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Review

Age-related driving mechanisms of retinal diseases and neuroprotection by transcription factor EB-targeted therapy

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From the Contents

Abstract

Retinal aging has been recognized as a significant risk factor for various retinal disorders, including diabetic retinopathy, age-related macular degeneration, and glaucoma, following a growing understanding of the molecular underpinnings of their development. This comprehensive review explores the mechanisms of retinal aging and investigates potential neuroprotective approaches, focusing on the activation of transcription factor EB. Recent meta-analyses have demonstrated promising outcomes of transcription factor EB-targeted strategies, such as exercise, calorie restriction, rapamycin, and metformin, in patients and animal models of these common retinal diseases. The review critically assesses the role of transcription factor EB in retinal biology during aging, its neuroprotective effects, and its therapeutic potential for retinal disorders. The impact of transcription factor EB on retinal aging is cell-specific, influencing metabolic reprogramming and energy homeostasis in retinal neurons through the regulation of mitochondrial quality control and nutrient-sensing pathways. In vascular endothelial cells, transcription factor EB controls important processes, including endothelial cell proliferation, endothelial tube formation, and nitric oxide levels, thereby influencing the inner blood-retinal barrier, angiogenesis, and retinal microvasculature. Additionally, transcription factor EB affects vascular smooth muscle cells, inhibiting vascular calcification and atherogenesis. In retinal pigment epithelial cells, transcription factor EB modulates functions such as autophagy, lysosomal dynamics, and clearance of the aging pigment lipofuscin, thereby promoting photoreceptor survival and regulating vascular endothelial growth factor A expression involved in neovascularization. These cell-specific functions of transcription factor EB significantly impact retinal aging mechanisms encompassing proteostasis, neuronal synapse plasticity, energy metabolism, microvasculature, and inflammation, ultimately offering protection against retinal aging and diseases. The review emphasizes transcription factor EB as a potential therapeutic target for retinal diseases. Therefore, it is imperative to obtain well-controlled direct experimental evidence to confirm the efficacy of transcription factor EB modulation in retinal diseases while minimizing its risk of adverse effects.

Key Words: age-related macular degeneration; anti-aging interventions; autophagy; calorie restriction; diabetic retinopathy; exercise; glaucoma; neuromodulation; phagocytosis; photoreceptor outer segment degradation; retinal aging; transcription factor EB

Introduction

Retinal diseases, such as diabetic retinopathy (DR), age-related macular degeneration (AMD), and glaucoma, are major causes of irreversible blindness worldwide (GBD 2019 Blindness and Vision Impairment Collaborators and Vision Loss Expert Group of the Global Burden of Disease Study, 2021). Although anti-vascular endothelial growth factor (VEGF) therapies offer potential benefits in the later stages of DR and AMD, a significant proportion of patients (15%–40%) do not respond to these treatments (Wallsh and Gallemore, 2021). Moreover, existing medical interventions for glaucoma may not consistently preserve vision throughout a patient's lifetime (Tribble et al., 2021). The prevalence and severity of these retinal diseases, despite their varied etiology, increase with age (Keay et al., 2022). The functional decline in age-related retinal diseases is associated with distinct cellular and physiological changes, including microvascular alterations, breakdown of the blood-retina barrier (BRB), synaptic changes, dysfunctional mitochondrial and energy metabolism, accumulation of advanced glycation end products (AGE), immune dysregulation, and para-inflammation (Chen et al., 2019; Eells, 2019; Nag et al., 2019; Jin et al., 2022; Zhao et al.,

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2023). While these cellular and physiological changes are not seen in the retinae of healthy young adults, the healthy aging retina, however, does undergo changes that resemble, to some extent, the pathophysiological alterations seen in retinal diseases (Chen et al., 2019; Eells, 2019; Nag et al., 2019; Jin et al., 2022; Zhao et al., 2023). Hence, as age advances, the healthy retina transitions along a spectrum, shifting from normal to diseased states, highlighting the role of aging as both a precursor and contributor to the development of retinal neurodegenerative diseases.

Recent meta-analyses and longitudinal cohort studies showed that healthy lifespan-extending behaviors, such as caloric restriction, time-restricted eating, and exercises, protect against degenerative retinal diseases (Tribble et al., 2021; Yan et al., 2021; Choi et al., 2022; Russo et al., 2022). Mechanistically, it has emerged that transcription factor EB (TFEB), the master regulator of autophagy, is a shared molecular target activated by these healthy behavioral interventions and also by rapamycin and metformin, two drugs associated with anti-aging effects (Abokyi et al., 2023). TFEB links altered lysosomal homeostasis to the activation of nuclear transcriptional programs, as part of an adaption mechanism, to restore cellular homeostasis and promote survival (Ballabio and Bonifacino, 2020). Under nutrient-rich conditions, TFEB is phosphorylated, inactive, and retained in the cytosol because it is bound to the lysosome surface (Abokyi et al., 2023). The dephosphorylation of TFEB occurs in response to starvation and stress, leading to the activation, nuclear translocation, and binding of TFEB to the promoter site of the coordinated lysosomal expression and regulation gene network (Abokyi et al., 2023). In the mouse brain, age-related decline in TFEB causes neuronal dysfunction whereas TFEB overexpression reverses neuronal senescence (Wang et al., 2021). In this review, we summarize evidence supporting the transcriptional autophagy regulator, TFEB, as a central nexus modulating the pathophysiological mechanisms of retinal aging and diseases. A detailed discussion of the retinal aging mechanisms and potential neuroregulatory effects of TFEB is presented.

Search Strategy and Selection Criteria

Relevant literature published from January 2019 up to November 2023 was identified by searches on PubMed, Web of Science, and Google Scholar databases, or the references cited in relevant reviews, using the following search terms "(aging retina OR age-related macular degeneration OR diabetic retinopathy OR glaucoma) AND (transcription factor EB OR neurodegeneration OR neuroprotection OR retinal pigment epithelium OR photoreceptor OR retinal ganglion cell OR retinal structure OR retinal protein expression OR retinal gene expression OR synaptic plasticity OR metabolic dysfunction OR retinal microvasculature OR vascular endothelium OR blood-retinal barrier OR neuroinflammation)". Only articles published in English were included.

Retinal Aging Biology and Transcription Factor EB

The investigation of aging-induced retinal changes and their underlying mechanisms have garnered significant interest among researchers because of their role as precursors to retinal diseases. This section provides an overview of the key indicators of retinal aging (**Figure 1**) and how they relate to the role of TFEB (**Figure 2**).

Loss of retinal proteostasis and TFEB

Proteostasis, a delicate balance between protein synthesis and protein turnover, is crucial for neuronal survival (Joshi et al., 2020; Reddy Addi et al., 2022). This balance relies on quality control mechanisms such as autophagy, the ubiquitin-proteasome system, the unfolded protein response, and molecular chaperones, which help reduce the accumulation of toxic protein aggregates (Joshi et al., 2020). Loss of proteostasis, characterized by changes in protein expression and the accumulation of non-degradable protein aggregates over time, is a key feature of retinal aging (Galloway et al., 2017; Karunadharma et al., 2022). These changes manifest in older eyes as drusen, basal laminar deposits, and the accumulation of complement proteins (Crabb, 2014; Galloway et al., 2017). Mass spectrometry proteomics of isolated retinal pigment epithelial (RPE) cells from non-diseased human donor eyes revealed age-related changes in proteins involved in metabolism, protein turnover, and stress response (Karunadharma et al., 2022). Specifically, the aged retina exhibited a decline in proteins involved in lysosomal degradation (tripeptidyl peptidase 1 and Cathepsin D) and chaperone activity (heat shock protein 60, prohibitin, and endoplasmic reticulum protein 29), confirming a decrease in autophagy and chaperone activity (Karunadharma et al., 2022). A study conducted in old WNIN-obese rats demonstrated that the accumulation of AGE played a substantial role in age-related neuronal damage, partly by affecting proteostasis. Moreover, AGE accumulation in the aging brain of the obese rats correlated with increased endoplasmic reticulum (ER) stress, impairment of the autophagy and the ubiquitin-proteasome system, β-amyloid accumulation, and neurodegeneration (Reddy Addi et al., 2022).

The retinal neurons and RPE cells are unable to divide into daughter cells, which prevents them from redistributing damaged intracellular proteins or organelles. This makes their protein quality control mechanisms crucial for maintaining cellular homeostasis and function (Sánchez-Vidaña et al., 2023). Consequently, impaired autophagy in the retina poses a risk to the physiology and survival of photoreceptor and RPE cells (Villarejo-Zori et al., 2021). Notably, autophagy contributes uniquely to retinal homeostasis by aiding in the daily cycle of renewal and shedding of the photoreceptor outer segments (POS) (Villarejo-Zori et al., 2021). The phagocytosis and degradation of the POS by RPE cells allow for the recycling of phototransduction proteins in photoreceptors. When autophagy in the RPE cell is impaired, there is a decrease in photoreceptor responses to light and an increased accumulation of waste and toxic materials in the retina, underscoring the importance of autophagy in the visual cycle and retinal proteostasis (Villarejo-Zori et al., 2021).

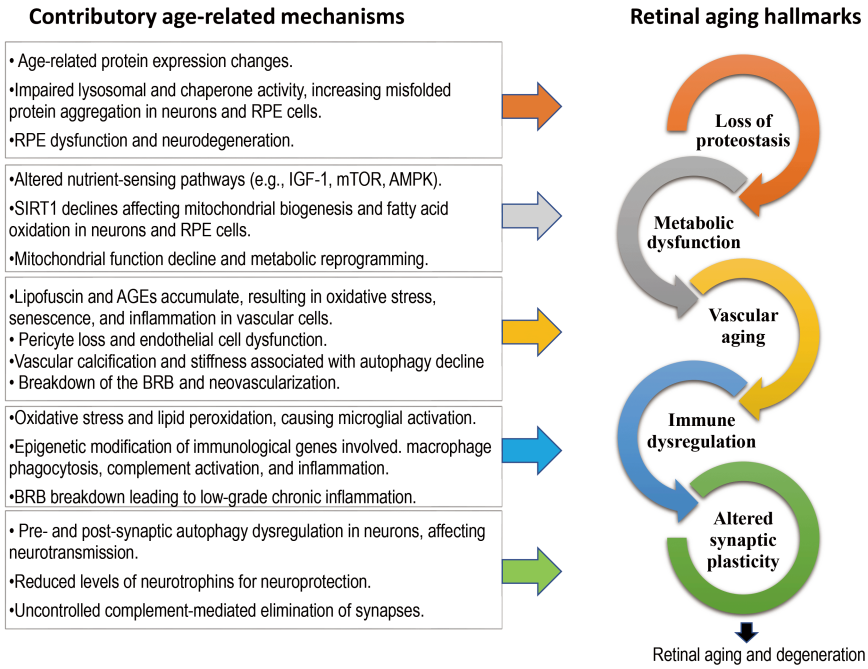

Figure 1 | **Illustration of the age-related mechanisms that contribute to the retinal aging phenotype.**
Aberrant proteostasis in retinal pigment epithelium (RPE) and neurons is the consequence of alterations in protein synthesis, coupled with impaired protein refolding and degradation mechanisms. Dysregulation of nutrient-sensing, energy metabolism, and a loss of mitochondrial homeostasis contribute to metabolic dysfunction. Microvascular defects, such as calcification, atherosclerosis, blood–retinal barrier (BRB) breakdown, choroidal neovascularization (CNV), and microaneurysms, may occur due to advanced glycation end products (AGE) and lipofuscin accumulation in endothelial cells (ECs), pericytes, and vascular smooth muscles. Oxidative stress or epigenetic modifications may trigger retinal inflammation through the activation of microglial cells and the complement system. Dysregulation of neuronal autophagy, neurotrophic levels, and synaptic regulatory proteins contribute to changes in synaptic plasticity. Created with Microsoft PowerPoint. AMPK: AMP-activated protein kinase; ER: endoplasmic reticulum; IGF-1: insulin growth factor 1; mTOR: mammalian target of rapamycin; SIRT1: sirtuin 1.

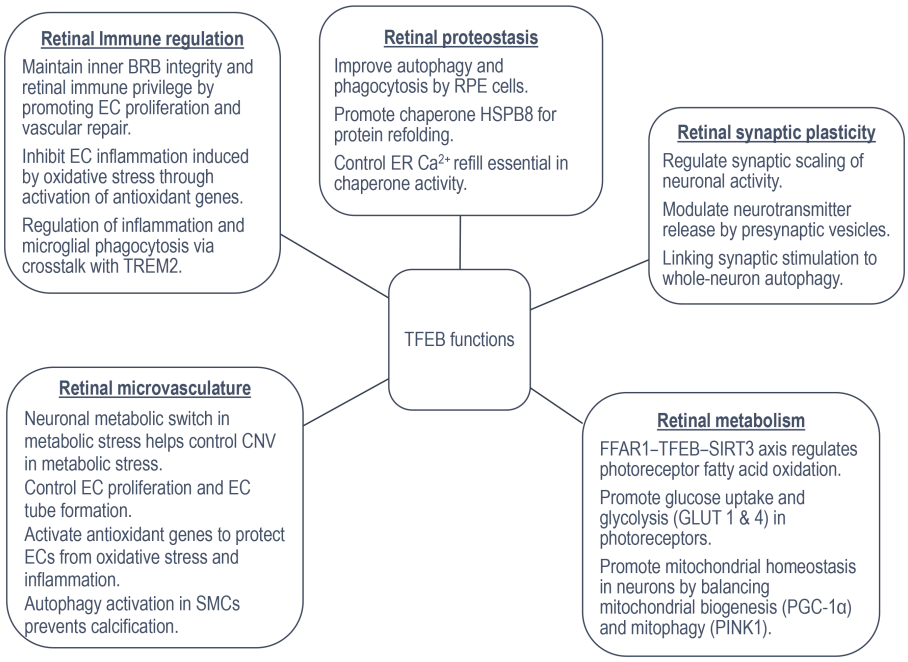

Figure 2 | **TFEB neuroprotection in the aging retina involves the regulation of various cell-type-specific functions.**
The anti-inflammatory effect of transcription factor EB (TFEB) in the retina depends on its impact on endothelial cells (EC) and microglia. By enhancing autophagy and phagocytosis in retinal pigment epithelium (RPE), TFEB plays a significant role in visual pigment regeneration and reducing lipofuscin deposits. Photoreceptors, as specialized neurons with high metabolic demand, rely on energy metabolism by mitochondrial processes, which are regulated by TFEB. The regulation of neurotransmission and synaptic scaling by TFEB greatly affects retinal plasticity. Transcriptional activation of antioxidant and autophagy genes by TFEB has vasoprotective effects. Created with Microsoft PowerPoint. BRB: Blood–retinal barrier; CNV: choroidal neovascularization; ER: endoplasmic reticulum; FFAR1: free fatty acid receptor 1; GLUT 1 & 4: glucose transporters 1 and 4; HSPB8: heat shock protein beta-8; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PINK1: PTEN-induced kinase 1; SIRT3: sirtuin 3; SMC: smooth muscle cell; TREM2: triggering receptor expressed on myeloid cells 2.

TFEB regulates the transcription of autophagy and lysosomal genes, controlling the endocytic and exocytotic functions of neuronal, microglial, and RPE cells, which are vital for recycling and retinal homeostasis (Huang et al., 2018; Xu et al., 2021). Consequently, the age-related decline of TFEB expression in the central nervous system and retina significantly impacts autophagy and proteostasis (Abokyi et al., 2023). Recent findings showed that TFEB activation via optineurin promoted RPE phagocytic clearance in the retina (Tan et al., 2023). The study revealed that TFEB activation effectively promoted POS degradation even under conditions of impaired autophagy, suggesting that TFEB could stimulate RPE phagocytosis independently of autophagy (Tan et al., 2023). Another recent study discovered that expression of the chaperone heat shock protein B8 (HSPB8), the ortholog of HSP67Bc in fly, which is known for its ability to decrease misfolded proteins in neurodegenerative models, is regulated by TFEB (Zhu et al., 2023b). The upregulation of HSPB8 by TFEB using silica nanoparticles was found to promote selective autophagy (Zhu et al., 2023b). Furthermore, the ER calcium content is strictly regulated to provide a favorable environment for protein folding (Carreras-Sureda et al., 2018). By controlling Ca^{2+} refilling in the ER through lysosomal Ca^{2+} uptake (Sbano et al., 2017), TFEB may influence other ER functions related to maintaining proteostasis.

Altered retinal synaptic plasticity and TFEB

Synapses are the fundamental units of the neural circuitry connecting neurons and facilitating the transmission of biochemical signals between them. When necessary, synapses fine-tune the neural circuitry, an adaptive response known as neuroplasticity (Fitzpatrick and Kerschensteiner, 2023). The retina contains two layers of synapses, the outer plexiform layer and the inner plexiform layer, which transmit neurosensory signals from photoreceptors to retinal ganglion cells (RGCs) (Sanuki et al., 2015). The outer plexiform layer contains specialized glutamatergic synapses between photoreceptors and interneurons (bipolar and horizontal cells). The inner plexiform layer has more synaptic connections between interneurons (bipolar cells, horizontal cells, and amacrine cells) and retinal output RGCs, with glutamate and gamma-aminobutyric acid as the main neurotransmitters. Histological and immunohistochemistry investigations in animal models or post-mortem human retina have revealed structural and neurotransmitter changes at the synapses of the aging retina (Chang et al., 2020; Sugita et al., 2020; Zhu et al., 2023a). Specifically, the changes include reductions in synapse density, alterations in synaptic vesicles, remodeling of neural dendrites, and altered expression of synaptic proteins and neurotransmitters in the aged retina (Samuel et al., 2011; Chang et al., 2020; Zhu et al., 2023a). Alterations and disintegration of synapses in the inner plexiform layer and outer plexiform layer usually precede the extensive neuronal death that characterizes the final stages of retinal diseases like glaucoma, AMD, and retinitis pigmentosa, which affect RGCs and photoreceptors, respectively. It is important to note that not all synaptic changes have a negative impact on retinal function. During synaptic remodeling, new synapses can form, or existing connections can be reorganized to compensate for areas of retinal cell loss, thereby promoting retinal activity (Fitzpatrick and Kerschensteiner, 2023). Various mechanisms contribute to age-related synaptic changes, including disrupted autophagy and mitochondrial dynamics, altered expression of synaptic regulatory proteins and neurotrophic factors, and increased complement activation (Williams et al., 2012; Sanuki et al., 2015; Chrysostomou et al., 2016; Grosso Jasutkar and Yamamoto, 2023).

While the literature supports the involvement of TFEB in general synaptic plasticity, the exact role of TFEB in retinal synaptic plasticity during aging remains uncertain. TFEB has been found to regulate synaptic scaling, a homeostatic mechanism that adjusts neuronal properties in response to activity changes, thereby promoting neuronal homeostasis (Wang et al., 2023). Evidence also suggests that TFEB activation, potentially enhanced by fish oil's neuroprotective effects, optimizes synaptic transmission in the brain (Almaspour et al., 2020). Sleep deprivation in rats was found to downregulate TFEB and synaptophysin, a synaptic vesicle protein, while fish oil supplementation boosts TFEB expression, upregulates lysosomal-associated membrane protein 1 and synaptophysin, and improves memory, indicating TFEB's role in controlling neurotransmitter release (Almaspour et al., 2020). Deep brain stimulation is a neurosurgical procedure that involves implanting electrodes to stimulate or silence synaptic activity. A recent investigation revealed that deep brain stimulation activates TFEB, modulating neuronal activity in neurodegenerative disorder treatment. Deep brain stimulation-stimulated mice show improved clearance of aggregate-prone proteins in neurons, linking synaptic activity, TFEB-mediated autophagy, and neuronal homeostasis (Akwa et al., 2023). Further research is needed to understand the impact of TFEB dysregulation on synaptic plasticity in retinal aging, as this may be leveraged for promoting neuroplasticity in the aged or diseased retina. Specifically, exploring how TFEB impacts synaptic regulatory proteins important for retinal organization, including protein-4.1G, and Ap4e1, could improve our mechanistic understanding of TFEB's role in synaptic plasticity (Sanuki et al., 2015; Albrecht et al., 2018).

Dysfunctional retinal metabolism and TFEB

The process of phototransduction requires a significant amount of metabolic energy due to the need for maintaining ion balance and proper neuronal signaling through active transport, the continuous cycle of regenerating visual pigments "bleached" by light, and the recycling of POS by RPE cells (Jaroszynska et al., 2021). Despite this high energy demand, the mammalian retina primarily relies on aerobic glycolysis, a relatively low efficient method for ATP generation, although fatty acid oxidation, a more efficient method, also contributes to the metabolic needs of photoreceptors (Fu et al., 2021; Jaroszynska et al., 2021). In retinal photoreceptors, approximately 80% of glucose is metabolized through aerobic glycolysis for energy, while the remaining 20% is metabolized through oxidative phosphorylation. This results in high glucose consumption in the retina compared to other brain tissues (Viegas and Neuhauss, 2021). Photoreceptors and RPE cells, due to their high metabolic demand, are particularly vulnerable and often the first sites of injury under metabolic

stress. Therefore, any event disrupting glucose and oxygen levels, as well as mitochondrial function, causes metabolic stress and retinal damage. For example, conditional RPE-specific deletion of the mitochondrial antioxidant enzyme manganese superoxide dismutase in mice caused a metabolic shift in RPE, leading to AMD-like changes in both the RPE and photoreceptors (Brown et al., 2019). In-depth reviews of the metabolic pathways in photoreceptors are available in these cited references (Fu et al., 2021; Jaroszynska et al., 2021).

Metabolic dysfunction, characterized by a decline in mitochondrial function and metabolic switch, is a key feature of retinal aging. Proteomic analysis of RPE samples from human donor eyes has shown significant age-related changes in metabolic proteins, including those involved in the glycolytic pathway (aldolase C, glycerol aldehyde phosphate dehydrogenase, phosphoglucomutase 1, and enolase1), the tricarboxylic acid cycle (Trans-aldolase 1 and MDH1), electron transport chain (ATPase subunit 5 and NADH: ubiquinone oxidoreductase core subunit S3), and ketogenesis (hydroxymethylglutaryl CoA synthase 2). These changes account for the decrease in RPE metabolic activity with age (Karunadharma et al., 2022). Moreover, the neuroretina and RPE cells from older mice and human eyes exhibit changes in nutrient-sensing pathways, such as insulin-like growth factor 1, mammalian target of rapamycin (mTOR), and AMP-activated protein kinase, which are crucial for glucose homeostasis and energy balance (Chen et al., 2010b; Cheng et al., 2020). Additionally, an age-related decrease in the expression of sirtuin 1, a nicotine adenine dinucleotide-dependent deacetylase, significantly contributes to impaired glucose and lipid metabolism in the aging retina (Luo et al., 2017). This could be due to the involvement of sirtuin 1 in regulating mitochondrial biogenesis, oxidative phosphorylation, and fatty acid oxidation, through interactions with other transcription factors and energy metabolic pathways, including peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α). Furthermore, retinal aging is associated with an increased accumulation of AGE, which is implicated in the retinal capillary abnormalities found in DR (Xu et al., 2018).

TFEB plays a crucial role in maintaining metabolic balance in retinal neurons and RPE cells through various mechanisms. A recent study revealed that mice with very-low-density-lipoprotein receptor (VLDLR) knockout developed retinal neovascularization due to an insufficient energy supply from fatty acid oxidation by high metabolic photoreceptors (Heckel et al., 2022). The study found that the insufficient energy metabolism in photoreceptors was not necessarily due to poor uptake of triglyceride-derived fatty acids, but rather due to the stimulation of the free fatty acid receptor 1 (FFAR1)-to-TFEB axis (Heckel et al., 2022). FFAR1, a G-protein-coupled receptor, sensed elevated fatty acid levels in circulation (caused by the reduced uptake of lipids in very-low-density-lipoprotein receptor deficient tissues) and inhibited TFEB. This led to decreased autophagy, SIRT3 expression, and mitochondrial respiration in photoreceptors (Heckel et al., 2022). These findings explain how higher serum levels of fatty acid impair autophagy and highlight the importance of TFEB in regulating photoreceptor fatty acid oxidation and energy metabolism, which are vital for their survival. Another study showed that by controlling retinal lipid metabolism, TFEB impacts the early prenatal stage of retinopathy of prematurity (phase I ROP) development (Fu et al., 2023). In neonatal mice with hyperglycemia-associated phase I ROP, the administration of fibroblast growth factor 21 induced normal physiological vascularization, by activating TFEB and promoting lipid transport and mitochondrial lipid oxidation (Fu et al., 2023). Further research is needed to understand how TFEB regulates the metabolic switch from glucose to lipid metabolism in hyperglycemia, and how this impacts angiogenesis. However, it is known that TFEB controls glucose uptake via glucose transporters (GLUT 1 and 4) and glycolysis in tissues or organs with high energy demand, such as the liver, muscles, and cancer cells (Mansueto et al., 2017; Zhang et al., 2022). TFEB also regulates mitochondrial biogenesis and mitophagy, which are quality control mechanisms for maintaining a healthy mitochondrial pool to meet the energy metabolic demands of cells (Abokyi et al., 2023; Jiménez-Loygorri et al., 2023). During retinal development, mitophagy is crucial for switching differentiating neuroblasts from a predominantly oxidative to a more glycolytic metabolism (Jiménez-Loygorri et al., 2023). In the adult retina, mitophagy is the most induced form of autophagy, particularly by photoreceptors in the outer nuclear layer due to their higher metabolic demand (McWilliams et al., 2019). Therefore, mitophagy may be necessary to eliminate damaged mitochondria and trigger mitochondrial biogenesis, via PTEN-induced kinase 1 (PINK1)-TFEB activation (Ivankovic et al., 2016).

Retinal microvasculature abnormalities and TFEB

The retina blood supply comes from two branches of the ophthalmic artery: the central retinal artery (supplying the inner retina) and the short posterior ciliary arteries (indirectly supplying the outer retina and RPE via the choroidal circulation). Similar to the central nervous system, the retina maintains a tightly regulated microenvironment that is regulated by the BRB, effectively separating it from the systemic circulation (O'Leary and Campbell, 2023). Anatomically, the BRB is found at two separate locations in the retina. The inner BRB consists of tight junctions between the endothelial cells (ECs) lining retinal capillaries, which together with its basement membrane, pericytes, neurons, and glial cells, form the neurovascular unit nourishing the inner retinal layers (O'Leary and Campbell, 2023). The outer BRB, however, comprises the single layer of RPE cells and their tight junctions, which separate the fenestrated choriocapillaris from the neuroretina (O'Leary and Campbell, 2023). Breakdown of this barrier interferes with the microenvironment and the immune privileges, and also results in fluid accumulation in the retinal layers, causing edema (Chen et al., 2019; O'Leary and Campbell, 2023). Aging affects the retinal microvasculature and the BRB. Structurally, retinal blood vessels in the eyes of older individuals have thicker walls, narrow vessel diameters, decreased vessel density, and altered blood flow velocity (Wei et al., 2017; Park et al., 2020). At the cellular level, retinal vascular aging is characterized by a reduction in RPE cells, ECs, pericytes, and astrocytes, thickening of the basement membrane, and a decrease in

tight junctions between the RPE cells and ECs (Chen et al., 2019; Antonetti et al., 2021). These abnormalities in retinal microvasculature and BRB are prevalent and more severe in age-related retinal diseases, such as DR, glaucoma, and AMD, suggesting that accelerated vascular aging might play a significant role in the pathophysiology of these conditions (O'Leary and Campbell, 2023; Taylor et al., 2023; Zhao et al., 2023).

Diverse mechanisms may be responsible for age-related abnormalities in the retinal microvasculature. As previously mentioned, the build-up of AGE with increasing age significantly disrupts the adult retinal microvasculature (Antonetti et al., 2021; Schalkwijk et al., 2023). By inducing oxidative stress, senescence, and inflammation, AGE causes EC dysfunction, pericyte loss, the formation of acellular capillaries, and vascular calcification and stiffening (Xu et al., 2018). Also, a study on the human donor eyes showed that advancing age increased oxidative stress, leading to early changes in the ECs, pericytes, and vascular smooth muscle cells (SMC) by the seventh decade of life (Nag et al., 2019). They observed an increase in lipofuscin accumulation and autophagic vacuoles in pericytes and SMC, indicating the involvement of dysregulated autophagy in retinal capillary damage in aging. In another study on human donor retina, the accumulation of the aging pigment lipofuscin was found to be associated with senescence in ECs and neurons, breakdown of the inner BRB, and leading to microaneurysm formation in the retinal capillaries in old age (López-Luppo et al., 2017).

As previously mentioned, TFEB's role in transitioning cells between different energy metabolic pathways helps to maintain energy homeostasis, which is crucial in preventing neovascularization (Heckel et al., 2022; Fu et al., 2023). TFEB also regulates retinal microvasculature development and functions in health and diseases. For example, TFEB controls the proliferation of ECs and EC tube formation, which is necessary for angiogenesis during the early fetal developmental stage and post-ischemia (Fan et al., 2018; Doronzo et al., 2019). In the streptozotocin-induced Sprague Dawley rat model of diabetes, TFEB overexpression mitigated the reduced TFEB expression and nuclear translocation in retinal capillary ECs, thereby reversing high glucose-induced autophagy dysfunction and protecting cells against hyperglycemia-induced oxidative stress, inflammation, and apoptotic damage (Cheng et al., 2023). A study discovered that laminar shear stress-induced TFEB activation protected against vascular aging associated with high-cholesterol diets in mice (Lu et al., 2017). EC-specific transgenic TFEB over-expression in aging mice on a high-cholesterol diet reduced atherosclerotic plaque development, and *in vitro*, TFEB induction in ECs increased the abundance of antioxidant genes, including heme oxygenase 1 (*HO1*) and superoxide dismutase 2 (*SOD2*) (Lu et al., 2017). Also, the activation of TFEB in SMC led to the induction of autophagy and reduced vascular calcification and atherogenesis, thereby improving vascular function (Chen et al., 2022). While most of the existing data attribute the regulatory effects of TFEB on retinal microvascular to the effects on ECs, TFEB may also impact other vascular cellular components of the BRB, including the tight junctions.

Immune deregulation, inflammation, and TFEB

Immune privilege, describing the spatial reduction in immune response or increased tolerance to antigens, is an essential adaptation in the retina that helps to protect against neuroinflammation and preserve retinal function (Chen et al., 2019). Maintaining the immune privilege of the retina is dependent on multiple factors, including the BRB integrity, immunosuppressive factors (e.g., transforming growth factor-beta and retinoic acid), and local immune regulation by the resident immune cells within the retina, such as microglia and astrocytes. These factors contribute to the avoidance, tolerance, and/or resistance to immunopathogenic injury (Chen et al., 2019). Aging, however, affects these factors in diverse ways, leading to low-grade local chronic inflammation in the aging retina (Chen et al., 2019). For example, dysfunctional RPE may lead to microglia activation, and the dysregulation of the complement system, causing inflammation drusen formation in the aging retina, as seen in AMD and other macular dystrophies (Crabb, 2014; Galloway et al., 2017). Increased oxidative damage and enhanced lipid peroxidation are also involved in the activation of microglia and the complement system during the retinal aging process. Activated microglia are capable of killing and phagocytosing photoreceptors (Karlen et al., 2020). Others have also implicated epigenetic modification of the genes involved in immunologic responses, including chemotaxis, endocytosis, complement activation, phagocytosis, and myeloid cell differentiation, as the effector mechanism behind the altered local inflammatory response in the aging retina (Chen et al., 2010a). Moreover, the accumulation of lipofuscin in the aging retina induces senescence in ECs and neurons, leading to impaired BRB integrity and a compromise of the retinal immune privilege (López-Luppo et al., 2017).

By promoting EC proliferation and tube formation, TFEB regulates retinal vascular development, and repair, and contributes towards the maintenance of the BRB integrity (Fan et al., 2018; Doronzo et al., 2019). In the context of local immune regulation, TFEB inhibits EC inflammation, partly by activating the antioxidant genes including *HO1* and *SOD2* (Lu et al., 2017). There may be numerous other mechanisms through which TFEB regulates immune homeostasis in the retina. For instance, in a mouse model of Parkinson's disease, TFEB demonstrates anti-inflammatory effects by modulating the activity of the NLRP3 inflammasome and microglia. TFEB signaling suppresses the NLRP3 inflammasome by boosting the expression of LAMP2A, which subsequently binds to NLRP3 and facilitates its degradation via chaperone-mediated autophagy (Chen et al., 2021). In a transgenic mouse model of Alzheimer's disease, overexpression of the triggering receptor expressed on myeloid cells 2 (TREM2) in microglial cells counteracts neuroinflammation (Shi et al., 2022). However, human microglia with mutated TREM2 exhibit defective lysosomal function due to the transcriptional downregulation of ATPase H^+-transporting lysosomal accessory protein 2 (involved in lysosomal acidification) and LAMP 2 (Filipello et al., 2023), suggesting potential interaction between TREM2 and TFEB. Therefore, TFEB's regulation of endothelial cell inflammation, the NLRP3 inflammasome, and microglial activity support its role in mediating local immunity in the retina.

Interplay between TFEB and biomarkers of aging

The interplay between TFEB and biomarkers of aging provides valuable insights into the mechanisms underlying retinal aging. While there is no universally accepted gold standard for aging "clocks" or biomarkers indicating biological age, cellular senescence has emerged as a reliable predictor of age-related outcomes and functional capability (Chen et al., 2023). In the context of retinal aging, the senescence-associated phenotype plays a crucial role in the development of various hallmarks, including metabolic dysfunction, neuroinflammation, breakdown of the BRB, and synaptic plasticity (Lee et al., 2021). Postmortem investigations on eyes from aged donors revealed that retinal microaneurysms development was associated with cellular senescence in neurons and blood vessels, evidenced by the upregulation of canonical senescence markers p16 and p21 in the microaneurysms of the aged human retina (López-Luppo et al., 2017). Furthermore, it was shown that progeric mice, which overexpress p21 in their retinal blood vessels, developed an aging phenotype characterized by the accumulation of lipofuscin and a high number of retinal microaneurysms (López-Luppo et al., 2017).

Understanding the relationship between retinal TFEB and the senescence-associated biomarkers p16 and p21 is of utmost importance. Studies have demonstrated that age-related DNA damage response in neurons induces senescence, characterized by increased detection of senescence-associated β-galactosidase (SA-β-gal) in a p21-dependent manner (Jurk et al., 2012). It is becoming increasingly clear that declining TFEB levels in aging are closely associated with increased senescence. In aging neurons from older mice, the nuclear TFEB protein level was reduced, accompanied by elevated senescence-associated biomarkers, including p16 and γ-H2AX (Gorostieta-Salas et al., 2021; Wang et al., 2021). However, older transgenic mice overexpressing TFEB showed delayed aging, characterized by the mitigation of markers of neuronal senescence and improved functional performance based on memory skills (Wang et al., 2021). In another study, TFEB-mediated activation of autophagy was found to be responsible for the beneficial effect of the nuclear export protein, chromosome region maintenance 1 (CRM1), in modulating brain aging-associated senescence (Gorostieta-Salas et al., 2021). In old mice, the accumulation of CRM1 in brain aging decreased nuclear TFEB, causing impaired autophagic degradation and increased SA-β-gal, indicating neuronal senescence. By inhibiting CRM1, TFEB nuclear localization improved autophagy flux and reduced SA-β-gal activity in an *in vitro* model of neuronal senescence (Gorostieta-Salas et al., 2021). Recent findings suggest that TFEB may contribute to the regulation of senescence through the control of lysosomal biogenesis and SA-β-gal activity, as well as the coordination of the mitochondrial-lysosomal axis (Curnock et al., 2023; Cui et al., 2024).

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is another aging biomarker due to its role in DNA damage response, metabolism, cellular senescence, and inflammaging. Persistent activation of NF-κB is implicated in driving senescence and mammalian aging, while inhibiting NF-κB has been shown to reduce senescence markers and enhance healthspan in mouse models of aging (Zhang et al., 2021). In diabetic db/db mice, TFEB activation was found to play an anti-atherosclerotic role by suppressing inflammation in ECs through the inhibition of NF-κB signaling (Song et al., 2019). Targeting the TFEB-NF-κB axis, therefore, has the potential as a therapeutic target for modulating inflammation in age-related vascular disorders associated with diabetes, including DR.

Therapeutic Potential of Transcription Factor EB in Common Retinal Disorders

Diabetic retinopathy

DR is a prevalent ocular complication of diabetes mellitus, impacting the retinal microvasculature and neural components, and often resulting in vision loss (Antonetti et al., 2021; Schalkwijk et al., 2023). It is still unclear whether neural or microvascular dysfunction occurs first in DR (Antonetti et al., 2021). Typical characteristics of DR include increased vascular permeability and impaired BRB. These conditions subsequently promote inflammation and the growth of fragile new retinal blood vessels, as observed in patients with diabetic macular edema (Antonetti et al., 2021).

The available evidence backing the therapeutic potential of targeting TFEB in DR currently is mainly from laboratory investigations in rodent models of diabetes. Decline in TFEB expression and activity together with impaired autophagy are observed in human ECs exposed to high glucose and in retina tissues from streptozotocin-induced DR-like pathologies in rats (Cheng et al., 2023), underpinning the central role of TFEB dysregulation in DR pathogenesis. *In vitro*, TFEB overexpression in human ECs reversed autophagy inhibition caused by high glucose and protected retinal capillary ECs against damage (Cheng et al., 2023). In db/db mice, a model of obesity-related type-2 diabetes, it was also shown that TFEB-mediated autophagy activation (by caloric restriction or rapamycin) promoted microvascular dilatation by inhibiting nitric oxide (NO) synthase monomerization, which affects NO production in ECs by reducing reactive oxygen species generation in mitochondria (Zhao et al., 2022). TFEB's involvement in regulating endothelial NO indicates its potential benefits in the prevention and treatment of DR and other retinal diseases with an underlying impaired blood flow (**Table 1**).

In addition to the benefits that are related to autophagy upregulation in ECs, TFEB affects glucose homeostasis and whole-body energy metabolism by: coordinating nutrient availability with the control of nutrient transporters, through endosomal recycling (Curnock et al., 2019); regulating insulin secretion by pancreatic beta cells (Pasquier et al., 2023); and enhancing glucose uptake, transport, and metabolism by the skeletal muscles (Mansueto et al., 2017). Moreover, the therapeutic role of TFEB inducers in DR is also dependent on the cytoprotective effect on the retinal and glial cells under hyperglycemia (De Faria et al., 2016). Trehalose is a naturally occurring disaccharide, which mimics the effects of caloric restriction. The oral intake of trehalose activates TFEB-mediated autophagy in the brain and retina. Mass

Table 1 | **Evidence supporting the neuroprotective potential of TFEB in retinal biology and diseases**

In vivo/*in vitro* models	TFEB changes observed or induced experimentally	Molecular targets/Outcomes	References
DR			
Streptozotocin-induced diabetes rats	Showed reduced TFEB levels in ECs	High glucose impairs autophagy in retinal capillary ECs, leading to the development of DR-like pathologies in rats.	Cheng et al., 2023
Human ECs	Overexpression of TFEB by transfection	Reversing the inhibition of autophagy induced by high glucose, thus safeguarding human ECs against inflammation, oxidative stress, and apoptosis-induced damage.	Cheng et al., 2023
db/db mice obesity-related type-2 diabetes mice	Calorie restriction- or Rapamycin-induced TFEB activation	Stimulated autophagy in ECs, enhancing microvascular dilatation and endothelial function through the inhibition of NO synthase monomerization.	Zhao et al., 2022
Mouse model of retinal angiomatous proliferation	FFAR1-TFEB inhibition	Inadequate energy metabolism and ultimately retinal neovascularization, due to impaired autophagy, reduced SIRT3 expression, and mitochondrial dysfunction in photoreceptors.	Heckel et al., 2022
Neonatal mice with hyperglycemia-associated phase I ROP	Fibroblast growth factor 21-induced TFEB activation	Induced normal physiological vascularization by promoting lipid transport and mitochondrial fatty acid oxidation.	Fu et al., 2023
Type-2 diabetes patients	Higher serum trehalose level	Associated with up to 86% decline in DR occurrence.	Guo et al., 2022
AMD			
RPE cells from the eyes of donor AMD patients	TFEB not investigated	Phagocytosis declined, increasing oxidative stress.	Inana et al., 2018
ARPE-19 cell line	Quercetin activated TFEB	Promoted RPE phagocytosis and autophagy.	Huang et al., 2018
Hydroquinone-RPE cell model (*in vitro* AMD model)	Trehalose activated TFEB	Reversed lysosomal and autophagy dysfunction, inhibited VEGF-A, and protected against hydroquinone-induced RPE damage.	Abokyi et al., 2020
Mouse model of neurodegenerative storage diseases	Trehalose activated TFEB	Protected against neurodegeneration and extended lifespan.	Palmieri et al., 2017
Mouse model of inherited macular degeneration	Optineurin-induced TFEB activation	Promoted RPE phagocytic clearance in the retina.	Tan et al., 2023
Diabetes patients without DR	Metformin intake; TFEB not investigated.	Low-to-moderate doses of metformin reduced the risk of AMD by 5%–10%.	Blitzer et al., 2021
Glaucoma			
Models of glaucoma and aging in mice	Calorie restriction; TFEB not investigated; activation	Enhanced neuroprotection by inhibiting oxidative stress, increasing neurotrophic factors, and preventing age-related changes that impede the normal outflow of aqueous humor.	Li and Wolf, 1997; Guo et al., 2016
Trabecular meshwork cells from glaucomatous eyes	TFEB not investigated	Dysregulated autophagy rendered cells vulnerable to oxidative stress and senescence, impacting the outflow pathway adversely.	Porter et al., 2015

AMD: Age-related macular degeneration; DR: diabetic retinopathy; EC: endothelial cell; FFAR1: free fatty acid receptor 1; NO: nitric oxide; ROP: retinopathy of prematurity; RPE: retinal pigment epithelium; SIRT3: sirtuin 3; TFEB: transcription factor EB; VEGF-A: vascular endothelial growth factor A.

spectrometry analysis in a cross-sectional study involving type-2 diabetes patients [those with DR (n = 69) compared to their cohorts without DR (n = 96)] revealed that having higher serum trehalose and lower serum glutamate levels was associated with up to 86% decline in DR occurrence (Guo et al., 2022).

Age-related macular degeneration

RPE cell dysfunction plays a crucial role in the development of AMD. Similar to neurons, RPE cells are postmitotic and are required to maintain proper retinal function and vision throughout an individual's lifetime (Lakkaraju et al., 2020). A healthy RPE contributes to retinal homeostasis and vision in several ways, including barrier and transepithelial functions, and regulation of crucial visual processes such as POS degradation and the visual cycle, which facilitate efficient photoreceptor function (Lakkaraju et al., 2020). RPE dysfunction in retinal aging is partly attributed to the intracellular accumulation of lipofuscin, which increases retinal phototoxicity and impairs POS degradation (Lakkaraju et al., 2020). Also, mitochondrial dysfunction, another characteristic of RPE aging, promotes oxidative RPE damage and cell death (Tong et al., 2022).

The retinal landmarks of AMD, which include RPE oxidative damage and increased accumulation of protein aggregates, indicate the dysregulation of RPE cell clearance pathways, such as phagocytosis, autophagy, and the ubiquitin-proteasome system (Lakkaraju et al., 2020). Physiologically, RPE cells from the eyes of donor AMD patients showed a significant decline in phagocytosing POS (Inana et al., 2018). Small-molecule TFEB activators, however, promoted POS uptake and RPE autophagy degradation and could be a potential remedy in AMD (Huang et al., 2018; Abokyi et al., 2020). Cigarette smoke is the most important environmental risk factor for AMD development in humans, and the chronic exposure of mice to cigarette smoke caused RPE damage and AMD-like phenotype. Recently, we showed that exposing human RPE cell culture to cigarette smoke prooxidant, hydroquinone, compromised autophagy, and nuclear factor erythroid 2-related factor 2 master antioxidant transcription factor, promoting oxidative damage in RPE cells (Abokyi et al., 2020). However, cells treated with the TFEB inducer trehalose were protected

from oxidative damage in an autophagy-dependent manner (Abokyi et al., 2020). Thus, by activating lysosomal biogenesis and autophagy in RPE cells, TFEB prevents the accumulation of oxidized biomolecules and damaged mitochondria that are cytotoxic to the RPE. Apart from autophagy, TFEB activation led to the transcriptional downregulation of the proangiogenic VEGF-A isoform, implicated in wet AMD (Abokyi et al., 2020; **Table 1**). Furthermore, our research revealed that the activation of TFEB by trehalose effectively mitigated neuroinflammation in the retina and brain of a mouse model with a lysosomal storage disorder, offering protection against retinal degeneration and significantly extending their lifespan (Palmieri et al., 2017). Metformin, an oral antihyperglycemic drug prescribed for diabetes, indirectly induces TFEB, and for this reason, may hold promise to act as an anti-aging agent. In a large case-control study in the US, it was found that low-to-moderate doses of metformin taken for at least two years by diabetes patients without DR were protective against developing AMD (5%–10% reduction) (Blitzer et al., 2021). Similar findings were observed in a meta-analysis involving about 1.5 million total participants sampled from nine studies conducted in the US, South Korea, the UK, and China (Liang et al., 2022). These promising results based on cross-sectional studies warrant interventional clinical trials to test the efficacy of metformin on AMD patients.

Glaucoma

Glaucoma is a progressive optic neuropathy characterized by the gradual damage of RGC axons, specifically the retinal nerve fiber layer and inner retinal layers (Liu et al., 2018). Elevated intraocular pressure (IOP) plays a significant role in causing RGC axon damage through ischemia, and mechanical stress, and by obstructing retrograde and anterograde axonal transport of neurotrophins in RGC axons (Chitranshi et al., 2018). The primary objective of medical treatment for glaucoma is to reduce IOP using ocular hypotensive drugs or surgery. Despite treatment efforts, many eyes still experience progressive retinal nerve fiber layer loss, leading to vision deterioration over time. Age-related changes in the outflow facility, the drainage point for aqueous humor, can increase IOP, thereby increasing the risk of glaucoma (Liu et al., 2018). In aging individuals, glaucomatous eyes often exhibit increased stiffness of the trabecular meshwork and Schlemm's canal due to extracellular matrix remodeling. This structural alteration hinders the outflow of aqueous humor, resulting in elevated IOP (Vahabikashi et al., 2019). Several other retinal aging "drivers", including oxidative stress, brain-derived neurotrophic factor decline, mitochondrial dysfunction, and impaired autophagy, may also contribute to glaucoma pathogenesis, irrespective of IOP.

Emerging evidence from human observational studies and animal models of glaucoma suggests that autophagy plays a neuroprotective role and contributes to the survival of RGCs (Tribble et al., 2023). Certain behavioral and lifestyle interventions known to activate autophagy via TFEB, such as physical activity and caloric restriction, have shown effectiveness in delaying the progression of glaucoma (Tribble et al., 2021, 2023; Russo et al., 2022). For instance, experimental evidence from studies involving glaucoma models and aged animals has elucidated that caloric restriction's neuroprotection in glaucoma is achieved through the inhibition of oxidative stress, the elevation of neurotrophic factors, and the prevention of age-related alterations that hinder the normal outflow of aqueous humor (Li and Wolf, 1997; Guo et al., 2016).

Furthermore, dysregulated mTOR/TFEB-dependent autophagy in trabecular meshwork cells has been implicated in increased oxidative damage and the development of a senescence phenotype in glaucomatous eyes (Porter et al., 2015). TFEB activation also plays a role in regulating retinal vascular development under ischemic conditions (Fan et al., 2018; Doronzo et al., 2019), potentially serving as an adaptive mechanism to preserve RGCs and their axons in chronic elevated IOP-induced ischemia (**Table 1**). Additionally, lysosomal degradation may modulate the levels of brain-derived neurotrophic factor, a crucial factor for RGC survival (Chitranshi et al., 2018). Therefore, TFEB activation has the potential to modulate trabecular outflow facility and promote neuroprotective pathways, offering significant benefits in the context of glaucoma.

Concluding Remarks

The understanding that aging significantly influences retinal function in both normal aging and as part of retinal degeneration has been recognized for decades. However, it is only recently that advancements in medical neuroscience research have enabled us to explore the mechanisms of retinal aging and their contribution to retinal pathologies. These advancements have also allowed us to investigate the neurotherapeutic benefits of anti-aging interventions such as caloric restriction, exercise, and drugs like metformin, rapamycin, resveratrol, berberine, and trehalose.

After critically evaluating existing research findings in this field, we have synthesized information to support the theory that specific age-related mechanisms drive retinal diseases such as AMD, DR, and glaucoma (**Figure 1**). Our literature review suggests that TFEB-mediated neuroprotection in retinal aging depends on cell-specific effects in the retina (**Figure 2**). For instance, the impact of TFEB on retinal microvascular likely hinges on its effects on ECs: controlling EC proliferation and tube formation; and NO generation (Fan et al., 2018; Doronzo et al., 2019; Zhao et al., 2022). However, TFEB also reduces vascular calcification and atherogenesis by affecting vascular SMC, not just ECs (Lu et al., 2017; Chen et al., 2022). These effects of TFEB on ECs have implications on neurovascular unit function and immune regulation, which are impaired in DR and glaucoma. In RPE cells, TFEB modulates POS recycling and the regeneration of visual pigments in photoreceptors, through autophagy and lysosomal dynamics. The control of RPE clearance of the aging pigment lipofuscin is crucial for RPE and photoreceptor survival and for maintaining retinal proteostasis (Villarejo-Zori et al., 2021). Another potential role of TFEB in the RPE is the control of VEGF-A expression, which promotes choroidal neovascularization (Abokyi et al., 2020). Therefore, by modulating these essential RPE functions, TFEB plays a significant neuroprotective role in retinal neurons. Targeting TFEB in microglia, and to some extent neurons, could

improve lysosomal degradation pathways and mitochondrial function. Lipofuscin accumulation in aging retinal neurons, similar to RPE cells, is associated with impaired lysosomes, the accumulation of damaged mitochondria, cell toxins, and cell senescence or apoptosis. The transcriptional activation of PINK-1, PGC-1α, and fatty acid oxidation genes by TFEB controls mitochondrial homeostasis and the energy metabolic needs of the photoreceptors (Fu et al., 2021). Therefore, TFEB plays a crucial role in the mitochondrial dynamics and energy metabolism of the neuroretina, with implications for glaucoma and DR.

In conclusion, dysregulation of TFEB in retinal cells during aging has significant implications for the development and progression of retinal diseases. TFEB's transcriptional regulation of several pro-longevity pathways, including AMP-activated protein kinase, mTOR, nuclear factor erythroid 2-related factor 2, sirtuins, and PGC-1α, makes it a promising molecular target for neuromodulation of the retinal aging process.

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References

Abokyi S, Shan S wan, To C, Chan HH, Tse DY (2020) Autophagy upregulation by the TFEB inducer trehalose protects against oxidative damage and cell death associated with NRF2 inhibition in human RPE cells. Oxid Med Cell Longev 2020:5296341.

Abokyi S, Ghartey-Kwansah G, Tse DY (2023) TFEB is a central regulator of the aging process and age-related diseases. Ageing Res Rev 89:101985.

Akwa Y, Di Malta C, Zallo F, Gondard E, Lunati A, Diaz-de-Grenu LZ, Zampelli A, Boiret A, Santamaria S, Martinez-Preciado M, Cortese K, Kordower JH, Matute C, Lozano AM, Capetillo-Zarate E, Vaccari T, Settembre C, Baulieu EE, Tampellini D (2023) Stimulation of synaptic activity promotes TFEB-mediated clearance of pathological MAPT/Tau in cellular and mouse models of tauopathies. Autophagy 19:660-677.

Albrecht NE, et al. (2018) Rapid and integrative discovery of retina regulatory molecules. Cell Rep 24:2506-2519.

Almaspour MB, Nasehi M, Khalifeh S, Zarrindast MR (2020) The effect of fish oil on social interaction memory in total sleep-deprived rats with respect to the hippocampal level of stathmin, TFEB, synaptophysin and LAMP-1 proteins. Prostaglandins Leukot Essent Fat Acids 157:102097.

Antonetti DA, Silva PS, Stitt AW (2021) Current understanding of the molecular and cellular pathology of diabetic retinopathy. Nat Rev Endocrinol 17:195-206.

Ballabio A, Bonifacino JS (2020) Lysosomes as dynamic regulators of cell and organismal homeostasis. Nat Rev Mol Cell Biol 21:101-118.

Blitzer AL, Ham SA, Colby KA, Skondra D (2021) Association of metformin use with age-related macular degeneration: a case-control study. JAMA Ophthalmol 139:302-309.

Brown EE, DeWeerd AJ, Ildefonso CJ, Lewin AS, Ash JD (2019) Mitochondrial oxidative stress in the retinal pigment epithelium (RPE) led to metabolic dysfunction in both the RPE and retinal photoreceptors. Redox Biol 24:101201.

Carreras-Sureda A, Pihán P, Hetz C (2018) Calcium signaling at the endoplasmic reticulum: fine-tuning stress responses. Cell Calcium 70:24-31.

Chang LYL, Ardiles AO, Tapia-Rojas C, Araya J, Inestrosa NC, Palacios AG, Acosta ML (2020) Evidence of synaptic and neurochemical remodeling in the retina of aging degus. Front Neurosci 14:161.

Chen J, Mao K, Yu H, Wen Y, She H, Zhang H, Liu L, Li M, Li W, Zou F (2021) p38-TFEB pathways promote microglia activation through inhibiting CMA-mediated NLRP3 degradation in Parkinson's disease. J Neuroinflammation 18:295.

Chen M, Luo C, Zhao J, Devarajan G, Xu H (2019) Immune regulation in the aging retina. Prog Retin Eye Res 69:159-172.

Chen M, Muckersie E, Forrester JV, Xu H (2010a) Immune activation in retinal aging: a gene expression study. Investig Ophthalmol Vis Sci 51:5888-5896.

Chen R, Wang Y, Zhang S, Bulloch G, Zhang J, Liao H, Shang X, Clark M, Peng Q, Ge Z, Cheng C, Gao Y, He M, Zhu Z (2023) Biomarkers of ageing: current state-of-art, challenges, and opportunities. MedComm – Future Med 2:e50.

Chen Y, Wang J, Cai J, Sternberg P (2010b) Altered mTOR signaling in senescent retinal pigment epithelium. Investig Ophthalmol Vis Sci 51:5314-5319.

Chen Z, Ouyang C, Zhang H, Gu Y, Deng Y, Du C, Cui C, Li S, Wang W, Kong W, Chen J, Cai J, Geng B (2022) Vascular smooth muscle cell-derived hydrogen sulfide promotes atherosclerotic plaque stability via TFEB (transcription factor EB)-mediated autophagy. Autophagy 18:2270-2287.

Cheng SY, Cipi J, Ma S, Hafler BP, Kanadia RN, Brush RS, Agbaga MP, Punzo C (2020) Altered photoreceptor metabolism in mouse causes late stage age-related macular degeneration-like pathologies. Proc Natl Acad Sci U S A 117:13094-13104.

Cheng Y, Fan H, Liu K, Liu J, Zou H, You Z (2023) TFEB attenuates hyperglycemia-induced retinal capillary endothelial cells injury via autophagy regulation. Cell Biol Int 47:1092-1105.

Chitranshi N, Dheer Y, Abbasi M, You Y, Graham SL, Gupta V (2018) Glaucoma pathogenesis and neurotrophins: focus on the molecular and genetic basis for therapeutic prospects. Curr Neuropharmacol 16:1018-1035.

Choi EY, Kim M, Lee CS, Byeon SH, Kim SS, Lee M (2022) Intermittent fasting is associated with a decreased risk of age-related macular degeneration. Am J Ophthalmol 243:1-9.

Chrysostomou V, Galic S, van Wijngaarden P, Trounce IA, Steinberg GR, Crowston JG (2016) Exercise reverses age-related vulnerability of the retina to injury by preventing complement-mediated synapse elimination via a BDNF-dependent pathway. Aging Cell 15:1082-1091.

Crabb JW (2014) The proteomics of drusen. Cold Spring Harb Perspect Med 4:a017194.

Cui M, et al. (2024) HKDC1, a target of TFEB, is essential to maintain both mitochondrial and lysosomal homeostasis, preventing cellular senescence. Proc Natl Acad Sci 121:e2306454120 .

Curnock R, Calcagni A, Ballabio A, Cullen PJ (2019) TFEB controls retromer expression in response to nutrient availability. J Cell Biol 218:3954-3966.

Curnock R, Yalci K, Palmfeldt J, Jäättelä M, Liu B, Carroll B (2023) TFEB-dependent lysosome biogenesis is required for senescence. EMBO J 42:e111241.

De Faria JML, Duarte DA, Montemurro C, Papadimitriou A, Consonni SR, De Faria JBL (2016) Defective autophagy in diabetic retinopathy. Investig Ophthalmol Vis Sci 57:4356-4366.

Doronzo G, Astanina E, Corà D, Chiabotto G, Comunanza V, Noghero A, Neri F, Puliafito A, Primo L, Spampanato C, Settembre C, Ballabio A, Camussi G, Oliviero S, Bussolino F (2019) TFEB controls vascular development by regulating the proliferation of endothelial cells. EMBO J 38:e98250.

Eells JT (2019) Mitochondrial dysfunction in the aging retina. Biology (Basel) 8:31.

Fan Y, Lu H, Liang W, Garcia-Barrio MT, Guo Y, Zhang J, Zhu T, Hao Y, Zhang J, Chen YE (2018) Endothelial TFEB (transcription factor EB) positively regulates postischemic angiogenesis. Circ Res 122:945-957.

Filipello F, et al. (2023) Defects in lysosomal function and lipid metabolism in human microglia harboring a TREM2 loss of function mutation. Acta Neuropathol 145:749-772.

Fitzpatrick MJ, Kerschensteiner D (2023) Homeostatic plasticity in the retina. Prog Retin Eye Res 94:101131.

Fu Z, Kern TS, Hellström A, Smith LEH (2021) Fatty acid oxidation and photoreceptor metabolic needs. J Lipid Res 62:100035.

Fu Z, Lundgren P, Pivodic A, Yagi H, Harman JC, Yang J, Ko M, Neilsen K, Talukdar S, Hellström A, Smith LEH (2023) FGF21 via mitochondrial lipid oxidation promotes physiological vascularization in a mouse model of Phase I ROP. Angiogenesis 26:409-421.

Galloway CA, Dalvi S, Hung SSC, MacDonald LA, Latchney LR, Wong RCB, Guymer RH, Mackey DA, Williams DS, Chung MM, Gamm DM, Pébay A, Hewitt AW, Singh R (2017) Drusen in patient-derived hiPSC-RPE models of macular dystrophies. Proc Natl Acad Sci 114:E8214-8223.

GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study (2021) Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the right to sight: an analysis for the Global Burden of Disease Study. Lancet Glob Health 9:e144-160.

Gorostieta-Salas E, Moreno-Blas D, Gerónimo-Olvera C, Cisneros B, Court FA, Castro-Obregón S (2021) Enhanced activity of exportin-1/CRM1 in neurons contributes to autophagy dysfunction and senescent features in old mouse brain. Oxid Med Cell Longev 2021:6682336.

Grosso Jasutkar H, Yamamoto A (2023) Autophagy at the synapse, an early site of dysfunction in neurodegeneration. Curr Opin Physiol 32:100631.

Guo C, Xu Y, Ma Y, Xu X, Peng F, Li H, Jin D, Zhao S, Xia Z, Lai M, Che M, Huang R, Wang Y, Jiang D, Zheng C, Mao G (2022) Individual and joint effects of trehalose and glutamate on diabetic retinopathy: a propensity score-matched case–control study. Endocr Connect 11:e210474.

Guo X, Kimura A, Azuchi Y, Akiyama G, Noro T, Harada C, Namekata K, Harada T (2016) Caloric restriction promotes cell survival in a mouse model of normal tension glaucoma. Sci Rep 6:33950.

Heckel E, et al. (2022) Triglyceride-derived fatty acids reduce autophagy in a model of retinal angiomatous proliferation. JCI Insight 7:e154174.

Huang Y, Chen Y, Shaw AM, Goldfine H, Tian J, Cai J (2018) Enhancing TFEB-mediated cellular degradation pathways by the mTORC1 inhibitor quercetin. Oxid Med Cell Longev 2018:5073420.

Inana G, Murat C, An W, Yao X, Harris IR, Cao J (2018) RPE phagocytic function declines in age-related macular degeneration and is rescued by human umbilical tissue derived cells. J Transl Med 16:63.

Ivankovic D, Chau KY, Schapira AHV, Gegg ME (2016) Mitochondrial and lysosomal biogenesis are activated following PINK1/parkin-mediated mitophagy. J Neurochem 136:388-402.

Jaroszynska N, Harding P, Moosajee M (2021) Metabolism in the zebrafish retina. J Dev Biol 9:10.

Jiménez-Loygorri JI, Benítez-Fernández R, Viedma-Poyatos Á, Zapata-Muñoz J, Villarejo-Zori B, Gómez-Sintes R, Boya P (2023) Mitophagy in the retina: viewing mitochondrial homeostasis through a new lens. Prog Retin Eye Res 96:101205.

Jin X, Liu J, Wang W, Li J, Liu G, Qiu R, Yang M, Liu M, Yang L, Du X, Lei B (2022) Identification of age-associated proteins and functional alterations in human retinal pigment epithelium. Genomics Proteomics Bioinformatics 20:633-647.

Joshi V, Upadhyay A, Prajapati VK, Mishra A (2020) How autophagy can restore proteostasis defects in multiple diseases? Med Res Rev 40:1385-1439.

Jurk D, Wang C, Miwa S, Maddick M, Korolchuk V, Tsolou A, Gonos ES, Thrasivoulou C, Jill Saffrey M, Cameron K, von Zglinicki T (2012) Postmitotic neurons develop a p21-dependent senescence-like phenotype driven by a DNA damage response. Aging Cell 11:996-1004.

Karlen SJ, Miller EB, Burns ME (2020) Microglia activation and inflammation during the death of mammalian photoreceptors. Annu Rev Vis Sci 6:149-169.

Karunadharma PP, Kapphahn RJ, Stahl MR, Olsen TW, Ferrington DA (2022) Dissecting regulators of aging and age-related macular degeneration in the retinal pigment epithelium. Oxid Med Cell Longev 2022:6009787.

Keay L, Ren K, Nguyen H, Vajdic C, Odutola M, Gyawali R, Toomey M, Peters R, Ee N, Dillon L, Hackett M, Ah Tong B, D'Esposito F, Faulmann D, Burton M, Ramke J, Jalbert I (2022) Risk factors common to leading eye health conditions and major non-communicable diseases: a rapid review and commentary. F1000Research 11:1289.

Lakkaraju A, Umapathy A, Tan LX, Daniele L, Philp NJ, Boesze-Battaglia K, Williams DS (2020) The cell biology of the retinal pigment epithelium. Prog Retin Eye Res 78:100846.

Lee KS, Lin S, Copland DA, Dick AD, Liu J (2021) Cellular senescence in the aging retina and developments of senotherapies for age-related macular degeneration. J Neuroinflammation 18:32.

Li Y, Wolf NS (1997) Effects of age and long-term caloric restriction on the aqueous collecting channel in the mouse eye. J Glaucoma 6:18-22.

Liang KH, Chen CH, Tsai HR, Chang CY, Chen TL, Hsu WC (2022) Association between oral metformin use and the development of age-related macular degeneration in diabetic patients: a systematic review and meta-analysis. Investig Opthalmology Vis Sci 63:10.

Liu B, McNally S, Kilpatrick JI, Jarvis SP, O'Brien CJ (2018) Aging and ocular tissue stiffness in glaucoma. Surv Ophthalmol 63:56-74.

López-Luppo M, Catita J, Ramos D, Navarro M, Carretero A, Mendes-Jorge L, Muñoz-Cánoves P, Rodriguez-Baeza A, Nacher V, Ruberte J (2017) Cellular senescence is associated with human retinal microaneurysm formation during aging. Investig Ophthalmol Vis Sci 58:2832-2842.

Lu H, Fan Y, Qiao C, Liang W, Hu W, Zhu T, Zhang J, Chen YE (2017) TFEB inhibits endothelial cell inflammation and reduces atherosclerosis. Sci Signal 10:eaah4214.

Luo H, Zhou M, Ji K, Zhuang J, Dang W, Fu S, Sun T, Zhang X (2017) Expression of sirtuins in the retinal neurons of mice, rats, and humans. Front Aging Neurosci 9:366.

Mansueto G, et al. (2017) Transcription factor EB controls metabolic flexibility during exercise. Cell Metab 25:182-196.

McWilliams TG, Prescott AR, Villarejo-Zori B, Ball G, Boya P, Ganley IG (2019) A comparative map of macroautophagy and mitophagy in the vertebrate eye. Autophagy 15:1296-1308.

Nag TC, Maurya M, Roy TS (2019) Age-related changes of the human retinal vessels: Possible involvement of lipid peroxidation. Ann Anat 226:35-47.

O'Leary F, Campbell M (2023) The blood–retina barrier in health and disease. FEBS J 290:878-891.

Palmieri M, Pal R, Nelvagal HR, Lotfi P, Stinnett GR, Seymour ML, Chaudhury A, Bajaj L, Bondar VV, Bremner L, Saleem U, Tse DY, Sanagasetti D, Wu SM, Neilson JR, Pereira FA, Pautler RG, Rodney GG, Cooper JD, Sardiello M (2017) mTORC1-independent TFEB activation via Akt inhibition promotes cellular clearance in neurodegenerative storage diseases. Nat Commun 8:14338.

Park SH, Cho H, Hwang SJ, Jeon B, Seong M, Yeom H, Kang MH, Lim HW, Shin YU (2020) Changes in the retinal microvasculature measured using optical coherence tomography angiography according to age. J Clin Med 9:7-18.

Pasquier A, Pastore N, D'Orsi L, Colonna R, Esposito A, Maffia V, De Cegli R, Mutarelli M, Ambrosio S, Tufano G, Grimaldi A, Cesana M, Cacchiarelli D, Delalleau N, Napolitano G, Ballabio A (2023) TFEB and TFE3 control glucose homeostasis by regulating insulin gene expression. EMBO J 42:e113928.

Porter K, Hirt J, Stamer WD, Liton PB (2015) Autophagic dysregulation in glaucomatous trabecular meshwork cells. Biochim Biophys Acta- Mol Basis Dis 1852:379-385.

Reddy Addi U, Jakhotia S, Reddy SS, Reddy GB (2022) Age-related neuronal damage by advanced glycation end products through altered proteostasis. Chem Biol Interact 355:109840.

Russo R, Nucci C, Adornetto A (2022) The promise of neuroprotection by dietary restriction in glaucoma. Neural Regen Res 17:45-47.

Samuel MA, Zhang Y, Meister M, Sanes JR (2011) Age-related alterations in neurons of the mouse retina. J Neurosci 31:16033-16044.

Sánchez-Vidaña DI, Li J, Abokyi S, Chan JNM, Ngai SPC, Lau BWM (2023) In vitro methods in autophagy research: applications in neurodegenerative diseases and mood disorders. Front Mol Neurosci 16:1168948.

Sanuki R, Watanabe S, Sugita Y, Irie S, Kozuka T, Shimada M, Ueno S, Usukura J, Furukawa T (2015) Protein-4.1G-mediated membrane trafficking is essential for correct rod synaptic location in the retina and for normal visual function. Cell Rep 10:796-808.

Sbano L, Bonora M, Marchi S, Baldassari F, Medina DL, Ballabio A, Giorgi C, Pinton P (2017) TFEB-mediated increase in peripheral lysosomes regulates store-operated calcium entry. Sci Rep 7:40797.

Schalkwijk CG, Micali LR, Wouters K (2023) Advanced glycation endproducts in diabetes-related macrovascular complications: focus on methylglyoxal. Trends Endocrinol Metab 34:49-60.

Shi Q, Chang C, Saliba A, Bhat MA (2022) Microglial mTOR activation upregulates Trem2 and enhances b-amyloid plaque clearance in the 5XFAD Alzheimer's disease model. J Neurosci 42:5294-5313.

Song W, Zhang CL, Gou L, He L, Gong YY, Qu D, Zhao L, Jin N, Chan TF, Wang L, Tian XY, Luo JY, Huang Y (2019) Endothelial TFEB (transcription factor EB) restrains IKK (IκB kinase)-p65 pathway to attenuate vascular inflammation in diabetic db/db Mice. Arterioscler Thromb Vasc Biol 39:719-730.

Sugita Y, Yamamoto H, Maeda Y, Furukawa T (2020) Influence of aging on the retina and visual motion processing for optokinetic responses in mice. Front Neurosci 14:586013.

Tan LX, Germer CJ, Thamban T, La Cunza N, Lakkaraju A (2023) Optineurin tunes outside-in signaling to regulate lysosome biogenesis and phagocytic clearance in the retina. Curr Biol 33:3805-3820.

Taylor TRP, Menten MJ, Rueckert D, Sivaprasad S, Lotery AJ (2023) The role of the retinal vasculature in age-related macular degeneration: a spotlight on OCTA. Eye 38:442-449.

Tong Y, Zhang Z, Wang S (2022) Role of mitochondria in retinal pigment epithelial aging and degeneration. Front Aging 3:926627.

Tribble JR, Hui F, Jöe M, Bell K, Chrysostomou V, Crowston JG, Williams PA (2021) Targeting diet and exercise for neuroprotection and neurorecovery in glaucoma. Cells 10:295.

Tribble JR, Hui F, Quintero H, El Hajji S, Bell K, Di Polo A, Williams PA (2023) Neuroprotection in glaucoma: mechanisms beyond intraocular pressure lowering. Mol Aspects Med 92:101193.

Vahabikashi A, Gelman A, Dong B, Gong L, Cha EDK, Schimmel M, Tamm ER, Perkumas K, Stamer WD, Sun C, Zhang HF, Gong H, Johnson M (2019) Increased stiffness and flow resistance of the inner wall of Schlemm's canal in glaucomatous human eyes. Proc Natl Acad Sci U S A 116:26555-26563.

Viegas FO, Neuhauss SCF (2021) A metabolic landscape for maintaining retina integrity and function. Front Mol Neurosci 14:656000.

Villarejo-Zori B, Jiménez-Loygorri JI, Zapata-Muñoz J, Bell K, Boya P (2021) New insights into the role of autophagy in retinal and eye diseases. Mol Aspects Med 82:101038.

Wallsh JO, Gallemore RP (2021) Anti-vegf-resistant retinal diseases: a review of the latest treatment options. Cells 10:1049.

Wang H, Muthu Karuppan MK, Devadoss D, Nair M, Chand HS, Lakshmana MK (2021) TFEB protein expression is reduced in aged brains and its overexpression mitigates senescence-associated biomarkers and memory deficits in mice. Neurobiol Aging 106:26-36.

Wang Y, Lin J, Li J, Yan L, Li W, He X, Ma H (2023) Chronic neuronal inactivity utilizes the mTOR-TFEB pathway to drive transcription-dependent autophagy for homeostatic up-scaling. J Neurosci 43:2631-2652.

Wei Y, Jiang H, Shi Y, Qu D, Gregori G, Zheng F, Rundek T, Wang J (2017) Age-related alterations in the retinal microvasculature, microcirculation, and microstructure. Investig Ophthalmol Vis Sci 58:3804-3817.

Williams PA, Piechota M, von Ruhland C, Taylor E, Morgan JE, Votruba M (2012) Opa1 is essential for retinal ganglion cell synaptic architecture and connectivity. Brain 135:493-505.

Xu J, Chen LJ, Yu J, Wang HJ, Zhang F, Liu Q, Wu J (2018) Involvement of advanced glycation end products in the pathogenesis of diabetic retinopathy. Cell Physiol Biochem 48:705-717.

Xu Y, Du S, Marsh JA, Horie K, Sato C, Ballabio A, Karch CM, Holtzman DM, Zheng H (2021) TFEB regulates lysosomal exocytosis of tau and its loss of function exacerbates tau pathology and spreading. Mol Psychiatry 26:5925-5939.

Yan X, Han X, Wu C, Shang X, Zhang L, He M (2021) Effect of physical activity on reducing the risk of diabetic retinopathy progression: 10-year prospective findings from the 45 and up study. PLoS One 16:e0239214.

Zhang C, Zhou L, Li S, Zhao J, Meng X, Ma L, Wang Y, Li C, Zheng L, Ming L (2022) Obesity accelerates immune evasion of non-small cell lung carcinoma via TFEB-dependent upregulation of Siglec-15 and glycolytic reprogramming. Cancer Lett 550:215918.

Zhang L, Zhao J, Mu X, McGowan SJ, Angelini L, O'Kelly RD, Yousefzadeh MJ, Sakamoto A, Aversa Z, LeBrasseur NK, Suh Y, Huard J, Kamenecka TM, Niedernhofer LJ, Robbins PD (2021) Novel small molecule inhibition of IKK/NF-κB activation reduces markers of senescence and improves healthspan in mouse models of aging. Aging Cell 20:e13486.

Zhao B, Zhu L, Ye M, Lou X, Mou Q, Hu Y, Zhang H, Zhao Y (2023) Oxidative stress and epigenetics in ocular vascular aging: an updated review. Mol Med 29:28.

Zhao L, Zhang CL, He L, Chen Q, Liu L, Kang L, Liu J, Luo JY, Gou L, Qu D, Song W, Lau CW, Ko H, Mok VCT, Tian XY, Wang L, Huang Y (2022) Restoration of autophagic flux improves endothelial function in diabetes through lowering mitochondrial ROS-mediated eNOS monomerization. Diabetes 71:1099-1114.

Zhu JD, Tarachand SP, Abdulwahab Q, Samuel MA (2023a) Structure, function, and molecular landscapes of the aging retina. Annu Rev Vis Sci 9:177-199.

Zhu Y, Zhang Y, Fan Z, Fang Y, Zheng Y, Li Y, Yang M, Guo C, Li Y, Zhou X, Sun Z, Wang J (2023b) Silica nanoparticles trigger chaperone HSPB8-assisted selective autophagy via TFEB activation in hepatocytes. Small 19:e2204310.

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