have also been observed in the aged DBA/2J mouse glaucoma model (Guo et al., 2014). A recent study uncovered important crosstalk between oxidative stress and mitophagy upregulation: mice deficient for the uncoupling protein UCP2 showed reduced RGC death in response to glaucoma induced by microbead injection (Hass and Barnstable, 2019b). The authors showed that deletion of *Ucp2* in astrocytes or RGCs increased the colocalization of mitochondrial proteins with LC3 and increased transcriptional levels of many mitophagy-related genes *in vivo* (Hass and Barnstable, 2019a). Interestingly, these protective effects of Ucp2 downregulation were independent of mitochondrial biogenesis, and were associated with increases in mitochondrial function and increased mitophagy (Hass and Barnstable, 2019b). Thus, while *Ucp2* overexpression decreases glaucomatous death (Hass and Barnstable, 2019a), downregulation appears to trigger a pro-mitophagy response that also protects RGCs from IOP-induced cell death. Interestingly, astrocyte-specific *Ucp2* deletion induced a similar level of protection against cell death to that observed for *Ucp2* deletion in Thy1-positive RGCs, suggesting that mitophagy may exert a direct cytoprotective effect in RGCs, but may also be associated with the elimination of RGC mitochondria within astrocytes during transmitophagy. Indeed, this phenomenon of transcellular mitochondria degradation had been previously described in optic nerve astrocytes (Davis et al., 2014) and has since been found in several contexts, including the heart (Nicolás-Ávila et al., 2020) and in Alzheimer's disease models (Lampinen et al., 2022).

Supporting the relevant role of mitochondrial homeostasis in glaucoma, mutations in the mitophagy receptor OPTN and its upstream activator TBK1 kinase have been associated with increased risk of developing open angle glaucoma (OAG), specifically normal-tension glaucoma (NTG). OAG can also involve reduced aqueous humor drainage and lead to chronically increased IOP, but presents slower progression nonetheless. The E50K-OPTN variant is the most prevalent mutation (Minegishi et al., 2016) and studies using RGC-differentiated human pluripotent stem cells (hPRCs) have shown that this mutation leads to increased cell death that is rescued by the TBK1 inhibitor Amlexanox (Sayyad et al., 2021). Analyses on retinal organoids revealed that E50K-OPTN leads to autophagosome accumulation and impaired autophagic flux (VanderWall et al., 2020). Surprisingly, similar alterations were found in E50K-OPTN astrocytes, indicating that glial cells might also be accelerating or contributing to neurodegeneration in OAG (Gomes et al., 2022). Autophagy is also impaired in mice expressing the E50K-OPTN risk variant, and mTORC1 inhibition with Rapamycin restored autophagic flux and improved visual function (Zhang et al., 2021). Less common M98K-OPTN variant also presents autophagy alterations and increased cell death susceptible to TBK1 modulation (Klionsky et al., 2021a; Sirohi et al., 2013). Regarding mitochondrial dynamics, E50K-OPTN has been shown to increase the fission/fusion ratio, leading to decreased mitochondrial function and increased basal mitophagy (Shim et al., 2016). In other study, glaucoma-associated OPTN mutants have been shown to have similar PINK1/Parkin-mediated mitophagy levels to WT OPTN (Chernyshova et al., 2019). Further research is required to determine how mitophagy is altered in OAG involving OPTN mutants, and whether these alterations are indeed mutant-specific. Pharmacological TBK1 modulation might represent an interesting druggable target to modulate mitophagy and improve RGC survival.

In conclusion, many questions remain regarding the mechanisms and role of mitophagy in RGCs. For example, how is defective mitochondrial function connected to ROS production and mitophagy in RGCs? A recent study found that excessive ROS production is followed by mitophagy via the KEAP1/PGAM5 complex (Zeb et al., 2021). Whether different forms of mitophagy occur within distinct subcellular compartments of RGCs also remains to be determined. Parallel induction of independent mitophagy pathways within different compartments could be beneficial for RGCs, which have long axons. Indeed, a recent report demonstrated that local translation of Pink1 supports local mitophagy in axons of

iPSC-derived neurons (Harbauer et al., 2022). Understanding how the different mitochondrial quality control pathways, including biogenesis, fusion, fission, and mitophagy, are regulated will be key to help design new strategies for the treatment of glaucoma and other degenerative diseases involving RGC damage (Table 3).

4.2. Diabetic retinopathy

Diabetic retinopathy (DR) is the most common complication associated with diabetes mellitus (DM), with a prevalence of 22.7% in DM patients (Teo et al., 2021). DR is characterized by long-term accumulation of glucose and a chronic state of hyperglycemia, which affects the retinal microvasculature and causes structural abnormalities and cellular damage, leading to visual impairment and eventual blindness (Gong et al., 2021). However, the pathogenic mechanisms underlying this disease are not fully understood. Even though DR can course with no visual affectation, fundus imaging can help ascertain the stage of the disease and the occurrence of microaneurysms, microvascular alterations or hemorrhages (Cheung et al., 2010). A chronic state of ocular hyperglycemia is associated with breakdown of the BRB, neovascularization, and loss of tight junctions as well as the death of pericytes and endothelial cells (ECs) (Duh et al., 2017; Roy et al., 2017). These events are accompanied by oxidative and ER stress, apoptosis, and dysregulation of autophagy. As DR develops, the activation of Müller cells and microglia promotes the production of multiple inflammatory mediators and various vascular growth factors (e.g. VEGF), as well as advanced-glycation end products (AGEs), thus exacerbating the pathogenicity of the disease and potentially affecting other retinal cell types such as RGCs and RPE (Bejarano and Taylor, 2019; Gong et al., 2021).

A growing body of evidence indicates a dual role of autophagy during DR. Autophagy serves as a protective mechanism, promoting cell survival in conditions of low glucose concentration, but can also have detrimental effects, exacerbating the progression and pathogenesis of DR in conditions of long-term exposure to and/or increasing concentrations of glucose (Dehdashtian et al., 2018). Mitochondrial dysfunction may be a key regulator during DR pathogenesis. For instance, studies of the human diabetic retina, as well as animal and cell models of DR, have described mitochondrial DNA damage, overproduction of mitochondrial ROS, inefficient mitochondrial DNA repair, and vacuolated mitochondria with disruption of the lamellar cristae (Ferrington et al., 2020; Hombrebueno et al., 2019). These alterations are sufficient to disrupt mitochondrial homeostasis, thus leading to exacerbated levels of ROS and mitophagy alterations (Kowluru and Mishra, 2018).

The BRB consists of ECs with tight junctions, which are almost impermeable to proteins. During DR, initial alterations affect the BRB, leading to the loss of tight junctions and increased permeability, thereby allowing the extravasation of proteins and molecules that disrupt retinal homeostasis (Duh et al., 2017). Tumor suppressor miR-204-5p was recently shown to reduce autophagic flux in diabetic rats and *in vitro* ECs by downregulating LC3-II expression (Mao et al., 2019), while miR-204-5p inhibition activated autophagy. Other proteins overexpressed in ECs during DR include matrix metalloproteinase-2 (MMP-2), HIF-1α, VEGF, and insulin-growth factor-1 (IGF-1), factors usually associated with neovascularization and exacerbation of DR, a situation that can be reversed by increasing expression of the deacetylase Sirt3 (Mao et al., 2017) or by treatment with the hormone melatonin (Doğanlar et al., 2021). More precisely, melatonin induces the expression of genes involved in mitochondrial biogenesis while inhibiting genes involved in mitochondrial fission (Doğanlar et al., 2021). Furthermore, hypoxia induced by bevacizumab (anti-VEGF) in an oxygen-induced mouse model of retinopathy promotes mitophagy via BNIP3 and FUNDC1, suggesting that this process may help mitigate oxidative stress and apoptosis in DR (Sun et al., 2021).

ECs are protected by pericytes in the retinal capillaries. In a rat model of DR, glycated low-density lipoproteins (LDL) can extravasate through the BRB into ECs, thereby promoting oxidative and ER stress (Fu et al., 2012). Accumulation of LDL in the retina shifts the protective role of autophagy towards cell death and apoptosis (Fu et al., 2016). In addition, interruption of the intercommunication between pericytes may account for the damage to these cells observed in DR (Alarcon-Martinez et al., 2022). Most evidence points to a key protective role of mitophagy in preserving BRB integrity and preventing neovascularization and edema in DR.

The potential role of antioxidant defense in DR is attracting growing attention. It is widely accepted that circulating levels of homocysteine, a precursor of cysteine and therefore of glutathione (GSH), are elevated in diabetic patients (Malaguarnera et al., 2014). Moreover, homocysteine accumulation is known to promote photoreceptor degeneration (Chang et al., 2011) and impairment of mitochondrial function in RGCs (Ganapathy et al., 2011), and upregulates mitophagy markers and apoptosis (Kowluru et al., 2020). Interestingly, a recent study of human ECs and retinas from donor DR patients demonstrated accumulation of homocysteine in the retinal microvasculature, with a 50% reduction in levels of the enzymes that metabolize this non-protein amino acid, (i.e. methylenetetrahydrofolate reductase [MTHFR] and cystathionine-γ lyase [CSE], which convert homocysteine to methionine and L-cysteine, respectively) (Kowluru et al., 2020). These alterations were accompanied by hypermethylation of the promoters of MTHFR and cystathionine β-synthase (CBS), reducing their transcription and corresponding protein levels. Furthermore, protein levels of DRP1, OPTN, and LC3 were upregulated while fusion machinery proteins (MFN2) were downregulated (Kowluru et al., 2020).

Another early and key event in DR is angiogenesis resulting from high glucose levels. Hyperglycemic conditions in RF/6A endothelial cells promote tube formation and cell migration together with ROS production and autophagy (Coughlin et al., 2017; Li et al., 2019). These observations suggest that autophagy inhibition may help prevent retinal angiogenesis during DR.

Table 3
Evidence of mitophagy alterations in glaucoma models.

Glaucoma					
Model	Approach	Cell types affected	Findings	Role of mitophagy	Reference
ONC, *Ambra1*$^{+/gt}$	*in vivo*	RGCs	Increased susceptibility in mitophagy-deficient mice, increased BNIP3/NIX expression, impaired ROS response	Beneficial	Bell et al. (2020)
ONC, primary RGCs	*in vivo, in vitro*	RGCs	Increased mitophagy in response to ONC and to different stressors (*in vitro*)	–	Rosignol et al. (2020)
Axotomy	*in vivo*	RGCs	Increased mitophagy, improved RGC survival an reduced ROS after rapamycin administration	Beneficial	Rodriguez-Muela et al. (2012)
DBA/2J	*in vivo*	RGCs	Decreased (3 days) and increased mitophagosome formation (2 weeks), increased RGC survival after Parkin overexpression	Beneficial	Dai et al. (2018)
DBA/2J	*in vivo*	RGCs	Reduced mitochondrial mass and mitophagy markers	–	Jassim et al. (2021b)
IOP, *Ucp2*$^{-/-}$	*in vivo*	RGCs	Reduced RGCs death, increased mitophagosome formation	Beneficial	Hass and Barnstable (2019b)

Although most studies have focused on autophagy alterations in the neuroretina, it is also important to assess the role of Müller cells during DR, as they are essential to maintain retinal homeostasis. Müller glia span the entire retina, and mediate the production and secretion of pro-angiogenic factors, leading to neovascularization, inflammation, and eventual cell death in DR (Coughlin et al., 2017). Several findings in retinas from DR patients suggest a pivotal role of autophagy and mitophagy dysfunction in Müller cells in DR. Autophagy induced by high glucose concentrations in Müller cells is not successfully completed due to autophagosome accumulation in the cytoplasm, which in turn leads to massive release of VEGF (Lopes de Faria et al., 2016). Cell cultures of rat Müller cells incubated with high concentrations of glucose (40 mM) show downregulation of autophagy and upregulation on apoptosis, which can be partially reversed using epigallocatechin gallate, a major polyphenol found in green tea (Wang et al., 2019a). Furthermore, notoginsenoside R1/NGR1 markedly inhibits apoptosis, suppresses VEGF expression, and reduces oxidative stress and inflammation in diabetic mice and Müller cells (rMc-1) cultured with high concentrations of glucose (60 mM for 48 h) (Zhou et al., 2019). This phenomenon occurs due to upregulation of mitophagy via PINK1.

Thioredoxin interacting protein (TXNIP) is a pro-inflammatory and pro-oxidative stress mediator that is upregulated in Müller cells exposed to hyperglycemic stimuli, promoting oxidative stress, gliosis, inflammation (Devi et al., 2012), and activation of autophagy and mitophagy (Ao et al., 2021; Devi et al., 2017; Hombrebueno et al., 2019). Some authors have proposed that this activation in hyperglycemic conditions is beneficial, promoting the degradation of damaged mitochondria via PINK1/PARKIN-mediated mitophagy and enabling cell survival (Devi et al., 2012; Huang et al., 2018; Su et al., 2020). On the other hand, upregulation of TXNIP in high glucose conditions (25 mM for 5 days or 35 mM for 48 h) elicits a detrimental response by promoting mitophagy and cellular apoptosis (Ao et al., 2021; Devi et al., 2017). It has been proposed that this response is due to partial inhibition of the PI3K/AKT/mTOR signaling pathway (Ao et al., 2021). These changes in mitophagy do not correlate with major changes in mitochondrial biogenesis markers such as PGC1α or TFAM, supporting a role of deficient mitophagy in DR (Hombrebueno et al., 2019). Studies in the mitophagy reporter animals mt-Keima mice have shown that silencing or pharmacological inhibition of TXNIP may normalize mitophagic flux and NLRP3 inflammasome activation, preventing or delaying DR progression (Singh et al., 2017). Overall, these data points to a protective effect of PINK1/Parkin-mediated mitophagy in Müller glia during the early pathogenesis of DR and its inhibition in late stages of the disease.

During DR, RGCs are highly sensitive to the increased concentrations of glucose in the retina, which cause selective death of these cells during early disease stages (Catalani and Cervia, 2020). Decreased autophagic flux and activation of mTOR and apoptosis have been demonstrated in murine retinal explants incubated with high concentrations of glucose (75 mM for 10 days) (Amato et al., 2018). Treatment with the neuroprotectant octreotide restored autophagic flux and inhibited mTOR. Immunohistochemical findings suggest that this compound exerts its effect at the level of the GCL and the bipolar and amacrine cells (Amato et al., 2018, 2020). Finally, Beclin-1 and LC3B-II/I ratio were slightly increased 4 and 8 weeks after induction of DR with streptozotocin. This phenomenon was accompanied by activation of AMPK and inhibition of mTOR (Park et al., 2018). These findings suggest that autophagy induction in RGCs exerts a beneficial effect, preventing RGC death and slowing DR progression.

Other studies have shown that in rats with streptozotocin-induced diabetes and in ECs treated with high doses of glucose (65 mM for 24 h), mitophagy has a detrimental effect on RGCs (Ma et al., 2017; Zhang et al., 2022). This phenotype was reversed using liraglutide, a GLP-1 analog that inhibits mitophagy via the PINK1/Parkin pathway (Zhou et al., 2020). Whether the beneficial role of autophagy and/or PINK1/Parkin-mediated mitophagy is indeed cell type-specific should be further studied.

A quantitative mass spectrometry analysis showed that lysine 108 of OPTN is specifically succinylated in vitreous humor samples from DR patients (Zhang et al., 2022). This finding was further corroborated in rat and cellular models. Succinylation of OPTN was accompanied by blockade of autophagic flux, which was reversed by SIRT5-induced desuccinylation. These findings point to novel targets for the treatment of RGC dysfunction during DR (Zhang et al., 2022).

Interestingly, changes in mitochondrial dynamics have been demonstrated during progression of DR in human retinas and in the diabetic murine reporter *mito*-QC-*Ins2*$^{Akita/+}$ (Hombrebueno et al., 2019). This animal model recapitulates the preclinical stages of DM type I. Young mice (2 months) show mild retinal neurovascular dysfunction and increased mitophagy in the IS-OPL layers, as revealed by the *mito*-QC reporter, together with reduced mitochondrial mass as evidenced by COXIV and TOMM20 immunostaining. By contrast, mitophagy is inhibited in 8-month-old mice, which exhibit severe retinal neurovascular dysfunction and with progressive senescence (Hombrebueno et al., 2019). These mice also display reduced mitochondrial biogenesis, which may be partially explained by mitochondrial DNA damage, which directly interferes with transcription (Hombrebueno et al., 2019).

As previously mentioned, the main sources of energy for the RPE in physiological conditions are fatty acids and lactate derived from glucose-driven photoreceptor metabolism. Therefore, excessive accumulation of glucose in DR directly affects this cell layer. It has been shown that long-term exposure of the RPE to glucose directly increased levels of ROS and promoted premature senescence (Chen et al., 2019). Short-term exposure of ARPE-19 cells to hyperglycemic glucose concentrations boosted autophagy while long-term exposure inhibited autophagy and enhanced apoptosis (Chen et al., 2019). Exposure of ARPE-19 cells to high concentrations of glucose (50 mM) has been reported to inhibit mitophagy due to ROS-promoted inactivation of PINK1/Parkin-dependent mitophagy, leading to cellular death by apoptosis (Zhang et al., 2019). Conversely, it has been described elevated intracellular ROS levels in ARPE-19 cells, together with increased expression of PINK1, Parkin, BNIP3L/NIX, and LC3-II, and elevated mitophagy, suggesting a protective role of mitophagy against high glucose-induced damage in these cells (Huang et al., 2018). Further studies are needed to elucidate the role of mitophagy in the intra-retinal immune system (astrocytes, microglia, Müller glia) and within the BRB interface.

Pharmacological modulation of autophagy and mitophagy regulators such as rapamycin and 3-MA have shown beneficial effects in animal and cellular models of DR. However, translation of these approaches to clinical practice remains elusive. To our knowledge, there is no effective treatment for DR, only palliative strategies that target the later disease stages (Evans et al., 2014). Current therapies are based on laser photocoagulation and anti-VEGF agents such as bevacizumab. Bevacizumab has been shown to reduce oxidative stress and apoptosis in Müller cells, ECs, and photoreceptors where inhibition of VEGF promotes mitophagy mediated via BNIP3 and FUNDC1 by HIF-1α activation (Sun et al., 2021). Another proposed mitophagy enhancer is RNG1, which has been validated in Müller cells both *in vivo* and *in vitro* (Zhou et al., 2019). RNG1 acts via the PINK1/Parkin pathway to reduce inflammation, oxidative stress, apoptosis, and VEGF levels.

Other promising drugs include the tetrapeptide elamipretide (SS-31), which targets mitochondrial CL and has shown promise in oxidative stress models (Bai et al., 2021; Birk et al., 2014). The small molecule SRI-37330 inhibits the expression of TXNIP and the secretion and function of glucagon, and may help reverse the effects of diabetes in mice (Thielen et al., 2020). In addition, dimethyl fumarate (DMF) attenuated vascular complications in a rat model of diabetes by activating Nrf2, decreasing oxidative stress and downregulating the ROS/TXNIP/NLRP3 inflammasome signaling axis (Amin et al., 2020). In recent years, mitophagy has been proposed as an upstream regulator of inflammasome activation through the reduction of some of its main

triggers (mitochondrial ROS, mtDNA release), removal of damaged mitochondria, and consequent mitigation of the cGAS/STING/NLRP3 inflammatory response (Lin et al., 2019; Sliter et al., 2018). DMF has also shown promise in a TNFα-induced RPE inflammation model, in which it also restored mitochondrial bioenergetic function and structure (Shu et al., 2022). While further studies will be necessary, current evidence points to an anti-inflammatory role of mitophagy induction, and suggests that drug repurposing may be one possible avenue for the development of DR therapies.

It is clear that autophagy and mitophagy play pivotal roles during DR (Table 4). However, many questions about these processes remain unanswered. An in-depth characterization of these processes is required, and will also shed further light on the pathogenesis of DR. Due to the dynamic nature of cell metabolism, glucose utilization by mitochondria and non-physiological oxygen concentrations *in vitro*, studies using hyperglycemic conditions should be interpreted carefully. Overall, *in vivo* studies with patient samples and animal models point to cell type-specific impaired mitophagy in DR. Standardization of animal and cellular models and more precise tools with which to study autophagy and mitophagy are other key requirements to facilitate the development of new and novel therapeutic strategies for DR patients.

4.3. Retinal degeneration associated with photoreceptor damage

Retinal dystrophies are a mixed group of diseases (global prevalence, approximately 1 per 4000) characterized by photoreceptor death and consequent progressive vision loss (Hartong et al., 2006). The retinal cells most affected in retinal dystrophies are photoreceptors, both cones and rods, resulting in long-term blindness once the patients reach mid-adulthood (Olivares-González et al., 2021). The phototransduction process to which the photoreceptors are subjected, together with the continuous daily turnover of POS, imposes a high metabolic demand. Photooxidative damage caused by capturing light, as well as the oxidative stress generated by recycling of photoreceptor OS membranes, can lead to cellular damage to photoreceptors. Other processes that can trigger photoreceptor death include altered calcium signaling, the cyclic nucleotide pathway, and cathepsin-mediated cell death (Murakami et al., 2013; Rodriguez-Muela et al., 2015; Wang et al., 2018).

Of inherited retinal diseases, the most widely studied is retinitis pigmentosa (RP). RP patients experience a progressive decrease in visual function. In the first stages, rods are affected, leading to loss of night and peripheral vision. Subsequently, patients lose their central vision (Hartong et al., 2006). Studies of the P23H rhodopsin (RHO^{P23H}) model of RP have indicated that balance between the autophagy and proteasome pathways is essential to ensure photoreceptor survival (Yao et al., 2018). We previously described alterations in autophagic flux in the RP *rd10* (Retinal degeneration 10) model caused by deficient lysosomal degradation due to lysosomal membrane permeabilization induced by calcium overload (Rodriguez-Muela et al., 2015). In this model, we have also shown that the use of cathepsin and calpain inhibitors decreases photoreceptor loss, pointing to autophagy inhibition as a possible therapeutic approach for the treatment of early rod death in RP. In recent years, treatments that increase autophagy have been shown to effectively delay photoreceptor death at different timepoints in different RP models. We have also shown that secondary death of cones in distinct RP models is correlated with an increase in the activity of histone deacetylases (HDACs), known upstream negative regulators of autophagy (Samardzija et al., 2021). Specifically, a single intravitreal injection of a HDAC inhibitor administered after rod death delayed cone death in these mice models, and also promoted transcriptomic upregulation of autophagy and increased autophagosome degradation within lysosomes (Samardzija et al., 2021). These findings suggest that autophagy may play a dual role, protective or detrimental, depending on the specific mutation and cell type affected.

A recent report demonstrated that the miR-211/Ezrin axis was responsible for lysosomal biogenesis during the light-dark transition of RPE cells. Pharmacological inhibition of Ezrin induces autophagy, rescuing retinal degeneration in miR-$211^{-/-}$ mice (Naso et al., 2020). A recent study found that by inhibiting Ezrin, and therefore increasing autophagy, photoreceptor death was decreased in the RHO^{P23H} model via increased removal of RHO^{P23H} aggregates and decreased ER damage due to oxidative stress (Intartaglia et al., 2022). PRPF8 (pre-mRNA processing factor 8), a participant in the spliceosome, is a key regulator of hypoxia-induced mitophagy. PRPF8 knockdown decreases mitophagosome formation, resulting in mitochondria accumulation (Xu et al., 2018). A similar phenomenon is observed in mice expressing the RP-associated PRPF8 mutant R2310K. Alterations in mitophagy caused by PRPF8 dysregulation therefore contribute to photoreceptor degeneration in these models (Xu et al., 2018).

RP can also be studied in pharmacological models that phenocopy the disease. For example, the SN2 DNA alkylating agent methyl methanesulfonate (MMS) specifically causes photoreceptor death (Meira et al., 2009). Mice treated with MMS show increased mTOR activity in photoreceptors, while inhibition of mTOR activity with rapamycin, which increases autophagy, significantly improves visual function (Meira et al., 2009). These data point to a protective role of autophagy and mitophagy in RP or RP-like models, repurposed drugs targeting mitochondria quality control could slow down or brake

Table 4
Evidence of mitophagy alterations in diabetic retinopathy models.

Diabetic retinopathy					
Model	Approach	Cell types affected	Findings	Role of mitophagy	Reference
OIR	*in vivo, in vitro*	Müller, EC, PR	Upregulation of BNIP3 and FUNDC1, decreased ROS and apoptotic cell death	Beneficial	Sun et al. (2021)
Human samples	*in vivo, in vitro*	EC	Upregulation of fission and mitophagy markers	Beneficial	Kowluru et al. (2020)
High glucose, db/db	*in vivo, in vitro*	Müller	Upregulation of PINK1-dependent mitophagy *in vivo* and in Müller cells *in vitro*, reduced retinal degeneration and improved visual function	Beneficial	Zhou et al. (2019)
High glucose	*in vitro, in vivo*	Müller	TXNIP-induced increase on mitophagy, concomitant with exacerbated astrogliosis	Detrimental	Devi et al. (2017)
STZ	*in vitro, in vivo*	RGCs	Abnormal mitochondria morphology, increased PINK1/Parkin-dependent mitophagy reverted upon liraglutide administration	Detrimental	Zhou et al. (2020)
Human samples, *Ins2*$^{Akita/+}$, High glucose	*in vivo, in vitro*	Müller, PR	Increased PINK1-dependent mitophagy at early stages (2 months) and ihibition at symptomatic stage (8 months), decreased mitochondrial biogenesis	Beneficial	Hombrebueno et al. (2019)
High glucose	*in vitro*	RPE	Inhibited PINK1/Parkin-mediated mitophagy concomitant with apoptotic cell death	Beneficial	Zhang et al. (2019)
High glucose	*in vitro*	RPE	Increased PINK1/Parkin-mediated mitophagy associated to elevated ROS production	Beneficial	Huang et al. (2018)

neurodegeneration in this rare disease.

Prolonged exposure to high-intensity light can lead to severe alterations in photoreceptors, mostly in the external segments of the rods and the RPE, leading to neurodegeneration and retinal remodeling. Long-term exposure to bright light results in the formation of autophagosomes, containing damaged mitochondria and cellular debris, in the IS and within the synaptic bodies (Kunchithapautham and Rohrer, 2007). The extent of the damage depends on the wavelength and intensity of light, as well as the genetic background of the mice used (Organisciak and Vaughan, 2010). In autophagy-deficient mice, such as Beclin-1 hemizygous or Atg7 rod-specific deletion mice (Chen et al., 2013), high-intensity light exposure results in neurodegenerative loss of photoreceptors and RPE damage, accompanied by parallel mitochondrial impairment (Chen et al., 2013). This study described compromised photoreceptor recycling in Abca4$^{-/-}$Rdh8$^{-/-}$ mice in response to light-induced damage, together with increased retinal levels of Parkin (Chen et al., 2013), a protein that is recruited to damaged mitochondria and drives PINK1/Parkin-mediated mitophagy (Narendra et al., 2010). The authors confirmed the role of mitophagy in this system using Parkin-deficient (Park2$^{-/-}$) mice. After exposure to high intensity light, these mice presented massive disorganization and reduced thickness of the photoreceptor outer/inner segment and ONL, together with pyknotic photoreceptor nuclei and nucleic acid deposition, a phenotype that was less pronounced in Park2$^{+/+}$ animals (Chen et al., 2013). Rapamycin administration in light-damaged mice has also been shown to increase rod survival by reducing caspase-mediated cell death (Kunchithapautham et al., 2011).

Finally, retinal dystrophies also include retinal detachment, which is characterized by the separation of the neuroretina from the underlying RPE. Retinal detachment can be secondary to other pathologies such as AMD or DR (Chinskey et al., 2014). Separation of the retina from the RPE causes a decrease in nutrient and oxygen supply to photoreceptors, increasing oxidative stress and resulting in cell death (Murakami et al., 2013). One study found that autophagy triggered by HIF-1α activation had beneficial effects in a mouse model of retinal detachment (Shelby et al., 2015). Supporting these findings, it has been shown that under normoxic conditions HIF-1α subunits are rapidly degraded by the ubiquitin–proteasome pathway following hydroxylation of proline residues by HIF prolyl-4-hydroxylases (PHDs) (Trollmann et al., 2014). When oxygen is not available (hypoxia) PHDs are less active, and HIF-1α is stabilized and translocated to the nucleus, inducing BNIP3/NIX transcription and promoting mitophagy (Mazure and Pouyssegur, 2010). Furthermore, in mouse models of retinal detachment treatment with inhibitors of PHDs resulted in HIF-1α stabilization and induction of mitophagy. Together these factors contributed to neuroprotection of photoreceptors following retinal detachment (Liu et al., 2016a). In a similar fashion to RP, mitophagy also plays a neuroprotective role in LD-associated PR degeneration and retinal detachment.

The aforementioned findings suggest that homeostatic autophagy is necessary to maintain proper photoreceptor function and sustain vision (Table 5). Specifically, mitophagy has been shown to play a fundamental physiological role in maintaining visual function, and may also constitute a therapeutic target for the treatment of retinal diseases.

4.4. Age-related macular degeneration

AMD is the most common ocular pathology in the elderly, and can lead to severe and permanent vision loss. Even though AMD has been associated with specific environmental (smoking, diet) and genetic factors, the main risk factor is age, and population aging is expected to double the incidence of AMD by 2040 (Fritsche et al., 2016; Wong et al., 2014). It is characterized by progressive bilateral degeneration of the macula, the central region of the retina that contains a high density of cone photoreceptors and is responsible for high-resolution, color vision. AMD is progressive and is usually detected in late disease stages, when it can be classified as "dry" or "wet" AMD. Wet AMD is driven by choroidal neovascularization that disrupts the RPE and invades the neuroretina, leading to exudative edema and local inflammation, eventually triggering photoreceptor cell death and vision loss. The wet form is more severe and accounts for approximately 10% of AMD cases, but can be clinically managed using anti-angiogenic immunotherapy (anti-VEGF) such as bevacizumab or aflibercept. Dry AMD is caused by a progressive buildup of extracellular debris (oxidized proteins, apolipoproteins, complement buildup), called drusen, in the subretinal space between the RPE and Bruch's membrane. The true origin of these structures remains to be elucidated. Drusen eventually disrupts the RPE monolayer, inducing RPE loss and cell death of adjacent photoreceptors, leading to geographic atrophy and central vision loss (Wong et al., 2014).

The RPE of AMD patients contains reduced numbers of mitochondria, which exhibit abnormal cristae, and decreased levels of ATP-synthase subunits (Feher et al., 2006; Nordgaard et al., 2008). Primary RPE cells from AMD patients also show reduced mitochondrial respiration and glycolytic function (Ferrington et al., 2017). These findings suggest that the RPE of AMD patients cannot obtain energy from its primary (OxPhos) or alternative (glycolysis) sources, leading to an energetic imbalance that ultimately impacts the adjacent neuroretina (Fisher and Ferrington, 2018). Improving mitochondrial function with drugs such as the antioxidant N-acetyl-L-cysteine or nicotinamide mononucleotide (NMN, which facilitates OxPhos) has shown beneficial effect *in vitro* (Ebeling et al., 2020). AMD has also been correlated with higher levels of mtDNA damage in the RPE (Terluk et al., 2015). Together, these observations point to abnormal mitochondrial morphology, number, and function in the RPE of AMD patients.

Owing to its dynamic nature, the study of autophagy in AMD patient samples is challenging and the most relevant findings have been observed in patient-derived *in vitro* cell culture systems. However, markers of autophagy such as ATG5 and lysosomal LAMP2 have been identified in drusen from donors with dry AMD (Wang et al., 2014). An age-associated increase in autophagosome number in the neuroretina and RPE of healthy donors, but not AMD patients, has also been described (Mitter et al., 2014). Primary RPE cell culture allows for manipulation of nutrient conditions and lysosomal degradation, which is essential to enable a more refined analysis of autophagy. *In vivo,* RPE cells from AMD patients show increased levels of LC3-II and decreased levels of SQSTM1/p62, suggesting induction of autophagy, together with enlarged autophagosomes (Golestaneh et al., 2017; Ye et al., 2016). However, use of protease inhibitors, revealed reduced autophagic flux in

Table 5
Evidence of mitophagy alterations in photoreceptor degeneration.

Photoreceptor degeneration					
Model	Approach	Cell types affected	Findings	Role of mitophagy	Reference
Prpf8^{R2310K}	*in vitro*	PR	Impaired hypoxia-induced mitophagy, aberrant mitophagosome formation	–	Xu et al. (2018)
LD, *Park2*$^{-/-}$	*in vivo*	PR, RPE	Mitochondrial damage and accumulation of mitophagosomes, increased susceptibility to LD in *Park2*$^{-/-}$ mice	Beneficial	Chen et al. (2013)
RD, subretinal injection	*in vivo*	PR	Increased BNIP3-mediated mitophagy, further boosting with PHIs alleviated ROS levels, mitochondrial damage and PR cell death	Beneficial	Liu et al. (2016b)

primary RPE cells, an effect that was further exacerbated upon nutrient starvation, pointing to inefficient autophagy (Golestaneh et al., 2017). In the same study, the authors observed swollen lysosomes in AMD donor cells, suggesting lysosomal stress and defective autophagic cargo degradation, and the accumulation of cytoplasmic glycogen and lipid granules (Golestaneh et al., 2017). Finally, stimulation of autophagy in AMD donor cells using rapamycin has been shown to improve mitochondrial function (Ebeling et al., 2020). Regarding mitophagy, decreased levels of PINK1 have been described in the perifoveal region of early-stage AMD patients (Datta et al., 2022). Similarly, alterations in mitochondrial dynamics have been observed in primary RPE cells from AMD donors in response to mitochondrial uncoupling (Fisher et al., 2022). AMD patient-derived cells also presented decreased PINK1 levels and were more reliant on BNIP3/NIX-mediated mitophagy to sustain mitochondrial homeostasis (Fisher et al., 2022). These findings point to induction of autophagy, and possibly mitophagy, in dry AMD pathology that cannot be fulfilled due to deficient lysosomal degradation. While there is very little evidence regarding the involvement of mitophagy in wet AMD, some specific single-nucleotide polymorphisms (SNPs) in autophagy genes have been linked to increased occurrence and efficacy of antiangiogenic VEGF treatment (Paterno et al., 2020).

Although evidence of autophagy dysfunction in AMD patients is scarce, several RPE-specific autophagy-deficient mouse models have been described. Deletion of the autophagy initiator RB1CC1/FIP200 results in intracellular debris accumulation, morphological abnormalities, and secondary loss of visual function (Yao et al., 2015). A similar phenotype has been observed in mice lacking the autophagy regulators Atg5/Atg7 or lysosomal membrane protein LAMP2 (Kim et al., 2013; Notomi et al., 2019; Zhang et al., 2017). A recent report phenotyped the RPE of Pink1-deficient mice and reported decreased mitophagy and deficient mitochondrial function, leading to transcriptional reprogramming and epithelial-mesenchymal transition (EMT) (Datta et al., 2022). Surprisingly, deficit in the antioxidant Nfe2l2/Nrf2 abrogated the EMT phenotype and enhanced susceptibility to cell death, indicating putative crosstalk between mitophagy and the oxidative stress response (Datta et al., 2022).

We recently performed an exhaustive analysis of the neuroretina and RPE of the *Ambra1*$^{+/gt}$ mouse (Fimia et al., 2007), which is characterized by organism-wide autophagy deficiency and a slight reduction in autophagic flux, but is both viable and fertile (Ramírez-Pardo et al., 2022). Defects in the RPE were already observed in young animals, which presented morphological alterations and disrupted proteostasis, concomitant with a decreased number of autophagosomes and signs of lysosomal damage. Decreased mitochondrial number and increased levels of glycolysis-related enzymes, such as the glucose transporter GLUT1 or GAPDH, suggest dysregulation of RPE metabolism. Aged *Ambra1*$^{+/gt}$ mice showed exacerbated accumulation of lipofuscin, as revealed by λ-scan confocal technology (Ramírez-Pardo et al., 2022). We postulate that these initial RPE alterations lead to the neuroretina alterations observed in middle-aged *Ambra1*$^{+/gt}$ mice, which are phenotypically characterized by mitochondrial dysfunction that leads to metabolic alterations. Combined with increased neuroinflammation and an impaired antioxidant response, this microenvironment ultimately leads to exacerbated age-related vision loss.

We also assessed the response of *Ambra1*$^{+/gt}$ mice to SI, a pharmacological model of dry AMD-associated geographic atrophy, and found that both the RPE and photoreceptors of autophagy-deficient mice were more sensitive to SI. INL thickness in SI-treated *Ambra1*$^{+/gt}$ mice was also decreased, while no alterations were observed in untreated *Ambra1*$^{+/+gt}$ littermates, indicating increased susceptibility to oxidative stress even in cell types not traditionally affected in this model or in dry AMD (Ramírez-Pardo et al., 2022). Study of AMD in rodent models is suboptimal, as they lack a true macula, which is only found in non-human primates. However, the central, innermost part of the rodent retina does share some features with the human macula (Volland et al., 2015). We also performed a transcriptomic analysis of samples from AMD patients (GSE135092) and found that, among all autophagy regulators studied, AMBRA1 was the only one for which downregulated gene expression was observed both in the RPE and the neuroretina of the macular region of AMD patients (Ramírez-Pardo et al., 2022).

In conclusion, defective mitophagy may play a key role in the pathophysiology of AMD, and boosting this process could constitute a valid therapeutic strategy (Table 6). While autophagy and mitophagy defects have been associated with phenotypes that resemble that of dry AMD, evidence supporting a role of mitophagy in neovascular AMD and other maculopathies –such as juvenile macular dystrophy or Stargardt disease– is scarce and should be further studied. Mitochondrial dysfunction could be used as a novel biomarker to detect earlier disease stages, and approaches that promote the maintenance of a healthy mitochondrial population could slow disease progression, or even prevent vision loss.

5. Concluding remarks and future directions

Mitophagy research is a novel and cutting-edge field that is attracting growing interest from the scientific community: indeed, most of the findings summarized in this review were published in the last decade. Proper mitochondrial function and integrity is essential to preserve cell homeostasis and ensure cell survival. Mitophagy plays an essential part of this process by removing damaged or superfluous mitochondria. While mitophagy appears to be dysregulated in most retinal diseases, studies using newly-developed methodologies will be required to confirm this association.

Therapies aimed at boosting mitophagy and restoring mitochondrial homeostasis are already being developed and have shown promise in clinical trials (Andreux et al., 2019; Singh et al., 2022). Mitochondrial peptide SS-31 improves mitochondrial function and has been shown to ameliorate age-associated photopic vision loss in mice (Alam et al., 2022) and is currently being tested in a clinical trial for dry AMD, with preliminary positive results (Allingham et al., 2022). Whether the neuroprotective effect of SS-31 involves mitophagy remains unknown. The natural mitophagy inducer Urolithin A (UA) has also been proven safe and is able to induce mitophagy and improve mitochondrial quality control in patients and animal models (Andreux et al., 2019; Singh et al., 2022; Ryu et al., 2016). Furthermore, it has shown neuroprotective potential in Alzheimer's and Parkinson's disease models (Fang et al., 2019; Qiu et al., 2022) which grants exploring its putative beneficial effects in age-associated retinal pathologies. Exploiting this approach to tackle age-associated and pathological vision loss is a crucial research avenue that warrants thorough investigation.

CRediT authorship statement

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Table 6
Evidence of mitophagy alterations in age-related macular degeneration.

Age-related macular degeneration					
Model	Approach	Cell types affected	Findings	Role of mitophagy	Reference
Human samples	*in vivo*	RPE	Decreased levels of PINK1 in the perifoveal region of AMD patients	–	Datta et al. (2022)
Human samples, *Ambra1*$^{+/gt}$	*in vivo*	RPE, retina	Altered *AMBRA1* levels in the macula of human dornors, abnormal mitochondrial homeostasis and metabolism, increased susceptibility to GA model in *Ambra1*$^{+/gt}$ mice	–	Ramírez-Pardo et al. (2022)

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Declaration of competing interest

The authors declare no competing interests.

Data availability

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