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New insights into the role of autophagy in retinal and eye diseases

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ABSTRACT

Autophagy is a fundamental homeostatic pathway that mediates the degradation and recycling of intracellular components. It serves as a key quality control mechanism, especially in non-dividing cells such as neurons. Proteins, lipids, and even whole organelles are engulfed in autophagosomes and delivered to the lysosome for elimination. The retina is a light-sensitive tissue located in the back of the eye that detects and processes visual images. Vision is a highly demanding process, making the eye one of the most metabolically active tissues in the body and photoreceptors display glycolytic metabolism, even in the presence of oxygen. The retina and eye are also exposed to other stressors that can impair their function, including genetic mutations and age-associated changes. Autophagy, among other pathways, is therefore a key process for the preservation of retinal homeostasis. Here, we review the roles of both canonical and non-canonical autophagy in normal retinal function. We discuss the most recent studies investigating the participation of autophagy in eye diseases such as age-related macular degeneration, glaucoma, and diabetic retinopathy and its role protecting photoreceptors in several forms of retinal degeneration. Finally, we consider the therapeutic potential of strategies that target autophagy pathways to treat prevalent retinal and eye diseases.

1. Introduction

The word autophagy, derived from the Greek term "self-eating", refers to the catabolic processes by which the cell degrades and recycles cellular components inside lysosomes (Galluzzi et al., 2017). There are three main types of autophagy, which differ according to how material destined for degradation is delivered to the lysosome (Fig. 1). In macroautophagy, the cytoplasmic material is enveloped in a double-membrane structure that seals to form an organelle called the autophagosome. The autophagosome subsequently fuses with the lysosome, where the cargo is degraded through the action of lysosomal hydrolases (Fig. 1A). Chaperone-mediated autophagy (Fig. 1B), a pathway described only in mammalian cells, selectively degrades proteins expressing a specific amino acid sequence that is recognized by the Hsc70 chaperone protein (Kaushik and Cuervo, 2018). In the third form of autophagy, known as microautophagy, the material to be degraded reaches the lysosome through invagination of the lysosomal or endosomal membrane (Schuck, 2020). Microautophagy is less well known, and the molecular regulators of this process are only beginning to be described (Fig. 1C). In this review we will focus specifically on macroautophagy, referred to hereafter simply as "autophagy".

Autophagy is primarily a cellular response to stress, and is classically induced by a lack of nutrients, in particular amino acids. This process is tightly regulated through signaling via the mTOR and AMPK pathways, the two main signaling routes responsible for monitoring the cell's nutritional status (Wong et al., 2013). Autophagy can also be induced by other forms of stress, including endoplasmic reticulum (ER) stress, oxidative stress, hypoxia, and infections (Fig. 2). Although autophagy is mainly regulated at the post-translational level, stress can also increase the expression of autophagy genes (Feng et al., 2015). One of the main regulators of these genes is transcription factor EB (TFEB). In resting conditions, TFEB is retained in the cytoplasm, but once phosphorylated it translocates to the nucleus where it activates the transcription of lysosomal genes and autophagy-related genes (ATG) genes involved in the regulation of autophagy, including many lysosomal proteins (Puertollano et al., 2018). To date, more than 42 genes have been implicated in the autophagy pathway and the list continues to grow (Mizushima, 2020).

While autophagosome formation is a key step, regulation of autophagy is dependent on several other steps (Fig. 2). In the induction

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phase, ATG1/ULK1 kinase forms a complex with ATG13, ATG101, and FIP200 (also known as RB1CC1) in response to mTOR inhibition or activation of AMPK signaling. Next, the kinase activity of ULK1 triggers the formation of the phosphatidylinositol 3-kinase (PI3K) complex, which is comprised of VPS34, BECLIN1, VPS15, and VPS14 and favors the formation of phosphatidylinositol 3-phosphate (PI3P) at phagophore initiation sites (Mizushima, 2020). Next, two ATG7-catalyzed ubiquitin-type conjugation systems are activated for autophagosome formation. The first mediates the conjugation of ATG12, ATG5, and ATG16L, while the second promotes the conjugation of phosphatidylethanolamine (PE) to LC3 (light chain 3 protein) to form the autophagosome-bound form of LC3 (the mammalian ortholog of ATG8), also called LC3-II. The continuous assembly of these protein-protein and protein-lipid complexes and the delivery of lipids to the autophagosome through ATG9, the only multimembrane-spanning protein in the pathway, allows elongation of the autophagosome membrane (Mizushima, 2020). The final stages of autophagy are controlled by molecules that regulate maturation of the autophagosome, its fusion with endosomes and lysosomes, and the degradation and recycling of metabolites within the lysosome (Yim and Mizushima, 2020).

While autophagy was initially considered a non-selective process, recent findings indicate that it is in fact highly selective. Selective autophagy refers to the process whereby certain types of cargo (e.g. organelles, misfolded proteins, intracellular pathogens) are specifically recognized and degraded (Johansen and Lamark, 2020). This process is triggered by recognition of the cargo through the binding of receptors or adapters containing LC3-interacting regions (LIRs) (Johansen and Lamark, 2020). Selective autophagy can be classified into several types depending on the nature of the specific cargo. These include xenophagy (degradation of pathogens), lipophagy (degradation of lipid droplets), and aggrephagy (degradation of protein aggregates) (Johansen and Lamark, 2020). Similarly, organelle-specific macroautophagy can be classified into ER-phagy (autophagy of the ER), peroxyphagy (autophagic degradation of peroxisomes), mitophagy (autophagic degradation of mitochondria), and lysophagy (autophagic degradation of lysosomes) (Johansen and Lamark, 2020). A recent study demonstrated that the Golgi apparatus can also be targeted for selective autophagic degradation (Nthiga et al., 2021). Alterations in selective autophagy can have important pathological implications. For example, the deficient removal of pathogenic protein aggregates has been linked to neurodegenerative and other diseases (Conway et al., 2020).

In this review we focus on the role of autophagy in the retina and the pathological consequences of alterations in autophagy. We first describe the main roles of autophagy in physiological conditions, focusing in particular on the retinal tissue and available tools used to measure autophagy. Next, we discuss the role of autophagy in the main diseases of the eye and retina, including age-related macular degeneration (AMD), glaucoma and diabetic retinopathy. We also address the putative role of autophagy in promoting photoreceptor survival and discuss alterations in autophagy described in photoreceptor degeneration. The findings reviewed here underscore the important role of autophagy in maintaining proper retinal function and highlight novel therapeutic approaches for the treatment of blindness and other diseases of the eye.

2. The adult retina

The retina is a light-sensitive tissue in the vertebrate eye that detects and processes visual images. It senses light and creates impulses that are transmitted to the brain via the optic nerve. Structurally, the retina consists of multiple cell types arranged in layers (Fig. 3): specifically, three layers of neuronal cell bodies and two layers of synapses. Light-sensitive photoreceptors (rods and cones) comprise the outer nuclear layer (ONL) (Fig. 1). In the outer plexiform layer (OPL), these cells form connections with amacrine, horizontal, and bipolar cells, the nuclei of which lie in the inner nuclear layer (INL). In the inner plexiform layer (IPL) amacrine and bipolar cells synapse with the retinal ganglion cells (RGCs). These cells are the only projecting neurons of the retina, and their axons form the optic nerve (Fig. 3). Other important cells of the retina are the retinal glia or Müller cells, which span the entire retina; astrocytes, which lie around the ganglion cell layer (GCL); and the retinal pigment epithelium (RPE) cells, which lie immediately outside the neuroretina, in close contact with the photoreceptors. RPE cells provide trophic support to photoreceptors and mediate the recycling of photoreceptor outer segments (POS) (Centanin and Wittbrodt, 2014).

The retina has several unique features that make it an ideal window into the central nervous system (CNS), enabling the study of a range of neuronal processes, from development to neurodegeneration (Corrochano et al., 2008; Mellén et al., 2009; Valenciano et al., 2008). Crucially, its location outside of the brain makes it the most accessible part of the CNS. In addition, the retina can be cultivated *ex vivo* under semi-physiological conditions in which cell-to-cell and cell-to-matrix communication are maintained (Valenciano et al., 2008). Only recently has research focused on the role of autophagy in the visual system. The eye, and in particular the retina, is exposed to a variety of environmental insults and stressors, including gene mutations and age-related changes, that lead to functional impairment (Boya et al., 2016). The development of new therapeutic strategies for retinal diseases requires a better understanding of the role of autophagy in retinal homeostasis.

3. Autophagy in the retina

3.1. Autophagy as a quality control mechanism

Autophagy mediates the degradation of cellular components, which are recycled to produce nutrients and building blocks to generate

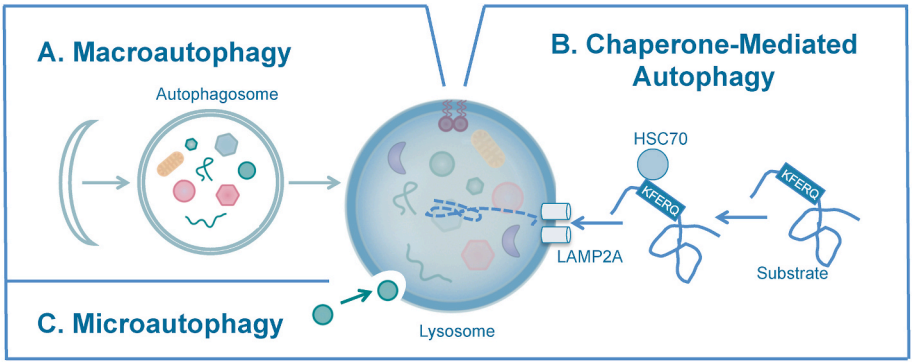

Fig. 1. Main autophagy pathways described in mammalian cells, classified according to the mode of cargo delivery to the lysosome. A, Macroautophagy facilitates the recycling of intracellular components, including organelles, through the formation of an autophagosome. B, Chaperone-mediated autophagy enables the degradation of proteins carrying a specific sequence (KFERQ motif) that is recognized by chaperones such as Hsc70. Recognition of the chaperone by LAMP2A, the CMA receptor in the lysosomal membrane, facilitates the unfolding and translocation of the protein inside the lysosomal lumen. C, During microautophagy, proteins are translocated directly through invagination of the lysosomal membrane. Once inside the lysosome acidic hydrolases degrade the intracellular components and recycle the degradation products, which will be exported from the lysosome.

cellular structures that maintain cellular homeostasis. Furthermore, autophagy plays an important role in the control of cell quality, particularly in neurons, in which the accumulation of components such as altered proteins or damaged organelles cannot be offset by redistribution to daughter cells through cell division. Besides autophagy, other proteolytic pathways such as the ubiquitin proteasome system are also key to preserve intracellular quality control (Giandomenico et al., 2021). Crosstalk between these pathways also serves to preserve the intracellular proteome and deficits in one pathway often result in the activation of other system; for example autophagy deficiency can be compensated by the ubiquitin proteasome and viceversa (Ryhanen et al., 2009). Also, crosstalk between autophagy and other lysosomal pathways such as cathepsins and calpains are also relevant as quality control pathways (Metwally et al., 2021).

The key role of basal autophagy in neurons was demonstrated more than 15 years ago in mouse experiments in which *Atg5* and *Atg7* were selectively deleted in neuronal precursors. While deletion did not result in the perinatal lethality observed in mice with whole-body knockout of *Atg5* and *Atg7*, death occurred before 3 months of age due to neurodegeneration (Hara et al., 2006; Komatsu et al., 2006) and the mice displayed degenerative changes in various brain regions, including loss of Purkinje cells, apoptosis of cerebellar granular cells, and axonal swelling. Accumulation of inclusion bodies and ubiquitin-positive protein aggregates was also observed in many brain regions (Hara et al., 2006; Komatsu et al., 2006). Furthermore, these mice displayed significant retinal alterations, including increased levels of the autophagy substrate p62, ubiquitin accumulation in all retinal layers, and photoreceptor cell death (Rodriguez-Muela et al., 2013). Crucially, these changes resulted in marked vision alterations as early as 5 weeks. These observations suggest that basal autophagy in neuronal precursors is critical to maintain normal retinal physiology and that decreased Atg5 levels result in photoreceptor neurodegeneration (Rodriguez-Muela et al., 2013).

Aging is linked to a general decline in the activity of proteolytic pathways (Kroemer, 2015), including macroautophagy, chaperone-mediated autophagy, and the ubiquitin-proteasome system (Martinez-Lopez et al., 2015). The exact reasons for this age-associated decrease in autophagic activity are not completely understood, although it has been proposed that it is a consequence of defective lysosomal function (Gomez-Sintes et al., 2016). Moreover, decreases in retinal mRNA expression of several autophagy regulators correlating with decreased autophagic flux have been described in 2-year old wild type mice, together with lipofuscin accumulation, morphological alterations in RPE cells and photoreceptor cell death (Rodriguez-Muela et al., 2013). These findings indicate that maintenance of autophagy activity in the eye is crucial to preserve the cellular proteome, and that decreases in autophagy caused by normal physiological aging or by the deletion of autophagy genes have very similar consequences for retinal function. The quality-control function of autophagy is also evident in the lens, in which insoluble, polyubiquitinated p62 and oxidized proteins accumulate in mice that are deficient in Atg5 or Vps34 (Morishita et al., 2013).

3.2. Autophagy and retinal metabolism

Maintenance of the neuronal excitation required for neurotransmission, phototransduction, and normal cellular function means that the retina has very high energy demands (Ames and Li, 1992). The retina produces energy through glycolysis, even in the presence of oxygen. This process was first described by Warburg and later confirmed by others (Ng et al., 2015; Warburg, 1956). One possible explanation for the so-called Warburg effect in the adult retina, despite its non-proliferative status, is that the retina has biosynthetic requirements similar to those of neoplastic tissues due to the recycling of visual pigments in POS membranes (Casson et al., 2013). Cellular compartmentalization provides an alternative explanation for the high level of glycolytic activity in photoreceptors: mitochondria are located in the inner segments, but are absent from the outer segments, potentially leading to dependence on glycolysis in the latter region (Ng et al., 2015). In addition, recent evidences show that a small fraction of pyruvate is also oxidized in photoreceptor mitochondria and is required for visual function, photoreceptor structure and viability (Grenell et al., 2019). Exactly how photoreceptors balance aerobic glycolysis and mitochondrial OXPHOS to regulate their survival is still unclear. However, new studies knocking down HK2 in rods in mice show that inhibition of glycolysis led to photoreceptor degeneration. On the one hand, metabolic reprogramming from glycolysis to mitochondrial OXPHOS may partially reduce the metabolic stress caused by deletion of HK2, on the other hand, excessive mitochondrial OXPHOS promotes the generation of reactive oxygen species (ROS), which can finally lead to mitochondrial dysfunction and photoreceptor degeneration (Zhang et al., 2020b).

As demonstrated in other tissues, autophagy facilitates the supply of metabolites that fuel anabolic reactions and sustain ATP levels, thus preserving cellular functions. In the developing chick retina, pharmacological inhibition of autophagy reduces ATP levels and alters apoptotic cell clearance (Boya et al., 2008; Mellén et al., 2008, 2009). Supporting this important metabolic role of autophagy, supplying retinas with methyl pyruvate (a permeable analogue of pyruvate) completely reverses these engulfment defects (Mellén et al., 2008). Interestingly, methyl pyruvate also reverses the neurogenesis defects observed in neuronal stem cells derived from autophagy-deficient animals (Vazquez et al., 2012). Atg5-deficient retinas also display alterations during embryonic development that include axonal defects and reduced numbers of differentiated RGCs, a phenotype also found in mitophagy-deficient animals (Esteban-Martinez et al., 2017a). The selective elimination of mitochondria via autophagy is crucial to support the metabolic shift towards glycolysis that is necessary for proper retinal neurogenesis (Esteban-Martinez et al., 2017a). These data demonstrate that autophagy helps sustain a variety of metabolic functions during

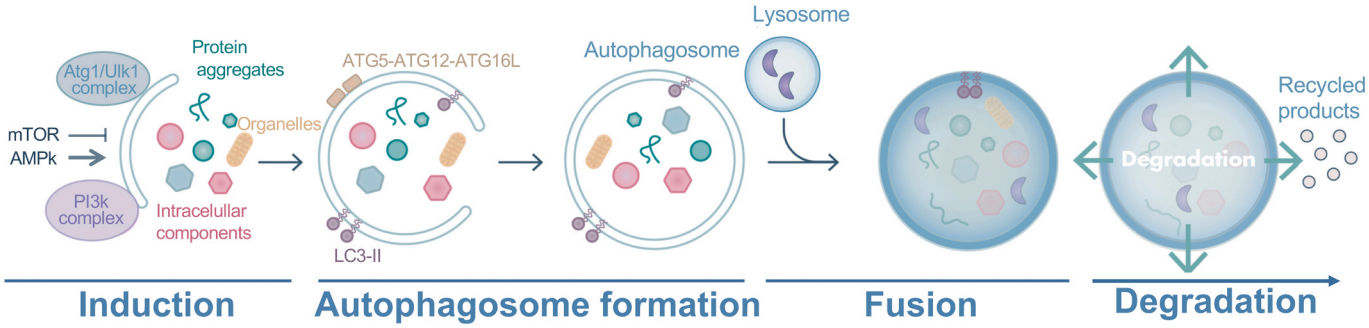

Fig. 2. Macroautophagy. The ULK1/PI3K complex participates in the induction of autophagy, at which point the autophagosome membrane is formed. This membrane becomes elongated and envelops specific cargo, subsequently closing to form the autophagosome. The next step involves fusion of the autophagosome with the lysosome, in which the cargo is degraded by lysosomal hydrolases. Finally, the resulting products are recycled to sustain cellular functions.

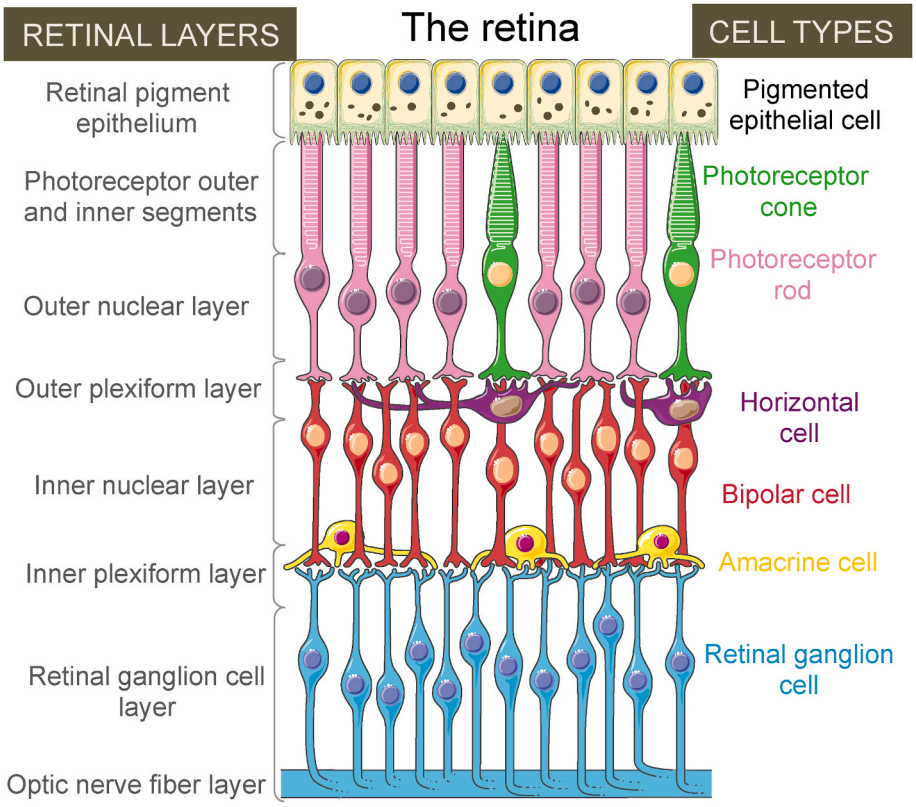

Fig. 3. The vertebrate retina. The retina is a tissue consisting of several layers of cells. The retinal pigment epithelium is a single layer of cells that is in close contact with the outer segments of the photoreceptor cells, which are classified as cones and rods. The soma of rods and cones form the outer nuclear layer. Photoreceptors form synapses with the bipolar and horizontal cells that make up the outer plexiform layer. The cell bodies of bipolar, horizontal, and amacrine cells form the inner nuclear layer. Synapses between retinal ganglion cells (RGCs) and bipolar and amacrine cells form the inner plexiform layer. The axons of RGCs form the optic nerve, which connects the retina to the brain.

neuronal differentiation. Further studies are needed to better understand the interaction between metabolism and autophagy during later stages of neuronal differentiation as well as during normal retinal function. In the adult retina, Zhou et al. demonstrated that starvation induced AMPK phosphorylation in cone cells. Specific *Atg5* deletion in cones results in impaired cone function as measured by electroretinogram at 10 months of age (Zhou et al., 2015b). Cones from 7-week-old $Atg5^{\Delta Cone}$ mice showed increased accumulation of mitochondria and p62 in photoreceptor inner segments as compared with control animals. Furthermore, cone-specific elimination of *Atg5* resulted in increased susceptibility to light-induced damage (Zhou et al., 2015b). *Atg5* deletion in cones thus renders these cells sensitive to both age- and light-induced degeneration.

Aerobic glycolysis is thought to be the most important mechanism to fulfil the metabolic demands of photoreceptors, whereas OXPHOS appears to be the main energy source for RGC dendrites in the vascularized retina. Metabolically, RGCs can be divided into 3 components: the soma, dendrites, and axon. Mitochondrial trafficking in the axon suggests that OXPHOS is the main energy source, although glycolysis may play an additional role, especially in thinner axons (Casson et al., 2021). The importance of OXPHOS for the metabolic status of RGCs was recently demonstrated in various glaucoma models treated with nicotinamide (Casson et al., 2021; Tribble et al., 2021). Mitochondrial quality control, and hence mitophagy, thus play an important role in RGCs. Further supporting this view, deletion of UCP2 (uncoupling protein 2) in RGCs exerts a neuroprotective effect, which is driven by increases in mitochondrial quality control and mitophagy (Hass and Barnstable, 2019). Whether this is also linked to a metabolic role after mitochondria degradation or not remains to be elucidated. The induction of autophagy and mitophagy thus appears to play an important role in retinal cells. However, given the complex structure of the retina and the cells within the retina, more detailed analyses of the links between autophagy and the metabolic status of retinal cells will need to be performed.

3.3. *LC3-associated phagocytosis and visual function*

Vision begins with the absorption of light by light-sensitive photoreceptors in the retina. This induces conformational changes in chromophores present in these cells, triggering the phototransduction cascade. To sustain vision, the chromophore 11-*cis*-retinal must be recycled back into its original conformation via a process known as the visual cycle. This involves tight regulation of the interaction between photoreceptors and the RPE, where POS, which are damaged by the impact of millions of photons per day, are degraded and visual pigment recycled each morning. Deletion of Atg5 in the cells of the RPE has revealed the importance of a non-canonical autophagy pathway for visual pigment and POS recycling (Boya and Codogno, 2013; Kim et al., 2013). In this pathway, known as LC3-associated phagocytosis (LAP), LC3 and Atg5 promote the degradation of extracellular cargo such as apoptotic cells, bacteria and, in the case of the RPE, POS (Heckmann and Green, 2019). LAP in the RPE is not autophagy in *sensu stricto*, as the material to be degraded is not derived from the cell itself. This material enters the cell via a phagosome, and the conjugation machinery adds LC3 to the phagosome membrane, generating what is known as a LAPosome. LAP thus occurs without the formation of a double-membrane and independently of the initiation complex, as evidenced by the recruitment of LC3 to the phagosome membrane in the absence of FIP200, ATG13, and ULK1 proteins. Essential LAP regulators include Rubicon (which is not essential for autophagy) and NOX2, which are required during LAP for localization of PI3P at the phagosomal membrane and the production of reactive oxygen species (ROS), respectively (Martinez et al., 2015). Other studies have shown that RUBCN expression peaks in the morning during maximal POS degradation (Muniz-Feliciano et al., 2017). Thus the pathway for delivery of apoptotic cells and pathogens to the lysosome (Mehta et al., 2014) also plays a central role in recycling POS and sustaining the visual cycle in the RPE (Kim et al., 2013).

3.4. Circadian rhythm and autophagy

In 1977 Remé et al. first reported a 24-h cyclic increase in the number of autophagosomes in rat rod photoreceptors immediately after light exposure (Remé et al., 1985; Remé and Sulser, 1977; Reme et al., 1999). More recent data indicate that autophagosome levels increase in photoreceptors due to translocation of transducin and arrestin from outer to inner photoreceptor segments, and vice versa, following a bimodal pattern after dark-to-light and light-to-dark transitions. This pattern is abolished when animals are kept in darkness, and mice deficient for transducin ($Gnat1^{-/-}$) and arrestin ($Sag^{-/-}$) do not display light and dark-induced LC3-II peaks, respectively (Yao et al., 2014). *Xenopus laevis* also shows an increase in autophagosome formation in photoreceptors after light exposure, an effect that is lost following CRISPR-mediated deletion of *GNAT1* or *RPE65*, indicating that phototransduction and chromophore availability, respectively, are essential for diurnal induction of autophagy (Wen et al., 2019). Streptozotocin-treated T1D mice and BBZDR/wor T2D rats, both of which are models of diabetic retinopathy, show dysregulated diurnal regulation of autophagy in the neuroretina and retinal vessels, an effect that is exacerbated in older animals (Qi et al., 2020).

In the RPE, engulfment and recycling of visual pigments can occur via non-canonical LAP (Kim et al., 2013). However, this process simultaneously triggers the formation of double membrane vesicles, corresponding to canonical autophagy, following the same bimodal pattern (dark-to-light and light-dark) as photoreceptors (Yao et al., 2014). Importantly, in contrast to what happens in photoreceptors, the increase of LC3-II levels during "dark hours" is independent of light exposure, suggesting concomitant circadian regulation of autophagy (Yao et al., 2014). All in all, autophagy appears to play an important role in regulating the levels of phototransduction proteins in photoreceptors and supporting visual function. In line with this view, transducin accumulation is described in $Atg5^{\Delta Rod}$ mice (Zhou et al., 2015a). These data also underscore the essential role of canonical autophagy in POS component post-processing and maintenance of overall photoreceptor and RPE homeostasis throughout the 24-h cycle, which appears to be altered in neurodegenerative diseases of the retina such as diabetic retinopathy (Qi et al., 2020).

4. Methods to monitor autophagy in the retina

Autophagosome formation is the key regulatory step of autophagy, and can be directly assessed by monitoring levels of the autophagosomal binding protein MAP-LC3 (microtubule-associated protein LC3) (Klionsky et al., 2021). Autophagosome formation involves ATG7-mediated lipidation of ATG8 proteins (LC3 in mammalian cells) by covalent attachment of phosphatidyl ethanolamine to the autophagosomal membrane. This lipidation process can be detected by Western blot because lipidated LC3 (LC3-II) migrates faster through the gel than non-conjugated LC3, and is visualized as a lower molecular-weight band, allowing differentiation of free from autophagosome-bound forms of LC3 (Kabeya et al., 2000).

While LC3 levels provide an indication of autophagosome number at a given time point, they do not constitute a direct read-out of autophagy activity *per se*, as autophagosome number can also be increased by lysosomal inhibition (Boya et al., 2005; Gonzalez-Polo et al., 2005). This, together with the fact that autophagy is a highly dynamic process (10 min between autophagosome formation and fusion with the lysosome), means it is essential to determine the rate of autophagosome turnover by assessing autophagic flux. This can be achieved by comparing autophagosome levels (measured by Western blot) in control conditions with those observed after lysosomal inactivation. In addition, it is probably prudent to monitor the turnover of LC3-II together with an autophagosome substrate, due to the fact that LC3 might be coupled to endosomal and other membranes and not just autophagosomes, and the levels of well-characterized autophagosome substrates such as SQSTM1/p62 can also be affected by proteasome inhibitors (Klionsky et al., 2021). This method is well described *in vitro*, and can also be applied to *ex vivo* samples such as retinal explants incubated in the absence or presence of lysosomal inhibitors (Mellén et al., 2008, 2009). Another key advantage of the retina in the context of research is that whole retinas can be cultured in defined media. Controlling the exact amount of metabolites and growth factors in culture conditions allows fine-tuning of metabolic substrates and determination of the consequences for autophagic flux (Esteban-Martinez et al., 2015, 2017b; Gomez-Sintes et al., 2017). More importantly, autophagic flux can be determined *in vivo* in animals, as the blood retinal barrier (BRB) is permeable to protease inhibitors (Esteban-Martinez and Boya, 2015). On the other hand, the study of autophagy flux by flow cytometry using reporter proteins has been described (Shvets et al., 2008). EGFP-LC3 is a substrate for autophagic degradation, total fluorescence intensity of EGFP-LC3 can be used to indicate levels of autophagy in living mammalian cells. When autophagy is induced, the decrease in total cellular fluorescence can be precisely quantified as the GFP is quenched inside the acidic environment of the lysosome. Flux can also be directly associated with an increase of detectable puncta (Klionsky et al., 2021).

The recent generation of autophagy and mitophagy reporter animals has enabled *in vivo* assessment of autophagy and mitophagy in the retina (McWilliams et al., 2019). The use of these animals has revealed differential activation of each of these processes in distinct retinal cell types during development, in adult mice (McWilliams et al., 2019), and after *in vivo* optic nerve crush (Rosignol et al., 2020). An increase in RGC mitophagy after optic nerve damage had been previously hypothesized, but was very difficult to detect and quantify. Cells isolated from reporter mice are also a very good source of primary RGCs (Rosignol et al., 2020). Using primary RGCs isolated from the mito-QC mouse, we demonstrated that induction of mitophagy exerts a neuroprotective effect in RGCs exposed to oxidative stress (Rosignol et al., 2020).

In conclusion, the development of new tools and methods has been pivotal in furthering our knowledge of the basic functions of autophagy in the retina both *in vitro* and *in vivo* (Boya et al., 2016). In the following sections of this review, we will discuss the main findings supporting a role of autophagy dysregulation in the onset and progression of the most common diseases of the retina.

5. Autophagy in glaucoma and optic neuropathies

Glaucoma and optic neuropathies are the two main groups of diseases that lead to vision loss and blindness due to irreversible damage of the optic nerve. The optic nerve is made up by the axons of RGCs, which represent the 3rd retinal neuron involved in transporting light signals to the brain and the innermost cellular retinal layer. Both glaucoma and other optic neuropathies lead to RGCs death, resulting in visual impairment or even blindness. However, although RGCs are the main target for these diseases, other cells, such as retinal glia, likely contribute to the pathogenesis of the diseases as well (Liao et al., 2017). This is also represented in various disease models primarily aiming to mimic different mechanisms of RGC death but also show different aspects of neuroinflammation (Soto and Howell, 2014).

5.1. Autophagy in glaucoma

Glaucoma is characterized by progressive, irreversible, painless loss of RGCs, leading to visual field defects and blindness. Because this condition generally progresses slowly, it tends not to be detected until later stages. Glaucoma is one of the leading causes of blindness worldwide. Although it is difficult to calculate its global prevalence, studies estimate that at least 111.8 million people will be affected by the year 2040 (Tham et al., 2014). The two main risk factors for glaucoma are increased intraocular pressure (IOP) and ageing (Tham et al., 2014). However, the pathophysiology of glaucoma still remains unclear. Genetic studies indicate a link between glaucoma and autophagy-related

genes (Wiggs, 2015). Of the genes that have been linked to glaucoma in genome-wide association studies (GWAS), both *Optn* (Swarup and Sayyad, 2018) and *Tbk1* (Sears et al., 2019) are implicated in autophagy regulation, as well as mitochondrial function (Choquet et al., 2020; Lang et al., 2017; Youngblood et al., 2019). Levels of autophagy in the brain and retina decline with increasing age (Lipinski et al., 2010; Rodriguez-Muela et al., 2013). This is thought to contribute to the pathogenesis of various age-related degenerative diseases, including glaucoma (Boya, 2017; Wong et al., 2019). We recently demonstrated an age-related increase in RGC vulnerability in the context of autophagy deficiency in young (3 months old) and aged (13 months old) *AMBRA1*$^{+/gt}$ heterozygote mice subjected to optic nerve crush (Bell et al., 2020). AMBRA1 (autophagy/beclin-1 regulator 1) participates in the initiation of the autophagy process (Fimia et al., 2007) but also is an important mitophagy receptor that can act in both a PINK1/PARKIN-dependent and -independent manner (Di Rita et al., 2018; Strappazzon et al., 2015; Van Humbeeck et al., 2011). We observed no differences in the rates of RGC death in young wildtype (WT) or *AMBRA1*$^{+/gt}$ mice. However, aged old *AMBRA1*$^{+/gt}$ showed significantly greater RGC loss after ONC than their WT littermates (Bell et al., 2020). This could be explained by a decrease in the oxidative stress response and a failure to increase Bnip3 levels and Bnip3l-mediated autophagy after injury.

Age-related dysregulation of autophagy in the retina, as well as the trabecular meshwork, has also been detected in an elevated IOP model of glaucoma (Nettesheim et al., 2020). Because increased IOP is a key risk factor for glaucoma, the trabecular meshwork, which serves as the main outflow pathway for aqueous humour, is especially important for maintaining normal IOP. Dysregulation of autophagy in the trabecular meshwork occurs during ageing and has also been associated with elevated IOP (Hirt et al., 2018). The importance of autophagy was recently demonstrated in the context of TGF-β-induced trabecular meshwork fibrosis (Nettesheim et al., 2020). While this review focuses on retinal cells, readers may be interested in the comprehensive review by Hirt and Liton on this extensive topic (Hirt and Liton, 2017).

In general, cells induce autophagy as a response to stress in order to ensure cell survival. This is also the case for injured RGCs. Induction of autophagy in the early phases after injury has been demonstrated in different mouse models of glaucoma, including damage induced by axonal injury (Rodriguez-Muela et al., 2012), in response to IOP elevation by occlusion of the episcleral vein, and after retinal ischemia-reperfusion (Park et al., 2012). There is strong evidence suggesting that autophagy induction exerts a neuroprotective effect on damaged RGCs in the context of glaucoma, although other findings contradict this view. Activation of autophagy by pharmacologic or genetic manipulation improves RGC survival in various *in vivo* experimental models of glaucoma. Using an optic nerve transection model, we demonstrated a 40% increase in RGC survival 10 days after axotomy in mice treated with rapamycin (Rodriguez-Muela et al., 2012). Rapamycin, which was first discovered as an antifungal agent produced by Streptomyces hygroscopicus, inhibits mTOR (mechanistic target of rapamycin) and therefore induces autophagy not only in peripheral organs but also in the CNS, including the retina and brain (Dehay et al., 2010; Rodriguez-Muela et al., 2012). By comparison, in Atg4b−/− mice RGC loss after ONT was 28% greater than in WT controls, and specific deletion of Atg5 in RGCs resulted in similar outcomes (33% decrease in RGC survival after ONT) (Rodriguez-Muela et al., 2012). In a rat model of IOP induced by laser, Kitaoka et al. demonstrated neuroprotection of the optic nerve axons following treatment with rapamycin, and an increase in axonal degeneration following treatment with 3-methyladenine (3-MA) (Kitaoka et al., 2013). Another study in which 3-MA was used to inhibit autophagy in a glaucoma model induced by episcleral vein cauterization reported neuroprotective effects (Park et al., 2012), although the studies differed in terms of the timing of 3-MA administration. The neuroprotective effect of autophagy induction with rapamycin was further demonstrated in a mouse ischemia/reperfusion model (Russo et al., 2011). Although there is strong evidence that autophagy induction has neuroprotective effects in the context of glaucoma, more detailed research is required to understand timing and dosing of autophagy modulators.

In conclusion, autophagy plays an important role in glaucoma by regulating both IOP and the response to RGC damage caused in this disease. A better understanding of the role of autophagy within the different RGC compartments and the relevance of age-related changes in autophagy will be necessary to fully realize the potential of autophagy as a therapeutic target in glaucoma.

5.2. Autophagy in optic neuropathies

Optic neuropathies, unlike glaucoma, generally present with acute or subacute symptom onset and focal rather than diffuse damage to the optic nerve or optic nerve head. The main causes of optic neuropathies are demyelinating processes such as multiple sclerosis, ischemic processes, and inflammatory and infectious lesions (Abel et al., 2019; Augstburger et al., 2020; Kale, 2016). Optic neuropathies can be hereditary, such as the mitochondrial disorder Leber's hereditary optic atrophy (LHON) (Yu-Wai-Man et al., 2002) and dominant optic atrophy (DOA) (Lenaers et al., 2012), or caused by toxins (Grzybowski et al., 2015) such as alcohol, tobacco, and ethambutol (which is used to treat tuberculosis). The list of causes continues to grow (Behbehani, 2007). Given the possible contributions of autophagy and mitophagy to optic neuropathies and the therapeutic potential of strategies that modulate autophagy, studies have sought to tease apart the roles of autophagy in LHON and DOA. Interestingly, genetic mutations in mitochondrial proteins have been described in both LHON and DOA, and although these mutations are not limited to RGCs or even the eye, the neuronal damage in most patients with disease-specific mutations is very specifically limited to RGCs (Heiduschka et al., 2010; Kirches, 2011). Mutations of *OPA1* account for the majority of DOA cases, although mutations in *OPA3* and *OPA7* have also been identified (Lenaers et al., 2012). *OPA1* is a well-conserved gene; the translated protein is located in the inner mitochondrial membrane and is essential for mitochondrial fusion and mitochondrial quality control (Gao and Hu, 2021). Splice variants, frame shifts, nonsense mutations, deletions, and duplications have all been detected in patients carrying *OPA1* mutations (Lenaers et al., 2012). Although evidence indicates that DOA mutations increase autophagy and mitophagy, the effect of these mutations on autophagy and, specifically, mitophagy can vary, particularly in cases of mutations that cause haploinsufficiency (Alavi and Fuhrmann, 2013; Kane et al., 2017; Moulis et al., 2017). Analysis of a nonsense *OPA1* mutation in a heterozygous *OPA1* mouse model revealed increased numbers of autophagosomal structures in RGCs on electron microscopy analysis (White et al., 2009). Increased mitophagy, measured by analyzing colocalization of LC3-positive puncta with TOM20-stained mitochondria or by counting the number of LC3-positive puncta in cells co-stained with lysotracker and mitotracker, has been described in fibroblasts from DOA patients with *OPA1* deletion and dominant negative mutations (Kane et al., 2017; Liao et al., 2017). A more detailed analysis of the effects on autophagy and mitophagy of mutations in the GTPase and the coiled-coil domains of *OPA1* revealed mitochondrial depletion in axons of RGCs expressing these mutations and accumulation of mito-autophagosomes in the axonal hillock (Zaninello et al., 2020). The increase in autophagy activation in this part of the cell could be explained by increased AMPK activation caused by *OPA1* mutations. The authors demonstrated that inhibition of autophagy restored axonal mitochondrial content in these cells. Moreover, inhibition of autophagy in the respective *OPA1* mutant mouse models attenuated the loss of vision.

Mutations affecting mitochondrial proteins have also been found in LHON, in all cases leading to amino acid changes in subunits of complex I of the mitochondrial respiratory chain. The most common mutations affect the proteins ND1 (13%), ND4 (69%), and ND6 (14%)

(Yu-Wai-Man et al., 2002). Less is known about alterations in autophagy and mitophagy in LHON. However, *in vitro* findings suggest that mitophagy is decreased in cells harboring mutations (Sharma et al., 2019). Two studies using cybrid cell lines reported decreased autophagy in cells carrying the LHON-specific ND4 and ND1 mutations, leading to an accumulation of dysfunctional mitochondria, and showed that induction of autophagy with rapamycin promoted the clearance of damaged mitochondria (Dai et al., 2014; Sharma et al., 2019). The less common ND5 mutation is also proposed to decrease levels of mitophagy (Zhang et al., 2018). In summary, further studies are needed to fully understand the role of autophagy in both these diseases, and more detailed analysis of the various mutations involved will be necessary to pave the way towards more personalized therapeutic approaches.

Little is known about the role of autophagy in optic neuropathies other than LHON and DOA. One important form of toxic optic neuropathy is that induced by ethambutol, a drug frequently used for the treatment of tuberculosis. In addition to RGC death, this drug can lead to autophagy dysregulation by blocking autophagic flux and neutralizing lysosomal pH, ultimately resulting in RGC apoptosis (Huang et al., 2015; Yamada et al., 2016).

6. Autophagy in diabetic retinopathy

Diabetes is a chronic disease that results in hyperglycemia, which occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Diabetic retinopathy is a complication of diabetes caused by the long-term accumulation of damage to small blood vessels in the retina. DR is an important cause of blindness, accounting for 2.6% of all cases of blindness worldwide (Bourne et al., 2013). Blood vessel damage can result in ischemia and neovascularization, eventually leading to blindness. Chronic hyperglycemia has multiple effects on retinal cells. It can induce ER-stress, mitochondrial and oxidative damage resulting in the death of neurons and pericytes, loss of synapses and dendrites, and alterations in synaptic activity (Oshitari et al., 2011; Ozcan et al., 2006). In addition, hyperglycemia, results in the formation of advanced-glycation end products (AGEs) and induces ocular tissue dysfunction and its contribution to the onset and development of eye disorders (Bejarano and Taylor, 2019). Furthermore, activation of microglia and Müller cells induces the production of vascular endothelial growth factor (VEGF), which promotes neovascularization, contributing to vision loss.

Pericyte loss is considered an initiating event in DR, as pericytes protect the endothelial cells in the retinal capillaries and are also responsible for maintaining integrity of the BRB. One hallmark of diabetes is post-translational modification, including glycosylation and oxidation, of plasma lipoproteins, including low-density lipoproteins (LDLs). Pericyte loss results in increased BRB permeability, favoring the extravasation of LDLs into the retina. Pericytes treated with sub-lethal doses of LDL show an increased autophagy that preserves cell viability. However, at high LDL doses this pro-survival autophagy response is no longer observed, and autophagy inhibition by deletion of the autophagy regulator Beclin-1 rescues pericytes from LDL-induced cell death. This dual effect of ER-stress-induced autophagy has also been described in a rat model of diabetic retinopathy (Fu et al., 2016). How autophagy levels are regulated in pericytes in human DR remains unknown. A recent study reported that retinal ischemia alters blood flow and neurovascular coupling by damaging intercellular communication between pericytes. Pericytes connect to one another and transfer organelles including vesicles and mitochondria via processes that resemble tunneling nanotubes (Alarcon-Martinez et al., 2020). How this intercellular communication impacts pericyte function in DR remains to be determined.

While DR is largely considered a vascular disease, recent evidence indicates that abnormalities in the neural retina and the adjacent RPE contribute to the pathogenesis of DR (Tonade and Kern, 2020) and that autophagy could represent a prosurvival response in those cells. For example, ARPE-19 cells cultured in high concentrations of glucose display upregulation of autophagy, which may constitute a pro-survival mechanism. Autophagy blockade increases oxidative stress and the activity of IL-1β and NLRP3 (a NOD-like receptor responsible for processing pro-IL-1β to produce the active form of IL-1β) (Shi et al., 2015). Recent findings suggest that this pro-survival effect may be mediated by the selective elimination of mitochondria by thioredoxin-interacting protein (TXNIP) via PINK1/PARKIN-mediated mitophagy (Huang et al., 2018; Su et al., 2020). A similar effect is observed in Müller cells, in which TXNIP increases the expression of HMGB1, a nuclear protein that is transported from the nucleus in conditions of oxidative stress and interacts with Beclin-1 to enable autophagy. Activation of autophagy may therefore represent a survival mechanism, degrading mitochondria damaged by ROS (Devi et al., 2012). Further studies will be needed to confirm this hypothesis as other evidence points to a detrimental effect of TXNIP-mediated mitophagy in the RPE in high glucose conditions (Devi et al., 2019). These dual effects of autophagy and mitophagy in DR may be associated with disease progression, as observed in a recent study in hyperglycemic mice (Hombrebueno et al., 2019).

7. Diseases associated to photoreceptor degeneration

Several blindness-associated diseases are caused by the progressive dysfunction and death of retinal photoreceptors. These are highly specialized neurons capable of detecting light stimuli and converting them into electrical impulses. There are two types of photoreceptors: cones, which are responsible for vision at high light intensity (photopic vision); and rods, which support vision at low light intensity (scotopic or night vision) (Lamb et al., 2007).

Phototransduction subjects photoreceptors to constant stress, and the need to continuously regenerate POS imposes a high metabolic demand. Damage caused by light and by oxidation of cell membranes, including those of the POS, can result in photoreceptor death. Photoreceptor damage can also be caused by calcium-activated enzyme signaling, cyclic nucleotide signaling, and cathepsin-mediated lysosomal cell death (Murakami et al., 2013; Rodriguez-Muela et al., 2015; Wang et al., 2018). Moreover, a wide-range of mutations, generally those that affect the phototransduction cascade or cause protein misfolding or mislocalization, can induce photoreceptor death. The role of autophagy in photoreceptor survival remains a topic of debate, and although most studies indicate a neuroprotective effect, some authors have proposed that autophagy inhibition may be beneficial under certain conditions. In this section, we will discuss the opposing roles of autophagy in photoreceptor survival.

7.1. Photoreceptor degeneration in autophagy-deficient animals

In recent years several laboratories have investigated the consequences of deleting autophagy genes in retinal photoreceptors. The first mouse with photoreceptor-specific deficiencies in autophagy, the *Atg7*$^{\Delta Rod}$ mouse, was generated by crossing *Atg7*$^{flox/flox}$ mice with rod-specific LMOP-Cre mice (Chen et al., 2013). These animals displayed no detectable phenotype in normal conditions. However, exposure of *Atg7*$^{\Delta Rod}$ mice to intense illumination resulted in retinal degeneration (Chen et al., 2013). Deletion of *Atg5* in rods by crossing rhodopsin-iCre-75 transgenic mice with *Atg5*$^{flox/flox}$ mice resulted in reduced ONL thickness at 5 months of age and rod photoreceptor degeneration, which was also observed when these mice were raised in darkness (Zhou et al., 2015a). Although there are differences between these two studies, deletion of the essential autophagy genes *Atg5* and *Atg7* in rods results in a clear detrimental phenotype in conditions of light stress.

Decreases in autophagy in cones have been achieved by crossing *Atg5*$^{flox/flox}$ mice with HRGP-Cre transgenic mice, in which Cre recombinase is controlled by a fragment of the promoters of the human red (OPN1LW) and green (OPN1MW2) opsin genes (Zhou et al., 2015b). The

resulting mice show a decrease in cone number at 2 months of age that correlates with reduced cone function on electroretinogram at 10 months of age. Moreover, an increased accumulation of mitochondria is observed in the inner segment of cones of 7-week-old *Atg5*$^{\Delta Cone}$ mice compared with control animals. Interestingly, these accumulations of mitochondria are age-dependent, indicating that autophagy down-regulation results in a phenotype characterized by progressive cone degeneration. Furthermore, cone-specific elimination of *Atg5* results in increased susceptibility to light-induced damage as well as a decrease in cone POS length and enlargement of inner segments, with accumulation of mitochondria (Zhou et al., 2015b). More recent studies have corroborated the importance of autophagic flux in sustaining cone function. For example, Vps34 (also called Class III PI3K) has an important role in cones. Vps34 selectively phosphorylates PI to PI(3)P, but does not phosphorylate other PIPs. The PI(3)P lipid generated by Vps34 plays an important role in endocytic membrane trafficking, canonical autophagy, and cell survival (Stenmark et al., 2002). Specific deletion of Vps34 in cones also results in impaired visual function (Rajala et al., 2020) and photoreceptor degeneration is observed as early as eye opening in mice deficient in Rabgef1, a protein implicated in endolysosomal function (Hargrove-Grimes et al., 2020). Rabgef1-deficient mice also display accumulations of autophagosomes and p62 in photoreceptor inner segments consistent with compromised autophagy (Hargrove-Grimes et al., 2020).

7.2. Autophagy in retinal dystrophies

Retinal dystrophies are a group of diseases that lead to progressive loss of vision due to the death of retinal cells. Photoreceptor death is a feature of most of these diseases (Olivares-González et al., 2021). The most common retinal dystrophy is retinitis pigmentosa (RP), a group of degenerative retinal diseases characterized by rod and cone degeneration (Olivares-González et al., 2021). Clinically, this disease is characterized by pigment accumulation and progressive blindness, and there is currently no cure. RP can be caused by mutations in over 80 different genes that alter photoreceptor homeostasis, ultimately leading to cell death (Olivares-González et al., 2021). RP-associated gene mutations encode enzymes (and their regulators) involved in the phototransduction cascade among others (Athanasiou et al., 2013).

Several genetic mouse models of these diseases have been used to identify the pathological changes associated with photoreceptor degeneration and to search for putative strategies to delay degeneration and preserve visual function. For example, in their 2009 study, Punzo and coworkers performed microarray analyses at peak cone cell death in four different RP models, and demonstrated upregulation of several genes involved in the insulin/mTOR pathway (Punzo et al., 2009). They found that insulin administration attenuated photoreceptor cell death, suggesting that cone starvation contributes to cell death in RP (Punzo et al., 2009). Overactivation of autophagy has also been described in a mice deficient in UXT, a ubiquitously expressed prefoldin-like chaperone that regulates mTOR activity (Pan et al., 2020). These mice display RP-like features including apoptotic photoreceptor degeneration and vision loss.

Recent studies have also demonstrated increased autophagy activation in P23H rhodopsin (RHO) mice. Interestingly, Yao and coworkers found that photoreceptor structure and function was improved in these mice by reducing autophagic flux either pharmacologically or by rod-specific deletion of the autophagy-activating gene *Atg5* (Yao et al., 2018), suggesting that a balance between autophagy and the proteasome pathway is essential to maintain photoreceptor homeostasis. Sizova et al. reported improved visual function in P23H mice 4 weeks after rapamycin treatment (Sizova et al., 2014). However, the beneficial effects of rapamycin treatment appeared to be linked to the activation of the unfolded protein response (UPR) and not to upregulation of autophagy. These data suggest that multiple pathways participate in preserving photoreceptor integrity and that proper functioning of these pathways, including the ubiquitin-proteasome pathway and the UPR, are essential for the elimination of toxic protein aggregates.

The results of a study performed using two different models of retinal degeneration suggest that upregulation of autophagy using trichostatin A (TSA) may delay cone death (Samardzija et al., 2021). In that study, secondary cone cell death was associated with exacerbated histone deacetylate (HDAC) activity. Inhibition of HDAC activity using a single intravitreal injection of trichostatin A (TSA), administered at an age at which most rods have degenerated, delayed cone death in both rd10 and rd1 mice. Transcriptional changes associated with cone survival included regulation of distinct pro-survival mechanisms, including autophagy and both MAPK and PI3K/Akt signaling (Samardzija et al., 2021). HIF-1 signaling and autophagy are also among the neuroprotective pathways proposed to be upregulated by the HDAC6 inhibitor tubastatin A in both atp6v0e1$^{-/-}$ zebrafish and rd10 mice (Sundaramurthi et al., 2020).

Changes in autophagic flux can also occur as a consequence of lysosomal alterations in RP. Rodriguez-Muela et al. found that intracellular calcium accumulation led to calpain activation in rd10 mice before peak rod cell death (Rodriguez-Muela et al., 2015). Moreover, the authors found that calpain and cathepsin inhibitors attenuated photoreceptor cell death in these mice *in vitro*, *ex vivo*, and *in vivo*, suggesting that calpain-mediated lysosomal membrane permeabilization underlies the lysosomal dysfunction and autophagy downregulation associated with photoreceptor cell death in RP (Rodriguez-Muela et al., 2015). Given that lysosome damage is often accompanied by reduced autophagic flux, candidate neuroprotective strategies for these pathologies should include restoration of lysosomal activity. One such example is trehalose-dependent TFEB upregulation, which reverses lysosomal damage and ameliorates vision loss in several models of retinal diseases (Abokyi et al., 2020; Lotfi et al., 2018; Naso et al., 2020; Rodriguez-Muela et al., 2015).

In general terms, proper autophagy can be considered essential to maintain vision. Deficient autophagy affects both the structure and function of rods. While autophagy is essential for recycling visual cycle proteins such as rhodopsin and transducin, overactivation of autophagy can be counterproductive in certain cases, exacerbating photoreceptor degeneration. As we mentioned above, misfolded proteins are typically degraded by one of two mechanisms. The first involves translocation of the misfolded protein out of the ER and shuttling to the proteasome. The second involves the induction of autophagy. In such cases, activation of the proteasome in the retina is triggered by autophagy blockade. This activation is necessary for the elimination of misfolded proteins and it can compensate for the degeneration produced by an overactivation of autophagy (Yao et al., 2018). Autophagy is also necessary to maintain photopic vision. It should be noted that in most models in which rod autophagy is specifically altered, cone neurodegeneration is also observed. Therefore, homeostatic autophagy is necessary to maintain proper photoreceptor function and sustain vision.

7.3. Autophagy in models of light-induced retinal damage and retinal detachment

Prolonged exposure to intense visible light can lead to photoreceptor cell damage. The consequences of light-induced retinal damage vary greatly, depending on the type of light and duration of exposure, as well as the genetic background of the animal model studied (Organisciak and Vaughan, 2010). Data from *Drosophila* studies support the view that autophagy helps protect against light-induced damage by eliminating rhodopsin-arrestin complexes that form during phototransduction (Midorikawa et al., 2010; Wang et al., 2009b). Beclin1 hemizygous mice are more sensitive to light-induced retinal damage and show reduced retinal thickness and alterations in RPE cells (Chen et al., 2013). A similar phenotype has been described in mice with rod-specific deletion of Atg7 (Chen et al., 2013). These findings suggest that autophagy primarily triggers a cytoprotective response in the light-challenged retina

(Chen et al., 2016). However, the results of other studies indicate that the induction of autophagy in response to light-induced retinal damage can also have detrimental effects. Kunchithapautham reported that injection of rapamycin for 10 days in a mouse model of light-induced retinal damage protected against rod cell death, although cone function was diminished (Kunchithapautham et al., 2011), and a recent study found that inhibition of ER stress-induced autophagy protected against light-induced retinal damage in mice (Song et al., 2020). In conclusion, these data demonstrate that the outcomes of autophagy induction in response to light stress can vary significantly, possibly depending on photoreceptor cell type. Further studies are necessary to understand the contributions of other extrinsic and intrinsic factors to photoreceptor survival.

Retinal detachment is an eye disorder in which the retina is separated from the RPE, resulting in photoreceptor cell death and blindness. However, vision restoration can be achieved if the detachment is repaired within 1 week. Research has thus sought to identify therapeutic strategies that prolong photoreceptor survival. One such mechanism is autophagy (Chinskey et al., 2014), where its downregulation decreases photoreceptor survival following retinal detachment (Besirli et al., 2011). Moreover, autophagy appears to be essential to degrade material produced by the retraction of photoreceptors during the process of retinal detachment (Xiao et al., 2021). Rapamycin has been proposed to protect against photoreceptor damage in retinal detachment (Ding et al., 2019): it prevents necroptosis by inhibiting ROS production and apoptosis inducing factor (AIF) release, and promotes photoreceptor cell survival by increasing autophagy (Ding et al., 2019). Retinal detachment-induced hypoxia also activates autophagy in photoreceptors via a HIF-1α-mediated mechanism, and silencing of HIF-1α decreases autophagy and increases cell death (Shelby et al., 2015). Together, these findings point to a clear pro-survival role of autophagy in photoreceptor cells during retinal detachment.

8. Age-related macular degeneration

AMD is a progressive bilateral neurodegenerative retinopathy that affects the macula, the cone-rich central region of the retina responsible for high-resolution color vision. Its complex etiology includes genetics, diet, smoking, and high blood pressure, among other environmental factors, although age is considered the primary risk factor (Mitchell et al., 2018). Variants in proteins involved in lipid metabolism, extracellular matrix remodeling, angiogenesis, and complement activation have also been implicated in AMD (Fritsche et al., 2016; Lim et al., 2012). It is estimated that around 25.3% of people aged over 60 years present early or intermediate AMD, while 2.4% present late AMD, and these numbers are expected to increase in the coming years due to population ageing (Li et al., 2020). Late AMD can be further classified as "dry" or "wet". The wet or exudative form of the disease affects only around 10% of patients and is driven by abnormal choroidal neovascularization into the macular subretinal space and neuroretina, where newly-formed leaky vessels cause macular edema, neurodegeneration and, ultimately, central vision loss. The dry form of the disease is characterized by the build-up of extracellular deposits, called drusen, between the RPE and Bruch's membrane. Drusen are composed of a mixture of apolipoproteins, oxidized proteins, complement components, and trace elements, among other components, and their formation remains poorly understood (Bergen et al., 2019). Dry AMD can eventually progress to geographic atrophy leading to loss of choriocapillaris, RPE cells and, subsequently, photoreceptors (Fleckenstein et al., 2018). Anti-VEGF immunotherapy has shown promising results, either stabilizing or improving visual acuity in wet AMD patients (Mitchell et al., 2018). However, to date there is no curative treatment for either dry AMD or geographic atrophy.

8.1. Importance of autophagy in age-related macular degeneration

The RPE is the first component of the retina affected in AMD. It consists of a monolayer of polarized epithelial cells containing melanin granules. In the apical compartment, microvilli form a meshwork with POS, the distal tips of which are shed, phagocytosed, and recycled daily by the RPE in the aforementioned visual cycle. The basal membrane of the RPE is part of Bruch's membrane, and forms part of the BRB, helping isolate the retina from the choroidal bloodstream. In addition to facilitating chromophore recycling, the RPE also supports glycolysis-driven photoreceptor metabolism by providing glucose and other essential nutrients (Fisher and Ferrington, 2018). Metabolically-demanding POS processing, high levels of production of OXPHOS-derived ATP, constant exposure to photo-oxidative stress, and choroidal blood flow all combine to create an environment of chronic oxidative stress in the RPE (Datta et al., 2017; Fisher and Ferrington, 2018). Furthermore, oxidized visual pigments cannot be fully degraded by lysosomal enzymes and accumulate in the form of the end product bis-retinoid (Sparrow et al., 2012). Within increasing age, the progressive build-up of oxidized bis-retinoid leads to the accumulation of lipofuscin inside lysosomes, altering lysosomal pH and inhibiting the degradation of both endogenous and exogenous material (Bergmann et al., 2004). The RPE is a post-mitotic tissue that generates and accumulates damaged intracellular components throughout its lifetime. Maintenance of RPE homeostasis therefore requires a tightly-regulated intracellular housekeeping system, which includes autophagy (Zhang et al., 2020c).

8.2. Autophagy-related phenotypes in age-related macular degeneration patients

In their study of donor eyes, Wang et al. detected markers of autophagy (ATG5) and exosomes (CD63, CD81, LAMP2) in drusen from the eyes of AMD donors (Wang et al., 2009a). By contrast, they detected only small ATG5-positive foci inside small deposits in the sub-RPE space in the eyes of age-matched healthy donors without previous eye diseases. Mitter and coworkers described an age-associated increase in the number of autophagosomes in the RPE and neuroretina of healthy donors that was not observed in early and late AMD donors, in which decreased ATG7 and ATG9 immunoreactivity was detected (Mitter et al., 2014). Another study reported that levels of LC3-II and p62 were increased and decreased, respectively, in the RPE of AMD patients, suggesting induction of autophagy (Ye et al., 2016). Primary RPE cells from AMD patients also contain enlarged autophagosomes and show impaired autophagy induction upon nutrient starvation, and reduced autophagic flux, evaluated in presence of protease inhibitors (Golestaneh et al., 2017). AMD donor cells contain swollen lysosomes, a sign of lysosomal stress, as well as cytoplasmic glycogen and lipid granules (Golestaneh et al., 2017). Zhang and coworkers reported marked metabolic alterations in AMD patient-derived RPE cultures, including overactivation of mTORC1 (the main inhibitor of canonical autophagy) and decreased glycerophospholipid metabolism (Zhang et al., 2020a). Decreased autophagy-mediated phagocytosis of POS has also been reported in a human cell model of AMD (Inana et al., 2018). Single-nucleotide polymorphisms (SNPs) in core autophagy regulators (mTOR, ATG5, ULK1, MAP1LC3A, SQSTM1) have been identified in patients with wet AMD, in some cases correlating with enhanced or attenuated responses to anti-VEGF treatment (Paterno et al., 2020). Overall, these data point to an induction of autophagy upon AMD onset that cannot be completed due to decreased lysosomal function, leading to an intracellular accumulation cell debris (Golestaneh et al., 2017; Mitter et al., 2014; Ye et al., 2016). The available evidence suggests that autophagy plays an essential role in the development of AMD and that blockade of autophagic flux could be a key contributor to the pathogenesis of AMD.

8.3. Role of autophagy in experimental models of age-related macular degeneration

The etiology of AMD is complex, and is influenced by both genetic and environmental factors. Given that only primates present a macula *per se*, there is no small animal model that fully recapitulates the disease (Soundara Pandi et al., 2021). Because AMD is characterized by primary RPE degeneration, the main *in vitro* model used is the ARPE-19 cell line, derived from the RPE of a 19-year-old male donor. ARPE-19 cells express characteristic RPE markers, including RPE65 and CRALBP, and can eventually form polarized monolayers and become pigmented if cultured in confluence for long periods of time in defined medium (Dunn et al., 1996). 3-MA-induced inhibition of autophagy in ARPE-19 cells leads to increased accumulation of endogenous lipofuscin, while inhibition with bafilomycin A1 leads to the accumulation of the oxidative stress-derived 4-HNE-protein adduct (Mitter et al., 2014; Piippo et al., 2014). Moreover, POS exposure increases autofluorescence in this cell line, an effect exacerbated by autophagy inhibitors (3-MA, leupeptin, chloroquine, NH_4Cl) and attenuated by autophagy induction with rapamycin (Lei et al., 2017; Mitter et al., 2014).

Sodium iodate (SI) is an inorganic salt that selectively induces geographic atrophy-like RPE degeneration, leading to subsequent photoreceptor cell death (Sorsby, 1941). It induces ROS generation, RPE atrophy, and cell death, and is commonly used as a pharmacological model to simulate AMD-like damage both *in vitro* and *in vivo* (Chowers et al., 2017). SI basifies acidic compartments, leads to autofluorescence accumulation, and partially blocks autophagy in ARPE-19 cells *in vitro* (Lin et al., 2018). Furthermore, SI-induced ROS generation is required to trigger autophagy and blocking autophagic flux with 3-MA or Baf-A1 results in decreased cell viability (Chan et al., 2019).

Supporting these findings, mice lacking the antioxidant enzyme SOD2 in the retina display a phenotype similar to that found in humans with AMD: increased autophagy in the early stages of degeneration (1 month) and blockade of autophagic flux at later stages (6 months) (Mitter et al., 2014). Mice lacking the antioxidant master regulator NFE2L2 or the mitochondrial biogenesis inducer PGC-1α also present visual dysfunction associated with primary RPE degeneration. Both KO mice show damaged mitochondria, mitophagy induction, and accumulation of LC3- and p62-positive autophagosomes in the RPE. This phenotype is further exacerbated in NFE2L2/PGC-1α double KO mice, which present higher levels of the aforementioned markers, as well as accumulation of autofluorescent material inside the RPE and extracellular drusenoid deposits (Felszeghy et al., 2019; Sridevi Gurubaran et al., 2020; Zhao et al., 2011). Therefore, a healthy mitochondrial pool and antioxidant response are required to maintain RPE homeostasis, and lack of any or both systems leads to AMD-like degeneration concomitant with dysregulated autophagy in the RPE. Smoking is one of the main environmental factors contributing to the development of AMD, and exposure of WT mice to cigarette smoke leads to increases in the levels of ubiquitinated proteins and p62, as well as LC3-II accumulation; although autophagic flux was not evaluated and there is a concomitant increase on p62 mRNA levels (Wang et al., 2014). This cigarette smoke-mediated induction of autophagy is diminished in NFE2L2-deficient mice (Wang et al., 2014). These data suggest a protective role of autophagy upon induction of AMD-like oxidative cellular stress in animal and cell models of AMD.

8.4. Alterations in the RPE of autophagy-deficient mice

Selective knock-out of genes in the RPE can be achieved using Cre-VMD2 mice, in which the BEST1 promoter is exclusively expressed in the RPE and testis (Le et al., 2008). RPE-specific deletion of the canonical autophagy initiator RB1CC1 (also known as FIP200) results in primary RPE degeneration, morphological abnormalities, accumulation of autofluorescent material, oxidized proteins, and intracellular debris, microglial infiltration, and disruption of Bruch's membrane upon aging, followed by secondary photoreceptor degeneration and vision loss (Yao et al., 2015). TSC1 is a negative upstream regulator of mTORC1 that promotes autophagy, and $Tsc1^{\Delta RPE}$ animals lacking TSC1 in the RPE present features of both wet and dry AMD, including fundus autofluorescence and atrophy of the choroid and RPE, ultimately resulting in progressive retinal degeneration (Go et al., 2020; Huang et al., 2019). Mice lacking the autophagy regulators *Atg5/Atg7* in the RPE also present age-dependent increases in levels of p62-positive aggregates, oxidative stress markers, RPE atrophy, and retinal degeneration (Zhang et al., 2017). These changes have been attributed to alterations in the non-canonical function of *Atg5* in LAP, leading to inadequate recycling of retinoids, accumulation of POS, and RPE atrophy, and can be reversed by supplementing mice with 9-*cis*-RAL to fuel phototransduction and visual function. While retinal morphology and rod/cone numbers remain normal throughout the life, $Atg5^{\Delta RPE}$ mice present reduced visual function upon aging (Kim et al., 2013). However, in another study of $Atg7^{\Delta RPE}$ mice, no retinal degeneration was detected and the authors concluded that autophagy was not involved in A2E (a component of lipofuscin) accumulation or maintenance of the visual cycle (Perusek et al., 2015). It is unclear whether these conflicting findings are due to differences between studies in the protocols used for Cre-mediated *Atg7* deletion or in the readouts used, and further studies will be required to resolve these discrepancies. Furthermore, the involvement of *Atg5* and *Atg7* in both canonical autophagy and LAP also complicates the interpretation of these results, making it difficult to determine which pathway is the main contributor to the resulting phenotype (Heckmann and Green, 2019).

LAMP2-deficient mice also exhibit some features of dry AMD, including increased fundus autofluorescence and atrophy of Bruch's membrane and the RPE, most likely caused by defective POS processing (Notomi et al., 2019). Deficits at any of the multiple stages of the autophagy process thus lead to RPE dysfunction and retinal degeneration, highlighting the importance of this process in maintaining cellular homeostasis. As previously mentioned, AMD patients also present impaired autophagy, lysosomal cargo accumulation, and autophagy-related proteins in drusen (Golestaneh et al., 2017; Mitter et al., 2014; Ye et al., 2016). These evidences suggest autophagy as one of the main drivers of AMD pathology, and should therefore be considered both as a cause and as a putative therapeutic target in the search for new curative treatments.

9. Conclusions and further challenges

The studies reviewed here highlight the significant role of autophagy in sustaining the function of both the neural retina and the RPE, and its involvement in some of the most prevalent diseases of these structures (Fig. 4). Key roles of autophagy proteins in the retina include quality control functions, elimination of toxic aggregates, and facilitation of POS degradation and visual pigment recycling to sustain photoreceptor function. However, overactivation of autophagy in a cell type-dependent manner may have detrimental consequences in the context of light-induced photoreceptor damage. In RGCs autophagy has been implicated in axonal homeostasis and exerts a protective function, possibly by minimizing ROS levels and sustaining mitochondrial function. In certain conditions, blockade of autophagy in a specific subtype of RGCs has been shown to ameliorate the pathogenic phenotype and attenuate vision loss. Finally, in the RPE autophagy is essential to preserve degradative capacity, provide metabolic support, and ensure quality control. Thus, it is clear from the literature that alterations in autophagy and lysosomal pathways are implicated in many if not all diseases of the eye. Moreover, the decline in lysosomal activity associated with age exacerbates alterations in autophagy, potentially aggravating related conditions. Future studies will undoubtedly help further our understanding of the potential of therapeutic strategies that target autophagy and the lysosomal pathway in diseases of the retina and eye. However, many challenges lie ahead.

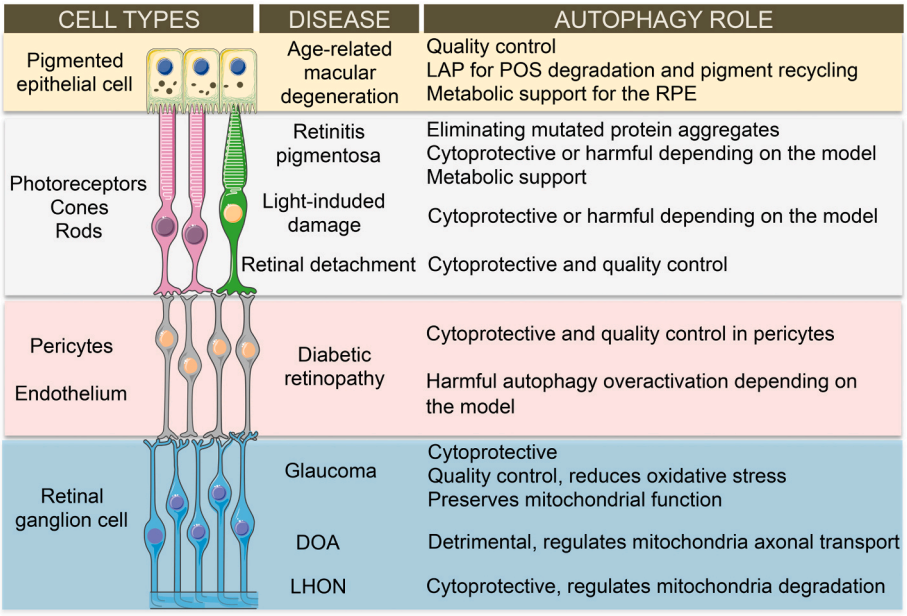

Fig. 4. Main roles of autophagy in retinal cells and in the most prevalent retinal diseases.

According to the WHO blindness is one of the most debilitating disabilities, resulting in significant impairment of social activity and changes in personality. Globally, cataracts account for the majority of cases of blindness in adults aged 50 years and older. However, in 2020 other less tractable and irreversible diseases such as glaucoma, diabetic retinopathy, and AMD collectively accounted for more than 19 million cases of moderate or severe vision impairment in adults aged 50 years and older, making these diseases important targets for prevention and treatment. The fact that the molecular bases of these diseases are not completely understood and the lack of good mouse models hinders the development of effective treatments. Therefore, identifying both the causes of these diseases and understanding how the retina responds to stress is crucial to facilitate the development of novel, effective therapies for eye diseases.

Another challenge is the complexity of the tissue itself. Retinal diseases can primarily affect different cell types that compose the retina, and thus how these respond under pathological conditions may vary considerably. For example, in the context of autophagy, how a photoreceptor deals with toxic waste products in its outer segment, which is completely devoid of degradative organelles such as lysosomes, is unique. RGCs are compartmentalized into the soma, axon, and dendrites, each of which are separately metabolically regulated (Casson et al., 2021). Removal of damaged mitochondria from the soma along the long axons of RGCs also poses a complex problem that does not arise in other retinal cells. Because autophagy plays an important role in removing damaged organelles and proteins in these different cell compartments (Stavoe and Holzbaur, 2019), it is crucial to understand how this process is specifically regulated in each compartment. Autophagy also provides the building blocks for synapses, and therefore contributes to synaptic plasticity and neuronal survival (Nikoletopoulou et al., 2017). These specific challenges, and the manner in which they are resolved in different cell types, can strongly impact the cell's response to stress. More research will be essential to understand how the autophagy process is specifically regulated in different cell types of the eye.

It is worth also mentioning that autophagy occurs in coordination with other degradative pathways such as chaperone-mediated autophagy and the ubiquitin-proteasome system (Koga et al., 2011). For example, in the retina, chaperone-mediated autophagy compensates for the age-associated decreases in (macro)-autophagy, at least for some time (Rodriguez-Muela et al., 2013). Similar compensatory effects are observed in *Atg5*-deficient retinas, underscoring the crucial role of chaperone-mediated autophagy in the retina (Rodriguez-Muela et al., 2013). Exploiting these compensatory changes when other pathways are downregulated, either due to mutations or aging, thus constitutes an interesting therapeutic avenue. Finally, boosting lysosomal activity is another potential means of simultaneously potentiating macroautophagy and chaperone-mediated autophagy, and may be the best option in cases of generalized lysosomal damage (e.g. caused by excessive ROS production or calcium-dependent calpain activation in photoreceptors) (Rodriguez-Muela et al., 2015). Moreover, therapies that increase levels of the transcription factor TFEB could prove promising for the treatment of retinal diseases and other neurodegenerative conditions (Cortes and La Spada, 2019).

Finally, there is an urgent need for disease models that better reproduce the alterations observed in human patients with retinal and eye diseases. Retinal organoids are a particularly promising tool to improve ophthalmic research (Kruczek and Swaroop, 2020). In conclusion, while our knowledge of autophagy in the eye and retina has increased greatly in the last decade, research must continue apace to facilitate the development of autophagy-targeting therapies to treat retinal diseases.

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Abbreviations

3-MA	3-methyladenine
AMD	Age-related macular degeneration
AIF	Apoptosis-inducing factor

AMBRA1 Autophagy/beclin-1 regulator 1
ARPE-19 Adult retinal pigment epithelial cell line-19
Baf-A1 Bafilomycin A1
BRB Blood retinal barrier
DR Diabetic retinopathy
DOA Dominant optic atrophy
GWAS Genome-wide association studies
HDAC Histone deacetylate
IOP Intraocular pressure
INL Inner nuclear layer
IPL Inner plexiform layer
LHON Leber's hereditary optic atrophy
LC3 Light chain 3 protein
LDLs Low density lipoproteins
NLRP3 a NOD-like receptor responsible for the processing of pro-IL-1β to the active form of IL-1β
ONC Optic nerve crush
ONL Outer nuclear layer
OPL Outer plexiform layer
POS Photoreceptor outer segment
PE Phosphatidylethanolamine
PI3P Phosphatidylinositol 3-phosphate
PI3K Phosphatidylinositol 3-kinase
ROS Reactive oxygen species
RGCs Retinal ganglion cell
RPE Retinal-pigmented epithelial
Retinitis pigmentosa RP
RGCL RGC layer
SI Sodium iodate
TXNIPT hioredoxin-interacting protein
TFEB Transcription factor EB
TSA Trichostatin A

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