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Autophagic Regulation of Retinal Pigment Epithelium Homeostasis

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Abstract

Retinal pigment epithelium (RPE) is a single layer of hexagonal pigmented cells located in the outmost part of the neurosensory retina. RPE cells are vital for the health of retina. Dysfunction of RPE resulted from consistent exposures to oxidative stress has been reportedly to cause retinal degenerations, such as age-related macular degeneration (AMD). RPE cells exert different types autophagy to maintain retina hemostasis. This review summarizes molecular and cellular autophagic mechanisms that are revealed in RPE to respond to stress. The evidence in support of autophagy dysfunction or aging that result in diseases is also discussed.

Keywords: Retinal pigment epithelium; Autophagy; Phagocytosis; Mitochondrial dynamics

Introduction

Retinal pigment epithelium (RPE) is a single layer of hexagonal pigmented cells located in the outmost part of the neurosensory retina. Several activities have been identified of these cells including the supplement of nutrients and oxygen to retina, the sustainment of visual cycle through metabolizing vitamin A, the absorbing of scattered light to reduce photo-oxidation via melanosomes, the performance of receptor-mediated phagocytosis of photoreceptor outer segment (POS) fragments for assuring viability and functionality of photoreceptors, the secretion of signaling modulators for communicating with adjacent cells, transportation of ions, and supporting of immune privilege [1]. These functions make RPE an important role in visual processing system. Dysfunction of RPE resulted from consistent exposures to oxidative stress has been reportedly to cause retinal degenerations, such as age-related macular degeneration (AMD).

Autophagy is a basic catabolic mechanism by which cells degrade intracellular unnecessary or dysfunctional components inside lysosomes (Figure 1). This process promotes cellular survival by saving cellular energy during extreme starvation through breakdown and recycle of cellular components. There are at least three types of autophagy addressed in mammalian cells, macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) [2]. Macroautophagy and CMA are prominent under stress conditions. Basal level of these two activities is detectable in most cell types. During macroautophagy, cytosolic components are enclosed within a double-membrane structure, autophagosome, which fuses with lysosomes to degrade the enclosed contents by hydrolases [3].

Mechanisms such as heat shock response [4] and unfolded protein response are effective regulatory machinery for proteostasis. Proteins can not only be degraded through lysosomal delivery approach such as macro/microautophagy, but also through chaperone-targeted approach to directly cross lysosomal membrane into lumen, known as chaperone-mediated autophagy [5]. The high removal selectivity of CMA makes this system an efficient degradation system, and assures CMA a regulatory role in cellular activity [6]. This review summarizes molecular and cellular autophagic mechanisms that are revealed in RPE to respond to stress (Table 1) [7-14]. The evidence in support of autophagy dysfunction or aging resulting in diseases is also discussed.

Autophagy and heterophagy in RPE

The heterophagy of POS by RPE is essential to the longevity of photoreceptors (Figure 1). The renewal of POS is regulated by circadian rhythms via the shedding of distal tips POS, which are degraded and engulfed by RPE, and are eventually digested by lysosomal enzymes. All-*trans*-retinol (ROL) in the degradation products are recycled and converted to 11-cis-retinal (11CR) by visual cycle to replenish chromophore for reproduction of photobleached pigments. Once converted by light, 11CR becomes all-*trans*-retinal (ATR), which is then flipped by ATP-binding cassette transporter 4 (Abca4) from lumen of the outer segment discs of photoreceptors to cytoplasm. The reduction of ATR is subsequently performed to generate ROL by retinol dehydrogenase 8 (Rdh8). As mentioned above, ROL is transferred to RPE to regenerate 11CR. It is indicated that delayed clearance of 11CR from photoreceptors in $Abca4^{-/-}Rdh8^{-/-}$ mice causes severe dystrophy of photoreceptors and RPE cells [15]. Mice deficient in Abca4 and Rdh8 (*Abca4−/−Rdh8−/−*) demonstrate increased levels of autophagy and mitophagy using microtubule-associated protein light-chan3II (LC3II) and Park2 as indicators, respectively [16]. Moreover, under strong photobleaching condition, ATR and 11CR form cytotoxic N-retinylidine-N-ethanolamine (A2E) and other bisretinoids, which are components of ocular lipofuscin and are accumulated in outer segments causing human dry and wet AMD [15]. It is not surprising that RPE cells gain lysosomal lipofuscin mostly from renal POS [17].

Recently, the linkage of heterophagy (phagocytosis) of POS and the regeneration of retinal is suggested via a noncanonical form of autophagy, LC3-associated phagocytosis (LAP), in which molecules of autophagy pathway are recruited to the process of phagocytosis [18]. Single-membrane phagosomes with lipidated LC3-II instead of canonical autophagy double-membrane (autophagosomes) are observed in LAP. In addition, *ATG5* gene knockout mice demonstrated poor ability in processing POS. These observations suggested that the convergence of autophagy and phagocytosis possibly offer better vision [18]. Additionally, this convergence can be revealed by a novel lysosomal component βA3/A1-crystallin, which regulates both autophagy and heterophagy [19]. This crystalline can be found

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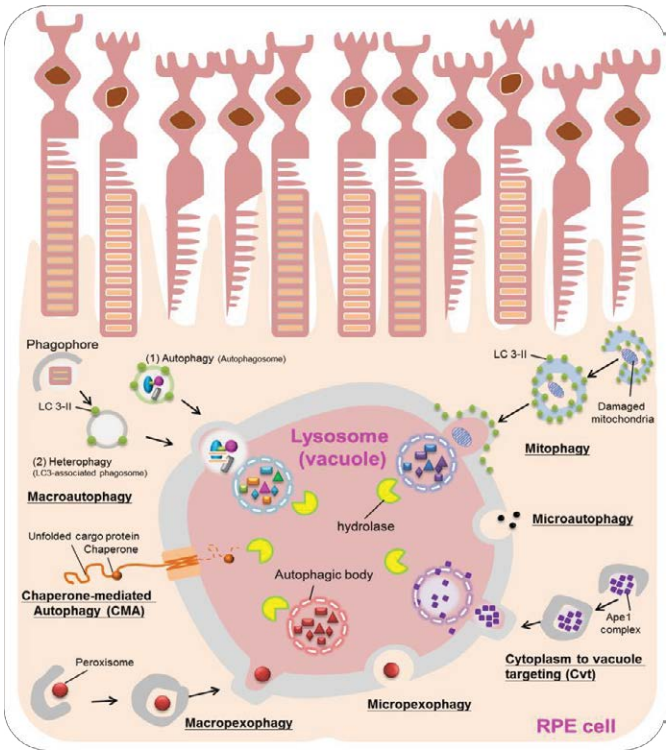

Figure 1: Different clearance systems in RPE cells. The RPE cell clearance system including micro-/macro-autophagy, chaperone-mediated autophagy (CMA), mitophagy, micro-/macro-pexophagy and cytoplasm to vacuole targeting (Cvt) effectively remove damaged organelles, wastes of cytoplasm components, and protein aggregates. The digestive process can be distinguished into selective or non-selective procedures dependent on the cargo specificity. Autophagy, a cellular housekeeping process of both selective and non-selective, avoids waste accumulation in RPE. Heterophagy, as a selective autophagy, is the phagocytosis of exogenous photoreceptor outer segments. A portion of cytoplasmic materials or POS is sequestered into a double-membrane autophgosome or LC3-associated phagosome, respectively, and then fused with lysosome vacuoles. The specific selected degradation of peroxisomes can be executed by either a micropexophagy or macropeoxphagy. The unique degradation of damaged mitochondria, known as mitophagy, takes place as well. A biosynthetic cytoplasm to vacuole targeting (Cvt) pathway is found in RPE cells.

in human drusen materials [20], and involves in the regulation of lysosome-mediated degradation in RPE [21]. Nuc1 rats with mutant Cryba1 gene (crystallins beta A1) form deposits between RPE and Bruch's membrane during aging. Thus, disrupted lysosomal functions impairs the activities of autophagy and heterophagy leading to the potential progression of AMD [22].

Autophagy maintains cellular homeostasis through nutrient recycling by lysosomal degradation pathway. This catabolism process induced by a spectrum of stimuli involves the engulfment of damaged organelles and cellular debris, and the adaption of nutrient and energy demand changes. Defects in autophagy are implicated in cancers and neurodegenerative syndromes such as Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS). Autophagy asserts the functions of RPE and retina [7]. In order to respond stimuli including light damage, oxidative stress, and mitochondrial malfunctions, autophagy associated molecules have been indicated to be highly expressed in ocular cells [23-25]. Macroautophagy plays an essential role in ARPE-19 cells to respond stimuli [24]. However, accumulated substances like oxidized lipids and lipofuscin, a toxic aging pigment derived from residues of lysosome incompletely digested POS [26], mainly composed of bisretinoid metabolites of vitamin A (A2E) [27], interfere with the function of autophagy leading to cell dysfunction and disease progression [28] (Figure 2). Lipofuscin bisretinoids last in RPE once formed and are causes of blinding retinal diseases. A2E inhibits autophagic clearance in RPE [29]. These cone-shaped lipids shift cholesterol from membrane bilayers and accumulate cholesterol in RPE lysosomes and late endosomes [30], which restrains the activity of autophagy since autopahgosome-lysosome interactions are modulated by membrane cholesterol levels [31-33]. Previous investigations indicate that lipofuscin are hard to be cleared, however, recent study reveals that these bisretinoids could be removed to treat macular degeneration and Stargardt disease [34]. Evidence indicates that lipofuscin can be removed from monkey RPE (36 of 48 monkeys) by treating with molecules belonging to tetrahydropyridoethers class [35]. Additionally, β-cyclodextrin (β-CD), consisted of seven D-glucose units, eliminates lipofuscin bisretinoids of RPE cells *in vitro* and eyecups of Abca4/Rdh8 double knock-out mice [36].

mTOR Regulation of Autophagy in RPE

The mammalian target of rapamycin (mTOR), an evolutionarily-conserved serine/threonine kinase, regulates the balance between cell growth and autophagy in response to external stimuli including stress, growth factors, and nutritional status [37]. The activity of autophagy is regulated by mTOR (Figure 3). The inhibition of mTOR initiates a series of actions including partial dephosphorylation of ATG13 (AuTophaGy13), recruitment of RB1CC1 (RB1-inducible coiled-coil 1) complex, and activation of ULKs (unc-51-like kinases) to activate autophagy [38]. The key mediator, ULK1/2-ATG13-RB1CC1 complex,

	Previous studies discussed the function of different manner autophagy in RPC cells	References
Macro-/ micro-autophagy		
Heterophagy	·Retinal homeostasis and shares many conserved signaling pathways with phagocytes. ·Decreased photoreceptor responses to light stimuli and decreased chromophore levels that were restored with exogenous retinoid supplementation.	[7-9]
Autophagy	·Autophagy regulates cellular homeostasis and response to environmental stress. Within the retinal pigment epithelium (RPE) of the eye, the level of autophagy can change with both age and disease.	[10]
Chaperone-mediated autophagy	·Recombinant hHsp70 protein offers protection against oxidative stress. ·RPE cells take up the exogenously delivered rhHsp70 and localize it in late endosomes.	[11]
Macro-/micro-pexophagy	·Peroxisomes are highly metabolic, autonomously replicating organelles that generate reactive oxygen species (ROS) as a by-product of fatty acid β- oxidation. ATM in metabolism as a sensor of ROS that regulates pexophagy in RPE cells.	[12]
Cytoplasm to vacuole targeting	·Sema4A regulates two distinct endosomal-sorting pathways that are critical for photoreceptor survival and phototransduction during the transition between daylight and darkness.	[13]
Mitophagy	·Parkin-mediated mitophagy presumably prevent the RPE- mitotic catastrophe cells from	[14]

Table 1: Autophagy related studies in RPE.

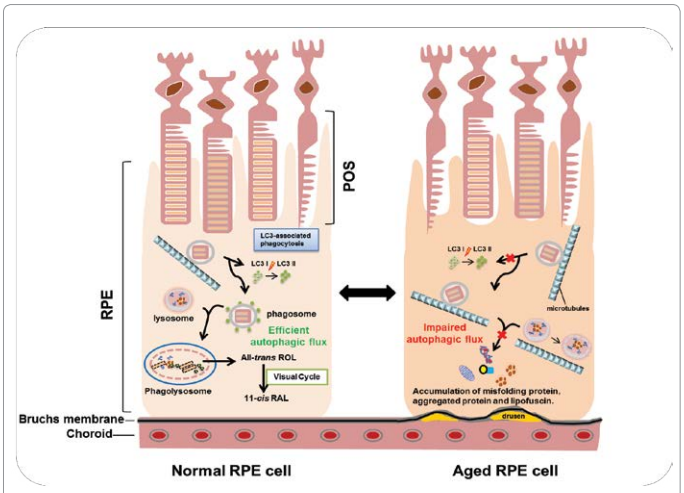

Figure 2: Dysregulated heterophagy in aged RPE cells is associated with the accumulation of lipofuscin. Incomplete digestion of POS accelerates the accumulation of vitamine A metabolites (lipofuscin) within aged RPE cells lysosomes and the deposits of lipid-protein complexes (drusen) between Bruch's membrane and RPE cells. These aggregates and deposits collaborate with microenvironmental and genetic factors to disturb normal functions of the RPE cells, leading to photoreceptor dysfunction and macular degeneration. Impaired lysosomal POS clearance increases lipofuscin trapped in lysosome that increases detrimental oxidative stress. Inefficient autophagic flux weakens lysosomal function, which increases exocytosis of damaged proteins and activates drusen formation-associated inflammasomes.

accompanied with other proteins such as ATG14, BECN1, PIK3C3, PIK3R4, and UVRAG regulate the formation of double-membrane autophagosomes [39]. LC3, a ubiquitin-like protein, facilitates autophagic proteolysis via ubiquitin and SQSTM1 (sequestosome 1, p62) binding sites [40]. The impairment of autophagy in RPE cells can result in cellular degeneration, aggregation-prone protein accumulation, and cell death. SQSTM1 accumulation in perinuclear aggregates or inclusion bodies due to autophagy failure has been reported in neurodegenerative diseases [41]. Decreased autophagic activity in RPE cells has been indicated as a cause of dursen formation, which may lead to the development of AMD [42]. RPE cells express two types of TOR multiprotein complexes, mTORC1 and mTORC221, executing distinct cell activities. The activation of mTORC1 promotes cell growth when energy/nutrients are sufficient, or regulates biosynthetic programs under stress. The suppression of mTORC1 activity is key to induce autophagy when nutrients are deprived. AKT/mTOR signaling mediates cell proliferation in RPE [43,44]. The activation of mTORC1 by growth factors or by mTORC2-activated AKT elicits the biosynthesis of proteins and lipids through S6K-regulated phosphorylation of rpS6 (ribosomal protein S6) and SREBP-regulated lipogenesis [45]. RPE cells undergo mTOR-mediated hypertrophy and dedifferentiation in responding to oxidative stress to increase cellular biomass and form thickened RPE in respond to stress. Interestingly, increased activation of mTORC1 has also been observed in RPE degeneration [46] and retards the production of RPE-characteristic proteins such as enzymes for conversion of all-trans-retinal to 11-cis-retinal (RPE65, LRAT, and RLBP1), and for phagocytosis of POS (MERTK) [46]. The activation of mTORC1 impairs autophagy through the inhibition of auto-lysosomal biogenesis by modulation of lysosomal membrane potential, and blocks ULK1 signaling in RPE cells. It is indicated that rapamycin activates autophagy through the inhibition of mTORC1 activity in animal studies [47]. Rapamycin therefore averts mTOR-mediated detrimental effects, which preserves photoreceptor functions [48] and reduces senescence in cultured RPE cells [49]. Additionally, the eye lens protein, CRYBA1/βA3/A1-crystallin, is critical to preserve the function of lysosome. It binds to V0 subunits of V-ATPase, a component of the mTORC1 pathway, to maintain normal lysosomal activity, and of course the activity of autophagy [50].

Mitochondrial Dynamics in Retina

Mitochondria are highly dynamic organelles. They generate energy via oxidative phosphorylation, and continually proceed repetitive cycles of fusion and fission to rearrange inter-organelle lipids and contents. Mitochondrial dynamics, namely fission, fusion, movement along cytoskeletal tracks, and mitophagy, regulate mitochondria properties of morphology, biogenesis, redistribution and mitochondrial DNA inheritance [51]. The rate of fission and fusion that determines the length of mitochondria and the closeness of formed network is fluctuated by metabolic conditions and environmental stimuli [52]. Mitochondrial fission is mediated by a phosphorylation and S-nitrosylation activated

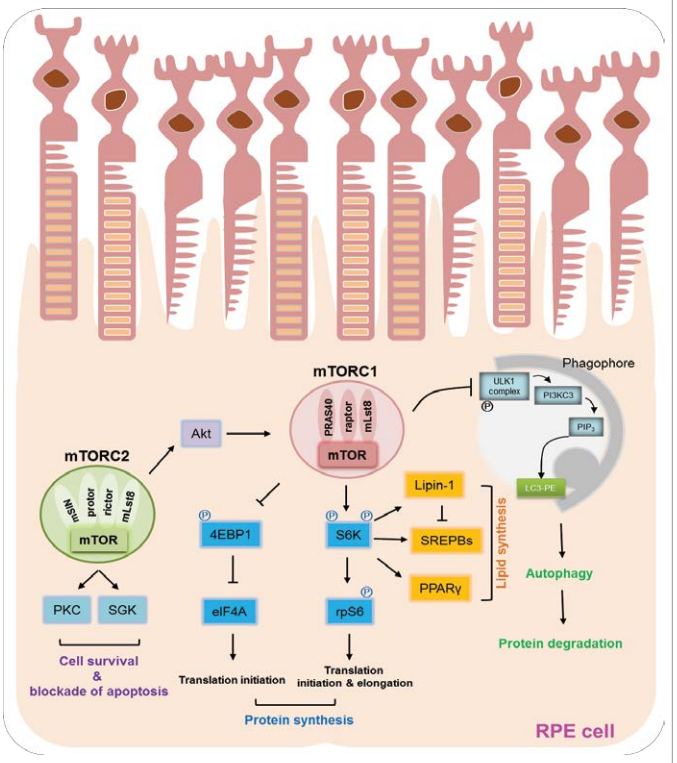

Figure 3: Regulation of mTOR pathway in RPE cells. mTORC1 is involved in protein synthesis, lipid synthesis and protein degradation in RPE cells. mTORC1 classically controls protein synthesis via the phosphorylation of several translation regulators, such as 4EPB1 and S6K. mTORC1 inhibits the activity of 4EBP1 through phosphorylation, which blocks the inhibitory effects of 4EBP1 on eIF4A leading to the initiation of translation. S6K1 phosphorylates ribosomal protein S6 (rpS6) to up-regulate translation initiation and elongation as well. Moreover, mTORC1 positively regulates SREBPs and PPARγ, lipid metabolism-associated transcription factors, via the phosphorylation of S6K. SREBPs, a downstream factor of phosphorylated S6K, trigger the expression of numerous genes, such as fatty acid and cholesterol synthesis. However, S6K also activates Lipin-1 which exhibits suppression effects on SREBPs transcription in lipid synthesis. Activated mTORC1 complexes block the activities of ULK1 and PI3KC3 complexes resulting in the suppression of the activation of phosphatidylinositol triphosphate (PIP3) synthesis. This reduces the formation of autophagosomes through the decrease of LC3-PE associated autophagophores induction in RPE cells. mTORC2 regulates autophagy via Akt pathway to mediate the function of mTORC1 in RPE cells. mTORC2 signaling pathways regulate cell growth and blockades apoptosis via activates several kinases such as serum- and glucocorticoil-induced protein kinase 1 (SGK1) and protein kinase C (PKC).

cytosolic GTPase protein, dynamin-related protein (Drp1) [53], which facilitate fission through the interaction with tail-anchored outer mitochondrial membrane protein, MFF [54]. In yeast, the recruitment of Drp1 is through mitochondria outer membrane protein, Fis1 [55]. Mitochondrial fusion require GTPase proteins, optic atrophy type 1 (OPA1) for outer, and mitofusins (Mfn1/2) for inner mitochondrial membrane fusion, respectively [52]. The manipulation of the activities of Drp1 and OPA1/Mfn would lead to elongated and fragmented mitochondria, respectively. These dynamic changes ultimately influence the fate of cells [53,56]. Intraocular pressure (IOP) promotes mitochondria fission. Elevated IOP levels reduce OPA1 mRNA levels in optic nerve head, which results in mitochondrial morphology changes (shortened length, boosted cristae numbers) in an animal model of glaucoma [57,58]. The survival of ganglion cells under glaucomatous stress (increased IOP) could be attributed to the up-regulated OPA1 expression [59].

Mitophagy, a selective degradation of damaged mitochondria by autophagy, functions to maintain quality control of organelles [60]. Dysfunction of mitochondria has been linked to the progression of AMD and other neurodegerative diseases such as PD, AD, and Huntington's disease (HD) [61-67]. Defective mitochondria are labeled and engulfed by isolation membrane followed by fusion with lysosomes [68].

Damaged and fragmented mitochondria in RPE resulted from intense light-induced high level of oxidative stress make cells vulnerable to cell death stimuli due to the depletion in ATP and the release of cytochrome c, which activate caspases and initiate apoptosis [51]. Prominent mitochondrial changes induced by oxidative stress in aged RPE cells (primary cells from donors at age >60-year-old) are observed in comparison with those of mid- (48-60-year-old) and young- (9-20-year-old) aged ones. These changes in number, size, shape, matrix density, cristae architecture, and membrane integrity correlate well with reduced ATP level, mitochondrial membrane potential ($\Delta\psi m$), cytosolic (Ca^{2+}), and increased mitochondrial (Ca^{2+}) [69]. It is intriguing that mitochondrial heat shock protein 70 (HSP70) is critical in the aging of mitochondria. The expression of this protein in RPE cells is suppressed under oxidative conditions. Besides, progeria-like phenotypes is shown in HSP70 knockdown *C. elegans* [70].

Chaperone-mediated Autophagy in Retina

Chaperone-mediated autophagy (CMA) is a process for protein degradation to constituent amino acids in most cells (Figure 4). Cytoplasmic materials can be engulfed through macroautophagy. Autophagosomes fuse with multivesicular bodies (MVB) or directly with lysosomes for degradation. Cytosolic proteins with specific pentapeptide motif (e.g. KFERQ) are recognized by a chaperone, heat shock-cognate protein of 70 KDa (HSC70), to be delivered to lysosomal receptor, lysosome-associated membrane protein type 2A (LAMP-2A) for directly translocation across membrane for degradation [71]. Multimerized LAMP-2A forms a translocation complex to facilitate the penetration of bound substrate proteins. Unfolded substrate proteins are subsequently translocated assisted by a luminal chaperone for complete degradation. Unique characteristics of CMA are the selectivity on specific protein and the unnecessary of formation of vesicles for lysosomal degradation. The HSC70 recognizes a pentapeptide motif in amino acid (AA) sequence of substrate proteins. The petapeptide consists 1) an invariant AA, a glutamine (Q) residue; 2) a positively charged AA (lysine, K or arginine, R residues) at either ends of the sequence (beginning or terminal ends), 3) a hydrophobic AA (phenylalanine, F, valine, V, leucine, L, or isoleucine, I residues), 4) a negatively charged AA (glutamic acid, E, or aspartic acid, D, residues), and 5) charged AA (either positively or negatively charged residues) [72]. The feature of CMA motif is to generate charged AA sequence. Post-translational modifications (phosphorylation and acetylation) change the charges of AA, which can modulate the subsequent chaperone binding [73]. The interplay of CMA and macroautophagy has been addressed that these two autophagic regulations are in a bidirectional relationship. Blockage of CMA promotes macroautophagy [74]; upregulation of CMA compromises macroautophagy [75]. However, this cross talk seems to be cell-type-dependent. Recently, evidence indicates that the autophagic cross talk in retinal cells is not bidirectional [76]. Reduced macroautophagy activity is found in aged retina, which coincided with elevated levels of CMA. Inhibition of macroautophagy in retinal cells provokes significant CMA *in vitro* and *in vivo* as well. However, downregulation of CMA failed to elicit increased macroautophagy, suggesting a uni-direction between these two autophagic pathways and a specific feature of visual lost in aging. This finding might reflect the observations of oxidative stress-induced RPE cell death that oxidative stress-induced suppression of HSP70 impairs the activity of CMA, which fails to trigger macroautophagy, resulting in subsequent induction of cell death.

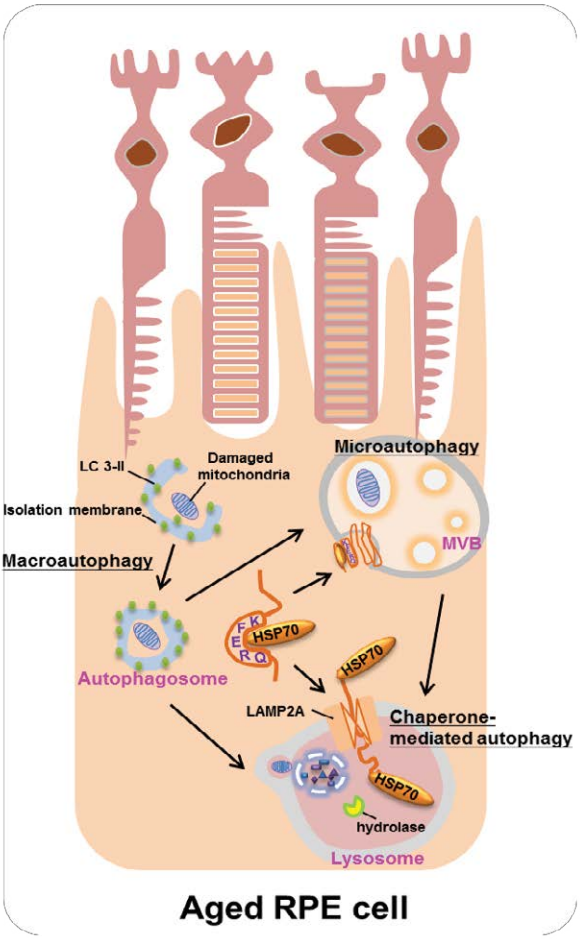

Figure 4: Degradation of damaged organelles and misfolded proteins via macroautophagy and chaperone-mediated autophagy. Damaged mitochondria can be degraded by macroautophagy through the formation of autophagosomes, which can directly fuse with lysosome or indirectly through MVB. Peptides with KFERQ motif can be degraded by chaperone-mediated autophagy. Cytosolic HSC70 interacts with target peptides, and translocates peptides into lysosome through LAMP-2A. HSC70- KFERQ peptide complex can enter MVB through microautophagy.

Regulation of Autophagy in AMD Treatments

Age-related macular degeneration (AMD or ARMD) is the leading cause of severe vision loss in older adults. AMD occurs when the small central portion of the retina field (macula) is deteriorated. Risk factors including aging, genetic background, smoking, unhealthy diet, obesity, high blood pressure, hypercholesterolemia and arteriosclerosis, induce the syndromes of AMD [38]. There are two main types, dry and wet forms, of macular degeneration that make visual impairment in aging people. The mostly common seen is dry AMD (nonexudative), which affects 90% of the people who have this vision disorder. Cellular debris (drusen) deposits between the retina and the choroid (in Bruch's membrane) causing atrophy and scarring to retina result in this type of AMD. With the accumulation of drusen, vision distortion appears. In the late stage, a thinning of the light-sensitive layer of retinal pigment epithelial cell (RPE) proceeds leading to retinal atrophy or cell death. On the other hand, the wet form of macular degeneration (exudative) is characterized by the growth of abnormal blood vessels from choroid, also known as choroidal neovascularization. Vision distortion, blind spots, and loss of vision on the central vision are caused by hemorrhage causeded by blood vessel leakage of exudate and fluid into retinal.

Currently, there is no available medical or surgical treatment for the cure of AMD. Nevertheless, evidence shows that some treatments against oxidative stress and in avoidance of lipofuscin accumulation potentiate the prevention of severe vision loss or delay the progression of AMD [77]. Autophagic dysregulation has been linked to neurodegenerative diseases including AMD [78]. The regulation of autophagy is optative for normal degenerative processes and prevention of AMD development. However, there is no consensus of opinions that whether the inhibition or acceleration of autophagy would be efficient in AMD treatments [79].

The early stage (upstream of autophagic pathway) autophagy inhibitors such as wortmannin, 3-methyladenine (3-MA) suppress autophagy through the inhibition of class III PtdIns3K (PI3K), an mTOR activiator. Blocking autophagy in early stage by 3-MA in developing retinal neuroepithelium results in abnormal retinal tissue formation and function [80]. The use of these inhibitors reveals the cellular protective role of autophagy in neurodegenerative diseases [81,82].

Likewise, the effects of late stage autophagy inhibitors demonstrate similar protective role of autophagic in retina as those of early stage inhibitors. Late stage autophagy inhibitors, such as fluoroquinolones, bafilomycin A1, impair the fusion of autopahgosomes with lysosomes in autophago-lysosomal pathway. Chloroquin (CQ) is reportedly to inhibit autophagy in lung, colon and breast cancer [83-85]. This antimalarial drug induces lipid accumulation and hinders phagocytosis in ARPE-19 cells, implicating lysosomal dysfunction in macular degernation [22]. However, excessive autophagy has been indicated to be involved in retinopathy or other visual disorder [86]. TAM, a nonsteroidal estrogen receptor antagonist against breast cancer [87], can induce macula-involved retinopathy [88,89], possibly through the triggering of Zn(II) associated autophagy. Moreover, dry AMD undergoes degeneration without cellular proliferation, whereas wet AMD involves choroidal endothelial cell proliferation. Rapamycin is a VEGF (vascular endothelial growth factor) inhibitor. It restricts choroidal neovascularisation (CNV) through interfering with the activity of VEGF-A [90]. Rapamycin is then beneficial for wet AMD treatment [91], although several off-target effects have been addressed [79].

In contrast to promote autophagy, blockage of autophagy may be beneficial to AMD. Reduction of lipofuscin accumulation is achieved by an agonist of 5HT1a receptor, 8-hydroxy-2-(dipropylamino) tetralin (8-OH DPAT), which protects retina from degeneration by reducing autophagy- and photo-oxidative stress-derived lipofuscin accumulation in cultured ARPE-19 cells, possibly through the stimulation of mTOR phosphorylation, which decreases the induction of autophagy [92]. It seems that appropriate manipulation of autophagy is critical in maintaining the normal function of retina.

Conclusions

Autophagy is critical to the normal function of retina. Dysfunction of lysosome resulted from microenvironmental and genetic factors such as lipofuscin/drusen accumulation, chronic inflammation, and mTOR activatusion, impairs autophagy leading to AMD progression. Although there is no effective treatments for AMD, properly manipulates autophagic flux would be pharmacologic strategy to treat degenerative diseases. Autophagy-regulating kinases such as mTOR and AMPK are potential candidates for direct or adjuctive treatments of RPE dysfunction or AMD progression.

Acknowledgments

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