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The endoplasmic reticulum: Homeostasis and crosstalk in retinal health and disease

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Abstract

The endoplasmic reticulum (ER) is the largest intracellular organelle carrying out a broad range of important cellular functions including protein biosynthesis, folding, and trafficking, lipid and sterol biosynthesis, carbohydrate metabolism, and calcium storage and gated release. In addition, the ER makes close contact with multiple intracellular organelles such as mitochondria and the plasma membrane to actively regulate the biogenesis, remodeling, and function of these organelles. Therefore, maintaining a homeostatic and functional ER is critical for the survival and function of cells. This vital process is implemented through well-orchestrated signaling pathways of the unfolded protein response (UPR). The UPR is activated when misfolded or unfolded proteins accumulate in the ER, a condition known as ER stress, and functions to restore ER

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homeostasis thus promoting cell survival. However, prolonged activation or dysregulation of the UPR can lead to cell death and other detrimental events such as inflammation and oxidative stress; these processes are implicated in the pathogenesis of many human diseases including retinal disorders. In this review manuscript, we discuss the unique features of the ER and ER stress signaling in the retina and retinal neurons and describe recent advances in the research to uncover the role of ER stress signaling in neurodegenerative retinal diseases including age-related macular degeneration, inherited retinal degeneration, achromatopsia and cone diseases, and diabetic retinopathy. In some chapters, we highlight the complex interactions between the ER and other intracellular organelles focusing on mitochondria and illustrate how ER stress signaling regulates common cellular stress pathways such as autophagy. We also touch upon the integrated stress response in retinal degeneration and diabetic retinopathy. Finally, we provide an update on the current development of pharmacological agents targeting the UPR response and discuss some unresolved questions and knowledge gaps to be addressed by future research.

Keywords

Endoplasmic reticulum; Protein homeostasis; Unfolded protein response; Integrated stress response; Autophagy; Mitochondria; Retina; Retinal degeneration; Diabetic retinopathy

1. Introduction

Seeing is believing. To the majority of people, vision is the foremost valued sense among others: auditory (hearing), olfactory (smell), tactile/haptic (touch), and gustatory (taste). Coincidently, vision is the most extensively studied sensory modality, in part due to the great complexity of the biological system responsible for generating and processing visual information in the eye and the brain (Hutmacher, 2019). Yet, many fundamental questions in the formation and regulation of visual signaling and the mechanisms of vision-threatening human diseases are far from being fully understood. The initial steps of the generation of vision are carried out in the retina, a thin sensory neural tissue located in the back of the eye. The retina consists of five major types of neurons, including photoreceptors, bipolar cells, amacrine cells, horizontal cells, and retinal ganglion cells (RGCs), which can be further divided into over 100 subtypes (West et al., 2022). Photoreceptor cells are the primary neuronal types that receive and convert light into an electrical signal, which is sequentially transmitted to the interneurons (e.g. bipolar cells) and RGCs. RGCs are the final output neurons of the retina, whose axons form the optic nerve that physically connects the eye to the brain and conveys the visual signals to the visual cortex for final processing. In vertebrates, the retina and the optic nerve originate as outgrowths of the developing brain (Amini et al., 2018). As such, the retina is considered an extension of the brain responsible for the generation of the visual signal and is a bona fide part of the central nervous system (CNS).

Apart from neurons, the retina contains large numbers of glial cells, including Müller cells, astrocytes, and microglia. These cells, like in other tissues of the CNS, have important functions including providing anatomical and functional support to the neural retina, producing neurotrophic factors and other cytokines, and closely interacting with

retinal neurons in response to environmental stresses and injuries (Fletcher et al., 2008). In addition, the retina is supplied by dual vascular systems derived from the central retinal artery and choroidal blood vessels, which efficiently deliver nutrients and oxygen to the inner and outer retinal tissue, respectively. The outer retina, consisting of cell bodies, inner segments (IS), and outer segments (OS) of photoreceptors, is an avascular zone. Photoreceptor cells obtain glucose and oxygen diffused from the choriocapillaris through the retinal pigment epithelium (RPE), a single layer of hexagonal epithelial cells lying between photoreceptors and the choroid. RPE cells are essential for the maintenance of neural retinal structure and function through many multiple activities, including diurnal phagocytosis of the aged and damaged photoreceptor OS, participating in a visual cycle that is important for vision formation, and acting as an integral part of the ecosystem for retinal metabolism (Hurley, 2021). They also form the outer blood-retinal barrier (BRB), which, together with the inner BRB formed by retinal endothelial cells, provides a stable microenvironment for retinal neurons (Simó et al., 2010). Dysfunction and loss of the RPE can lead to photoreceptor cell death and degeneration and consequently, vision impairment.

Proteins are the fundamental building blocks of all complex organisms and are involved in almost every aspect of biological processes. Maintaining a healthy and homeostatic proteome is critical for neuronal survival and function. In addition, the retina has several unique features that require a higher level of protein synthesis and quality control than any other CNS counterparts. For example, photoreceptor cells, which are the most abundant retinal neurons, have a very high protein turnover rate to maintain the phototransduction machinery (Pearring et al., 2013). Other processes, including the formation and remodeling of neural synapses, production and release of neural transmitters, and regulation of signaling pathways to adapt to environmental and metabolic changes in the retina, all involve a large variety of proteins with distinct structures and functions. The highly complex nature of the retinal neuronal networks and the tightly controlled interactions between retinal neurons and their supporting systems – the RPE, glial cells, and vascular cells, further renders the retina susceptible to perturbations in protein homeostasis. Disruption of protein homeostasis results in increased ER stress and activation of the ER stress signaling (Kaufman, 1999). In this review, we will summarize the recent progress on the role of ER homeostasis in maintaining retinal neuronal survival and function and discuss the implication of ER stress signaling in the pathogenesis of a broad range of retinal diseases including inherited retinal degeneration (IRD), achromatopsia, age-related macular degeneration (AMD), and diabetic retinopathy (DR). We will highlight how the ER interacts with other intracellular organelles such as mitochondria and how ER stress signaling crosstalk with other stress response pathways such as autophagy. We will discuss the implication of integrated stress response (ISR), an important cellular response pathway activated by a variety of stress conditions targeting protein synthesis, in retinal diseases. Finally, we will review the current development of pharmacological agents targeting ER stress signaling and discuss the needs of future research to tackle some of the unresolved questions for improving our understanding of ER stress signaling in retinal health and disease.

2. Structure and function of the ER in the retina and retinal neurons

The endoplasmic reticulum (ER) is a large, membrane-bound organelle responsible for a diverse range of important functions including the biosynthesis, folding, quality control, and trafficking of membrane proteins and secretory proteins, lipid and steroid biosynthesis, and carbohydrate metabolism, and intracellular calcium storage and gated release (Schwarz and Blower, 2016). Although the ER was among many other intracellular organelles first identified by light microscopy in the late 19th century, the term of ER was not given until the 1950s following the discovery of the ER ultrastructure – a “lace-like” structure in the perinuclear region of the cytoplasm under electron microscope [reviewed in (Sree et al., 2021)]. As the largest endomembrane system, the ER comprises about 10% of the total cell volume with its membrane comprising about half of the total membrane in a eukaryotic cell (Voeltz et al., 2002). The structure and morphology of the ER are highly heterogeneous forming specific domains to carry out distinct functions. The flat sheet-like rough ER with the presence of ribosomes attached to the outer membrane that gives rise to a studded appearance is the major compartment for protein biosynthesis, protein folding, and post-translational modifications, such as disulfide bond formation and N-linked glycosylation. The smooth ER, on the other hand, is tubular and primarily responsible for sterol biosynthesis, lipid droplet formation, carbohydrate metabolism, detoxification, and intracellular calcium storage. The distribution and content of the ER and the ratio between the rough and smooth ER vary significantly across cell types associated with their specialized functions. For example, secretory cells such as pancreatic acinar cells possess abundant stacks of sheet-like rough ER while hepatocytes have a large smooth ER network responsible for carbohydrate/lipid metabolism and waste detoxification (Goyal and Blackstone, 2013). Recent research taking advantage of live-cell microscopy and *in situ* cryo-electron tomography identified specialized ER subdomains, namely ribosome-associated vesicles (RAV), a dynamic sub-compartment of the rough ER in cultured cells across various cell types including secretory cells, fibroblasts, endothelial cells, and neural cells, and in neurons of human brain tissue (Carter et al., 2020; Ning et al., 2023). The formation of RAV is believed to be associated with an increased demand of protein synthesis in secretory cells and local translation in the dendrites of developing neurons to meet the protein requirement for synaptic plasticity and remodeling (Carter et al., 2020). In addition, RAVs were found to directly contact with the mitochondria, suggesting that these newly identified rough ER sub-compartments may participate in the regulation of calcium signaling and mitochondrial function (Carter et al., 2020).

In neurons, the ER has unique morphological features to befit the structural and functional requirement to fulfill the neural activity (Sree et al., 2021). While the ER exists in all compartments of a neuron, the morphology and size of ER sheets and tubules are substantially different in the area of cell body or soma, dendrites, and axons. In neuronal soma, the ER consists of predominantly highly packed rough ER sheets, which were initially identified as Nissl bodies or Nissl substance (Palay and Palade 1955). The fission or fragmentation of the Nissl substance, also known as chromatolysis, which indicates the disruption of the protein machinery, can lead to apoptosis and demyelination in neurons with axonal injury and is observed in motor neurons in amyotrophic lateral sclerosis

patients (Sree et al., 2021). In addition, the ER makes extensive contact with the plasma membrane in the neuronal soma and this contact is reduced following excitation (Sree et al., 2021). In dendrites, the proximal somato-dendritic regions are enriched in rough ER. The distal dendritic regions and dendritic spines, which are tiny protrusions that form functional contacts with the axons of neighboring neurons, contain predominantly tubular ER. Similarly, the ER in neuronal axons is mostly tubular with intermittent small cisternae in the synaptic varicosities. The narrow ER tubules run parallel along the axon and form physical contact with several organelles including the mitochondria and microtubules, possibly contributing to the transportation of organelles in the axon elongation (Fig. 1) (Khan, 2022; Sree et al., 2021). Mutations of genes that are involved in the regulation of axonal ER morphology and/or the dynamics of ER membrane contacts with other organelles can lead to dysregulated calcium homeostasis and mitochondrial dysfunction contributing to axonal degeneration in several human diseases including hereditary spastic paraplegia (HSP) (Öztürk et al., 2020).

In retinal neurons, the ER is most well characterized in the photoreceptors (Križaj, 2012; Mercurio and Holtzman, 1982). As discussed earlier, photoreceptors are highly compartmentalized cells consisting of elongated OS, connecting cilium, IS, cell body, and synaptic terminal. OS is a highly special structure consisting of tightly stacked membrane discs for phototransduction and does not contain an ER network. The IS enriched in rough ER sacs, where proteins, such as rhodopsin, are synthesized and transported through the connecting cilium to the OS discs (Mercurio and Holtzman, 1982). Photoreceptors also contain abundant smooth ER tubules, which continuously span the IS and cell body and extend into the synaptic terminal (Fig. 1). The smooth ER plays a critical role in the regulation of photoreceptor function, in particular controlling the amplitude, response speed, and sensitivity of photoreceptor signals in synaptic transmission (Križaj, 2012; Suryanarayanan and Slaughter, 2006). In addition, the ER in the synaptic terminal may also contribute to local protein synthesis for establishing and modulating the synaptic proteome and neurotransmitter production. Similar extensive distributions of the ER in other types of retinal neurons have been reported, although the specific features of the ER in individual neuronal cell types are sparsely studied. Using subretinal injection and electroporation of Emerald-Sec61β under control of the mGluR6 promoter that specifically labels the ER in ON-Bipolar cells, Agosto et al. demonstrated that the ER network is distributed throughout the cell body and extends into axons and dendrites, but not in the dendritic tips of bipolar cells (Agosto et al., 2018). In cultured *Xenopus laevis* RGCs, the axonal ER is undergoing dynamic remodeling through lysosome-driven ER tubule elongation that supports axonal growth (Lu et al., 2020). Disruption of ER-lysosome contacts leads to ER fragmentation and axon growth defects, suggesting a potentially important role of targeting ER dynamics in axonal regeneration for the treatment of neurodegenerative disease.

3. The unfolded protein response (UPR)

Given the important functions of the ER involved in governing protein, lipid, and carbohydrate biosynthesis and metabolism and intracellular calcium signaling, disturbance of the homeostatic status of the ER environment is detrimental to cell survival and function. Perturbation of ER homeostasis results in an accumulation of unfolded proteins or misfolded

proteins in the ER lumen, a condition known as ER stress. ER stress can be induced by genetic factors that impair protein glyco-sylation or protein folding and environmental factors such as aging, oxidative stress or hypoxia, glucose deprivation or hyperglycemia, calcium dysregulation, and disturbed autophagy in retinal cells [reviewed in (Chen et al., 2023; McLaughlin et al., 2022)]. To eliminate the misfolded or unfolded proteins, cells activate a sophisticated adaptive mechanism namely the unfolded protein response (UPR) via three trans-ER-membrane proteins: inositol-requiring protein-1 (IRE1), protein kinase RNA- (PKR-) like endoplasmic reticulum kinase (PERK), and activating transcription factor-6 (ATF6). The activation of these ER stress-sensing proteins appears to be controlled in a temporal manner eliciting a well-programmed cellular response to eliminate or adapt to ER stress and also allow the functional recovery of the ER. Failure of the UPR in restoring the ER homeostasis can lead to cell death and dysfunction contributing to the development of human diseases.

3.1. The IRE1 pathway

The IRE1 pathway is the most conserved UPR branch existing from yeast to humans. There are two isoforms of IRE 1 proteins, namely IRE1α and IRE1β, encoded by ERN1 and ERN2 in humans, respectively. IRE1α is the most abundant isoform expressed in all types of cells and tissues whereas the expression of IRE1β is restricted to epithelial cells in the gastrointestinal and respiratory tracts (Bertolotti et al., 2001; Iwawaki et al., 2009). Structurally, IRE1 consists of an N-terminal luminal domain, which acts as an ER stress sensor, a transmembrane domain, and a cytoplasmic domain that contains regions possessing protein kinase function and endoribonuclease function [reviewed in (Siwecka et al., 2021)]. A simplified process of activation of the IRE1/XBP1 pathway is illustrated in Fig. 2. In resting cells, IRE1 is kept inactive by binding to GRP78 which maintains IRE1 in a monomeric state. Upon ER stress, GRP78 dissociates from IRE1 and binds to misfolded proteins facilitating their refolding. The dissociation allows IRE1 dimerization or oligomerization in cells, which brings the cytoplasmic kinase domains in close proximity in a face-to-face orientation that stimulates autophosphorylation (Prischi et al., 2014). The autophosphorylation then triggers conformational changes that activate the endoribonuclease domain of the enzyme (Li et al., 2010). The activated endoribonuclease domain initiates an unconventional splicing process that converts the mRNA of unspliced X-box binding protein 1 (XBP1u) into the mRNA of spliced XBP1 (XBP1s) (Yoshida et al., 2001a). This process is so-called unconventional splicing because it occurs in the cytoplasm as opposed to the “conventional nuclear splicing” and does not require *de novo* synthesis of the protein to be spliced (Uemura et al., 2009). It is important to note that the activation of the RNase domain and the kinase domain can occur independently. Complete activation of the RNase function requires a dimerization/oligomerization-dependent intermolecular autophosphorylation (Siwecka et al., 2021). Preventing dimerization/oligomerization or phosphorylation can lead to an inhibition of IRE1-mediated UPR activation.

The splicing product, XBP1s, encodes a transcription factor that regulates a large array of UPR-related genes, including ER chaperones such as BiP, p58IPK, ERdj4, PDI-P5, and HEDJ, genes responsible for ER-associated degradation (ERAD) machinery such as HRD1, EDEM, Derlin-2, and Derlin-3, and genes encoding proteins involved in lipid synthesis and

ER biogenesis (Lee et al., 2003; Sriburi et al., 2004). Ablation of XBP1 in pancreatic β cells, hepatocytes, and antibody-producing plasma cells results in a loss of their secretory functions, suggesting an essential role of XBP1 in secretory cells (Gass et al., 2004). The unspliced XBP1, on the other hand, is believed not to act as a transcription factor because it lacks a transcription activation domain (Iwakoshi et al., 2003). However, recent studies identified that XBP1u also possesses several important functions in regulation of the UPR, autophagy, and other cellular processes. For example, XBP1u negatively regulates the UPR by targeting XBP1s and activated ATF6 for proteasomal degradation (Chen et al., 2014b; Yoshida et al., 2009). It also binds to other proteins such as β-catenin and FoxO4 (Forkhead box protein O 4) in vascular cells and inhibits aneurysm formation and vascular calcification (Yang et al., 2022; Zhao et al., 2017). Interestingly, a recent study shows that expression of XBP1u, but not XBP1s, increases the Gal4-CREB reporter activity and rate-limiting gluconeogenic gene expression in cultured hepatocytes, suggesting a novel role of XBP1u in the regulation of gluconeogenesis in the liver (Peng et al., 2022a).

Although XBP1 mRNA is the foremost studied substrate of IRE's RNase activity, IRE1 also takes advantage of this mechanism to remove selected mRNAs and micro-RNAs, a process known as regulated IRE1-dependent decay of mRNA (RIDD) [reviewed in (Maurel et al., 2014)]. Most RIDD-targeted mRNAs contain XBP1u-like stem-loop endomotifs that can be cleaved by IRE1. Intriguingly, recent research identified that in ER-stressed cells IRE1α can also remove mRNAs that do not harbor canonical endomotifs; this process was named "RIDD lacking endomotif (RIDDLE)" (Le Thomas et al., 2021). Functionally, RIDD can promote ER homeostasis and cell survival. For example, RIDD activity is increased during ER stress to partially deplete mRNAs for protein translation thus reducing the client protein load of the ER. It can also induce apoptosis and cell death when being constitutively activated by a sustained ER stress (Maurel et al., 2014). In addition to regulation of ER stress-related cell fate, RIDD and RIDDLE also target genes involved in other important cellular functions. For example, DGAT2 mRNA, encoding the rate-limiting enzyme in TAG biosynthesis, can be cleaved by IRE1. Inhibition of IRE1α results in DGAT2-dependent accumulation of TAGs in lipid droplets and sensitizes cells to nutritional stress (Almanza et al., 2022). In addition, several mRNAs including IRF4, PRDM1, IKZF1, KLF13, NOTCH1, ATR, DICER, RICTOR, CDK12, FAM168B, and CENPF were identified as potential RIDD targets, contributing to cell survival and proliferation in myeloma cells (Quwaider et al., 2022). In Drosophila retina, mutation of IRE1 increases the levels of RIDD-targeting mRNAs in photoreceptors, resulting in XBP1-independent defects in rhodopsin-1 protein delivery and rhabdomere morphogenesis (Coelho et al., 2013). The implications of RIDD in mouse and human photoreceptors and other retinal neurons have not been thoroughly studied.

3.2. The PERK pathway

The PERK branch of the UPR is an enzymatic signaling cascade aimed at maintaining homeostatic conditions through regulation of the cellular response to stress (Liu et al., 2000). PERK, one of four eukaryotic translation initiation factor 2 alpha (eIF2α) kinases in mammals (Taniuchi et al., 2016), is the canonical regulator of protein synthesis in response to stresses of the ER, specifically in the form of the UPR (Bertolotti et al., 2000; Liu et

al., 2000; Walter and Ron, 2011). At the onset of ER stress, PERK phosphorylates eIF2α to diminish protein synthesis rates (Bertolotti et al., 2000; Ma et al., 2002; Taniuchi et al., 2016). Not only does PERK phosphorylate its namesake translation factor, eIF2α, but, as will be covered in detail, its activity also results in the downstream activation of altered translational and transcriptional programs (Fig. 3) (Jiang and Wek, 2005).

Canonically, PERK is held inactive by the interaction of its ER luminal domain with GRP78 (Bertolotti et al., 2000; Kopp et al., 2019; Walter and Ron, 2011). Upon GRP78's dissociation from PERK due to the preferential binding of GRP78 to hydrophobic residues of misfolded proteins, PERK dimerizes to form an active homodimer (Kopp et al., 2019; Wang et al., 2018). Following dimerization, PERK becomes activated by phosphorylation at Thr 980 b y autophosphorylation, meaning PERK enzymes phosphorylate each other (Ma et al., 2002; Sood et al., 2000). PERK is also known as eukaryotic translation initiation factor 2-alpha kinase 3 (EIF2AK3), named after its first described role in the phosphorylation of the α-subunit of the eIF2α complex. An active PERK (p-Thr 980) phosphorylates eIF2α at Ser 51 (Gorbatyuk et al., 2020; Sood et al., 2000), a post-translational modification that alters eIF2's interaction with eIF2B (Kashiwagi et al., 2017; Sudhakar et al., 1999, 2000). The eIF2 complex consists of α, β, and γ subunits, each with distinct roles. The role of eIF2 in translation initiation involves the complex bringing methionine-tRNA (Met-tRNA), the initiator tRNA, to a start codon on a messenger ribonucleic acid (mRNA) in a process dependent on guanosine triphosphate (GTP) being bound to the γ-subunit (Walton and Gill, 1975). eIF2, Met-tRNA, and GTP- called the ternary complex (TC)-converge on the 40 S ribosomal subunit with other translation initiation factors, or eIFs, to form the 43 S pre-initiation complex (PIC) [reviewed extensively in (Hinnebusch et al., 2016; Sonenberg and Hinnebusch, 2009)]. The PIC then scans the mRNA until a start codon is located. When this initiator codon is recognized and bound by the anti-codon on the Met-tRNA, GTP is hydrolyzed by eIF2 and the now inactive ternary complex, is released from the PIC and therefore, must be reactivated before it can participate in another round of protein synthesis. For this to occur, GDP must be exchanged by eIF2B, the nucleotide exchange factor for eIF2. EIF2B binds eIF2β in order to exchange GDP for GTP on eIF2γ (Alone and Dever, 2006; Kimball et al., 1998). Once the exchange occurs, eIF2 can once again participate in translation. However, stress induced eIF2α phosphorylation prevents canonical translation initiation resulting from the failed guanine nucleotide exchange between eIF2 and eIF2B. This is probably due to eIF2B having a higher affinity for p-eIF2α (S51) than it does for eIF2β; therefore, a normally transient complex between eIF2B and eIF2β instead becomes a stable inhibitory complex of eIF2B and p-eIF2α (Gross et al., 1987; Sudhakar et al., 1999). This is thought to result in eIF2B proteins, which are rate-limiting components of TC formation, becoming trapped and preventing traditional translation. When general translation ceases, synthesis of most proteins is repressed; however, translation of some stress-associated mRNAs is promoted in these circumstances, for example, the one encoding activating transcription factor 4 (ATF4) (Vattem and Wek, 2004a). Together with the phosphorylation of eIF2α and the subsequent halt in translation, this alternative translational program is known as the integrative stress response, or ISR. The ISR will be discussed in detail in a later section. ATF4 is a core protein involved in the second part of PERK signaling, one of stress-activated transcription. ATF4 promotes the transcription of various

genes including those encoding Growth arrest and DNA-damage inducible 34 (GADD34), C/EBP homologous protein (CHOP), and tribbles homolog 3 (TRB3), each of which has been studied in retinal degeneration and will be discussed in detail in later sections. Of note, CHOP is a pro-apoptotic protein so its production paves the way for ER-stress triggered cell death. GADD34's primary role in ER stress signaling is promoting the dephosphorylation of eIF2α by protein phosphatase 1 (PP1), thus restoring traditional protein synthesis and sequestering non-canonical protein synthesis (Brush et al., 2003; Connor et al., 2001; Zadorozhnii et al., 2019).

PERK.—PERK is a ~125kD enzyme that spans the ER membrane. PERK contains multiple domains such as the ER luminal domain, the transmembrane domain, and the cytoplasmic portion containing its kinase domain. The crystal structure of PERK's luminal domain has been delineated. The structure of PERK is similar to that of other two-lobed membrane kinases. The luminal domain of PERK is comprised of its smaller N-terminal lobe (N-lobe), whereas a larger C-terminal lobe (C-lobe) constitutes its cytosolic domain. The C-lobe of PERK contains its catalytic site. The cytoplasmic domain is similar to those of other eIF2α kinases (Cui et al., 2011).

PERK, being studied so extensively in ER stress signaling and neurodegeneration, one may be under the impression that PERK is inherently bad; however, like many proteins of the UPR, transient alterations in their activity can be vital for cellular and organismal survival. For instance, knocking out PERK or inhibiting PERK in young mice leads to very poor survivability in inbred strains (Zhang et al., 2002). This is thought to mainly be due to pancreatic cells' need for PERK to tightly regulate the production of secreted proteins. Therefore, though PERK signaling may be hyperactive and deleterious in certain neurodegenerative diseases (including those of the retina, as will be discussed in a later section) other tissues simply cannot go without this enzyme.

Though the canonical route to PERK activation remains the most studied, there may be more to this enzyme. For example, Wang et al. recently demonstrated that mammalian PERK can interact with misfolded proteins with a region of its luminal domain, meaning that upon induction of ER stress, PERK itself can act as a sort of chaperone as it binds misfolded polypeptides to initiate its dimerization and ensuing activation, directly arguing against canonical UPR activation (Wang et al., 2018). In addition, this group provided evidence that PERK activation may be independent of its interaction with BiP as cells expressing mutant PERK lacking an active luminal domain did not experience higher than normal PERK signaling but were still susceptible to pharmacological induction of the UPR. Whether this is cell-type specific or a common mechanism across a range of cell types is unknown. van Vliet et al. demonstrated that PERK may be necessary for the formation of ER-plasma membrane associations, a process important for regulating Ca^{2+} stores in the ER (van Vliet et al., 2017).

In people, genetic variants of PERK increase the risk for tauopathy neurodegenerative diseases – Progressive Supranuclear Palsy (Ferrari et al., 2014; Höglinger et al., 2011b; Sanchez-Contreras et al., 2018) and some forms of Alzheimer's Disease (Liu et al., 2013a; Wong et al., 2019). These variants include amino acid changes that are predicted

to disrupt H-bonds in PERK's ER stress-sensing luminal domain (Park et al., 2023) and impair stability and function in response to ER stress (Yuan et al., 2018). iPSC-generated neurons carrying disease-associated hypomorphic PERK variants displayed increased vulnerability to ER stress toxins and increased tau protein misfolding (Yuan et al., 2018). Chemical or genetic inhibition of PERK increased tau aggregation while activation of the PERK/ISR pathway reduced tau aggregation *in vitro* (Park et al., 2023). These findings support that people carrying these PERK disease alleles have increased risk for tauopathy neurodegeneration due to reduced PERK signaling that in turn increases tau proteotoxicity and ER stress-induced damage. The role of these hypomorphic PERK alleles in human ocular diseases remains to be studied.

eIF2α.—eIF2α, as mentioned in the previous sections, is a part of a trimeric translation factor complex essential for canonical translation. eIF2α is an ~37kD protein with a key amino acid that is central to stress-induced ternary complex inhibition, S51. eIF2α-S51 appears to largely exist to maintain translational homeostasis. Homozygous mutations at key sites (i.e. S51A) can lead to embryonic lethality in mice (Back et al., 2009; Longo et al., 2021). Therefore, it is of significant importance to use cell-type specific knockouts, knockdowns, or overexpression of dominant mutants of eIF2α when studying this protein mechanistically. Due to eIF2α being the central target of the ISR, it will be covered in more depth in the ISR section.

ATF4.—As mentioned above, one of the following downstream elements of PERK signaling under stress conditions is ATF4. ATF4 is composed of 351 amino acids and is organized into domains crucial for its stability and response to ER stress (Ameri and Harris, 2008). Belonging to basic leucine zipper (bZIP) family transcription factor - ATF4 was described in many reviews (Baird and Wek, 2012; Pavitt and Ron, 2012; Sonenberg and Hinnebusch, 2009). It can function in homodimeric or heterodimeric complexes. Homodimeric complexes are less stable and heterodimeric complex can bind to other bZip family members such as CCAAT box/enhancer-binding protein b (C/EBP) which makes it stable. Heterodimers find DNA targets by binding with cAMP response element (CRE) to regulate transcription (Ebert et al., 2022; Podust et al., 2001).

The *ATF4* gene carries two upstream open reading frames (uORF) before the main *ATF4* coding region. These two uORFs (1 and 2) act as different critical elements during stress with inhibitory and activating properties. uORF1 facilitates ATF4 coding region translation and uORF2 by contrast blocks ATF4 translation (Pavitt and Ron, 2012; Vattem and Wek, 2004a; Yamaguchi and Wang, 2004). Human ATF4 contains 3 uORF regions. Under stress conditions, scanning starts from the second uORF (Harding et al., 2000; Lu et al., 2004; Pakos-Zebrucka et al., 2016; Pavitt and Ron, 2012; Vattem and Wek, 2004b). Interestingly, a similar mechanism has been characterized for yeast transcriptional activator general control nonderepressible 4 (GCN4) (Hinnebusch, 2005). Chan et al. studied human ATF4 and reported that translation of ATF4 is mediated by internal ribosome entry site (IRES) (Chan et al., 2013). ATF4 was shown to activate C/EBP homolog protein (CHOP or GADD153) and promote ER stress-mediated apoptosis (Marciniak et al., 2004). Enhanced expression of CHOP under ATF4 activities was demonstrated in arsenite-treated rat cells (Fawcett et al.,

1999). A study led by Kaufman et al. identified that ATF4 interacting with CHOP can lead to cell death (Han et al., 2013). Therefore, ATF4/CHOP regulation plays an important role in pro-apoptotic events of the cellular stress response.

GADD34.—GADD34, first identified as a pro-apoptotic member of the GADD (growth arrest and DNA-damage) family of proteins, is now perhaps most studied for its role as a phosphatase regulatory subunit responsible for assisting protein phosphatase 1 (PP1) in dephosphorylating eIF2α to promote translational recovery after transient ER stress. In this role, GADD34 provides the ISR with a much-needed feedback loop in order to restore translational homeostasis following a bout of stress. Importantly, ATF4 acts on the *GADD34* promoter to facilitate its transcription and restore protein synthesis rates. In addition, c-Jun has been shown to upregulate the *GADD34* gene during DNA damage and proteotoxic stress (i.e., Alzheimer's disease) (Xu et al., 2015b). GADD34 upregulation well correlates with apoptotic signaling; however, the mechanism of GADD34's induction of apoptosis is not well understood. In one interesting study, Farook et al. showed that its pro-apoptotic role could stem from GADD34-mediated inhibition of AKT phosphorylation (Farook et al., 2013). This group reported that GADD34 interacts with TRAF6 to block polyubiquitination of AKT, a process that would set AKT up for subsequent phosphorylation. In addition, Shi et al. reported that GADD34 interacts with and initiates the PP1-mediated dephosphorylation of SMAD7 (Shi et al., 2004).

Interestingly, there is also evidence that GADD34 may have anti-apoptotic functions, which appear to be independent of its role in restoring protein synthesis. For example, Krokowski et al. demonstrated that GADD34 is essential for the survival of cultured corneal cells subjected to hyperosmotic stress (Krokowski et al., 2017). This group highlighted that GADD34 may be important for the integrity of the Golgi as a lack of GADD34 led to a fractionated Golgi body in hyperosmotic corneal cells. Of note, fractionated Golgi further led to less membrane translocation of receptors in these cells, suggesting that GADD34's functions may be far more complicated than previously thought. In fact, Dedigama-Arachchige et al. revealed that GADD34/PP1 could act on hundreds of proteins to alter the metabolic state of a cell (Dedigama-Arachchige et al., 2018). The reality that GADD34/PP1 could act on so much more than eIF2α is only recently coming to light.

CHOP.—CHOP, also known as GADD153, is a well-characterized transcription factor that regulates several stress-response genes. CHOP is one example of a transcription factor with a very interesting function: it can form heterodimers with ATF4 and alter ATF4's transcriptional activity (Talukder et al., 2002). In fact, ATF4/CHOP interaction has been proposed to be a prerequisite for transcription of TRB3 (Ohoka et al., 2005).

It is generally accepted that chronic or prolonged PERK signaling can lead to apoptosis and CHOP appears to be a primary player in this process. CHOP activation leads to the transcription of apoptosis-promoting genes (Sano and Reed, 2013) and inhibition of pro-survival proteins. For example, the genes encoding Bcl-2 interacting mediator of cell death (BIM) (Altman et al., 2009; Puthalakath et al., 2007) and death receptor 5 (DR5) (Kim et al., 2008; Kouhara et al., 2007; Yamaguchi and Wang, 2004) are targets of CHOP. In addition, CHOP down-regulates B-cell lymphoma 2 (BCL-2), a vital inhibitor of apoptosis

(McCullough et al., 2001). ATF6 can also promote transcription of CHOP (Yoshida et al., 2000), and therefore may support programmed cell death in prolonged ER stress. BIM can activate another pro-apoptotic protein known as BCL2 antagonist/killer (BAK), which can signal for mitochondria-mediated apoptosis (Ord and Ord, 2003). In addition, Li et al. reported that CHOP can activate endoplasmic reticulum oxidore-ductase 1 alpha (ERO1α), which hyperoxidizes the ER and may lead to programmed cell death (Li et al., 2009a). The group also reported that ERO1α promotes IP3R migration to the mitochondria, further promoting apoptosis. Calcium pumping into the mitochondria promotes the release of cytochrome C, which can result in apoptosis signaling through caspases (Li et al., 2009a).

TRIB3.—TRIB3, or Tribbles homolog 3, has been extensively studied due to its crucial role as a signal mediator binding with various proteins such as kinases, phosphatases, and transcription factors. TRIB3 was reported as a novel gene with different names such as TRB3, NIPK, SKIP3, and SINK (Ord and Ord, 2017). Matsuda et al. studied cell death induced by neuronal growth factor depletion and identified a novel gene called NIPK (neuronal cell death inducible putative kinase) with unknown function (Mayumi-Matsuda et al., 1999). This was the beginning of TRIB3 discovery. The original name of TRIB3 came from homology of tribbles gene in Drosophila. The novel tribbles gene was characterized as a crucial regulator of oogenesis (Rorth et al., 2000). In addition, tribbles was shown as an important regulator of mitosis in Drosophila development (Mata et al., 2000). An interesting systemic analysis from Hernández-Quiles et al. showed a conservative similarity of 55% in pseudokinase domain between human TRIB1/2 and 3; However, they only observed a 9% similarity in the C terminal domain of TRIB1 and TRIB3, which is assumed to be due to their unique functions (Hernandez-Quiles et al., 2021). Structurally, TRIB3 has a pseudokinase domain, PEST (proline, glutamic acid, serine, and threonine rich region) and COP1 binding domain (Eyers et al., 2017; Stefanovska et al., 2021). It was reported that TRIB3 in association with E3 ubiquitin ligase protein COP1 leads to the degradation of Acetyl–coenzyme carboxylase (ACC) in adipose tissue (Qi et al., 2006). Its pseudokinase domain has 12 subdomains with a lack of phosphorylation sequence, and since it lacks a true kinase function, is termed a pseudokinase (Hanks and Hunter, 1995; Hegedus et al., 2007; Prudente et al., 2012). Mouse and human amino acid sequence of TRIB3 is highly conservative. Its biological function includes regulation of cell growth, apoptosis, differentiation, and metabolism (Prudente et al., 2012). TRIB3 has been found to interact with AKT, NF-κB, mTORC2, MAPK (Du et al., 2003; Kiss-Toth et al., 2004; Salazar et al., 2015; Wu et al., 2003).

Various stress conditions induce TRIB3 gene expression, for instance, ER stress (Ohoka et al., 2005; Ord and Ord, 2005) and toxic chemicals (Ord et al., 2009). Earlier reports identified TRIB3 as an interacting partner of ATF4 and characterized its transcriptional activity in yeast two-hybrid analysis (Ord and Ord, 2003). Ord et al. showed that TRIB3 can regulate ATF4 expression in a negative feedback mode with induced stress *in vitro* (Ord and Ord, 2005). Interestingly, the functions of both ATF4 and CHOP during ER stress are regulated in cooperation with TRIB3 and are important in regulating cell death (Ohoka et al., 2005). Other evidence showed that neuronal cells respond to ER stress-mediated apoptosis through TRIB3 (Zou et al., 2009). These studies indicate that TRIB3 serves as a sensor for

ATF4/CHOP axis cell death occurring during ER stress. Conversely, several publications determined involvement of TRIB3 in cell survival (Ord et al., 2007, 2015; Schwarzer et al., 2006) and death mechanisms (Humphrey et al., 2010; Ohoka et al., 2005; Salazar et al., 2013; Wu et al., 2003).

One of the interesting functions of TRIB3 is in the cell's response to toxic chemicals. A report from Ord et al., described cytotoxic effects of arsenite and molecular changes based on TRIB3 expression transcriptionally and translationally (Ord et al., 2016). In that study, the level of TRIB3 mRNA and protein was increased in response to arsenite-induced stress. When TRIB3 was silenced, CHAC1 (glutathione degrading enzyme) expression was elevated, inducing cell death. Importantly, the sensitivity of cells to arsenite-induced stress was decreased by TRIB3-mediated reduction of CHAC1.

3.3. The ATF6 pathway

ATF6 controls a key UPR signal transduction pathway (Walter and Ron, 2011). ATF6 encodes a basic leucine zipper (bZIP)-domain transcription factor that is tethered to the endoplasmic reticulum membrane and found in all cells (Haze et al., 1999). Under resting conditions, ATF6 may form intermolecular disulfide bridges between luminal domains to generate ATF6 dimers and oligomers in the ER (Koba et al., 2020; Nadanaka et al., 2007). In response to increased ER/oxidative stress, ATF6 is fully reduced (Nadanaka et al., 2006, 2007), and the ATF6 monomer then traffics from the ER to the Golgi (Chen et al., 2002; Sato et al., 2011; Shen et al., 2002). In the Golgi, site-1 and site-2 proteases cleave ATF6 in its transmembrane domain to liberate the bZIP portion of ATF6 into the cytosol (Ye et al., 2000). The severed ATF6 transcription factor then migrates to the nucleus where it transcriptionally upregulates target genes (Fig. 4) (Shoulders et al., 2013; Yoshida et al., 2000, 2001b). ATF6's transcriptional targets have been identified through genetic ablation, microarray/RNA-seq, and chromatin immunoprecipitation experiments and include ER protein folding chaperones; protein folding enzymes such as oxidoreductases and protein disulfide isomerases; and proteasomal degradation cofactors (Bommiasamy et al., 2009; Kroeger et al., 2018, 2021; Lee et al., 2020, 2022; Okada et al., 2002; Wu et al., 2007; Yamamoto et al., 2004, 2007). These chaperones and enzymes improve the fidelity of protein folding, ensure redox balance within the cell, and promote the degradation of damaged proteins (Adachi et al., 2008). The overall result of ATF6 activation in the cell is the reduction of levels of damaged proteins and the reduction of oxidative and ER stress levels (Nadanaka et al., 2004). Hence, ATF6's transcriptional program helps cell survival during physiologic, pathologic, and environmental conditions that cause oxidative or ER stress.

To probe the role of ATF6 signaling in diseases linked to oxidative and ER stress, ATF6−/− mice were generated in 2007 independently by two research teams (Wu et al., 2007; Yamamoto et al., 2007). Mouse embryonic fibroblasts (MEFs) from ATF6−/− mice showed abnormal responses to oxidative and ER stress including: 1) defective induction of ER protein folding chaperones, ER protein folding enzymes; and proteasomal degradation factors. 2) increased cell death in response to chemical agents that induce ER and oxidative stress in cell culture. 3) impaired clearance of misfolded proteins in cell culture (Wu et al.,

2007; Yamamoto et al., 2007). Despite these defects in cell culture, ATF6−/− knockout mice are viable, develop to adulthood and produce offspring at normal Mendelian ratios (Wu et al., 2007; Yamamoto et al., 2007). These findings reveal that ATF6 is not essential for mouse development, viability, and survival under normal laboratory environments.

However, ATF6−/− mice show heightened sensitivity to many different physiologic and pathologic stresses. ATF6−/− mice are prone to pancreatic b-cell failure when fed a high-fat diet (Usui et al., 2012). ATF6−/− mice are prone to liver steatosis when they are given intraperitoneal injections of the oxidative and ER stress-inducing toxin, tunicamycin (Yamamoto et al., 2010). Dopaminergic neurons from ATF6−/− mice are prone to die in response to the oxidative stress-inducing neurotoxin, MPTP (Egawa et al., 2011). These studies suggest that ATF6 is important for protecting tissues and cells in animal metabolic and brain disease paradigms experimentally induced by oxidative and ER stress.

In people, ATF6's link to metabolic disease is less clear: over 20 variants of ATF6 were reported to be associated with type 2 diabetes including Met67Val, Pro145A1a, or Ser157Pro coding changes in ATF6 in Pima Indian and Dutch cohorts (Meex et al., 2007; Thameem et al., 2006). However, these ATF6 variants showed no significant association in another study of Pima Indian, Caucasian, and Chinese patients with type 2 diabetes (Chu et al., 2007). The Met67Val ATF6 variant was linked to increased plasma cholesterol levels in a study of Dutch families with familial combined hyperlipidemia, the variant was found to increase ATF6 transcriptional activity (Meex et al., 2009). However, another study found no differences in ATF6 transcriptional activity when residue 67 was converted from methionine to valine (Lee et al., 2020). While ATF6's role in the pathogenesis and progression of human metabolic diseases requires more rigorous evaluation, more recently, a separate group of ATF6 variants were identified that directly cause photoreceptor disease in patients. ATF6's essential role in human vision will be the focus of Section 6.

4. ER stress signaling in the RPE and AMD

The RPE plays a key role in supporting the function and survival of photoreceptor cells in the retina. The RPE is composed of a single layer of cuboidal epithelial cells situated between the choroidal vasculature and the outer segments of the photoreceptors. The RPE cells form the outer BRB through tight junctions at their basolateral side. This monolayer of RPE cells also adheres to a well-organized basement membrane known as Bruch's membrane, which separates the RPE from the fenestrated endothelium of the choroidal capillaries (Fields et al., 2020; Strauss, 1995). On its apical side, the RPE faces the photoreceptor OS and directly envelops them with its microvilli. The ideal anatomical location allows the RPE to perform essential functions to support the neuroretina, in particular photoreceptor cells. Dysfunction of the RPE can lead to photoreceptor degeneration and contribute to the development of retinal disorders, such as AMD (Bird, 2021; Bonilha et al., 2006).

AMD is the most frequent cause of vision impairment resulting in progressive loss of the central vision in the elderly (Mitchell et al., 2018). In developed countries, approximately 10% of individuals over 65 years and 25% of those over 75 years have been diagnosed with

AMD. As life expectancy rises, the prevalence of AMD is increasing, with an estimated prevalence of nearly 300 million people worldwide being affected by 2040 (National Eye Institute, 2019; Wei et al., 2019). The increasing prevalence of AMD highlights its significance as a global health concern. Clinically, AMD can be classified into two stages: early and late AMD. The early stages of AMD are characterized by the presence of small extracellular yellowish deposits or drusen as well as depigmentation and impaired functioning of the RPE layer (Fleckenstein et al., 2021; Lim et al., 2012). Late stages of the disease can be subcategorized as non-neovascular (dry) or neovascular (wet) AMD. Both forms of advanced AMD are characterized by the loss of photoreceptors and the development of geographic atrophy (GA). Neovascular AMD (nAMD) is defined by the presence of pathological angiogenesis in the macula, known as macular neovascularization (MNV) (Chen et al., 2020; Spaide et al., 2020). Common consequences of MNV include exudate formation, hemorrhages, edema in the macula, and fibrotic scar formation often resulting in severe visual impairment (Fleckenstein et al., 2021; Hadziahmetovic and Malek, 2020). Damage or stress to the RPE is believed to promote the production of pro-angiogenic factors and may contribute to MNV (Ambati and Fowler, 2012).

4.1. Role of the ER in maintaining the RPE function

A well-maintained ER machinery is required for the RPE to fulfill its vital supportive roles through a diverse range of intracellular events such as visual cycle that regenerates the visual pigments, phagocytosis that removes the damaged and aged photoreceptor OS, and secretion of neurotrophic and growth factors to nourish photoreceptors and choroidal vessels, just to name a few. The RPE cells are enriched with tubular smooth ER, which occupies a large volume of the cytoplasm in particular in the basal portion of the cells (Porter and Yamada, 1960). The smooth ER forms close tridimensional lattice and can also present but less frequently as the myeloid body (Porter and Yamada, 1960). The smooth ER is the primary site in the RPE where the classic visual cycle occurs. It harbors several key enzymes, such as RPE65, which catalyzes the isomerization of all-trans retinyl esters to 11-cis-retinol, and lecithin: retinol acyltransferase (LRAT), which generates fatty acid retinyl esters providing substrates for RPE65. These enzymes are critical for the regeneration of visual pigments, which are required for photoreceptor cells to respond to light stimuli (Cheng et al., 2020b; Fisher and Ferrington, 2018; Viegas and Neuhauss, 2021). Mutations of RPE65 or LRAT genes lead to congenital or early-onset retinal degeneration, such as Leber congenital amaurosis (LCA) (Cai et al., 2009; Sears and Palczewski, 2016). In diabetes, the visual cycle function is compromised contributing to vision impairment. Inhibiting ER stress successfully restored the expression levels of RPE65 and several other key visual cycle enzymes in the RPE, suggesting that maintaining ER homeostasis is critical for visual cycle function (Kang et al., 2018).

An important and well-studied role of the RPE is detoxifying and phagocytosis of shed photoreceptor OS. The phagocytosis process in the RPE involves phagosome formation and maturation followed by breakdown and resolution of the ingested photoreceptor OS and the membrane-associated components are then recycled back to photoreceptors for their use (Kwon and Freeman, 2020). The sequential stages of phagosome maturation in the RPE were also observed in macrophages exposed to photoreceptor outer segment (POS),

suggesting similarities in the phagocytosis process in these cell types (Silène T. Wavre-Shapton et al., 2014). In phagocytes of the innate immune system, the ER plays a critical role in phagosome formation, maturation, and possibly phagolysosome repairing by forming the ER-phagosome contact sites (Ghavami and Fairn, 2022). In macrophages, upon particle entry the ER is recruited and fused with the plasma membrane providing building material for phagosome formation to avoid the use of a highly specialized plasma membrane(Gagnon et al., 2002). In neutrophils, ER transmembrane proteins, such as stromal interaction molecule (STIM) proteins, are responsible for the remodeling of the ER membranes near adjacent phagosomes (Orci et al., 2009). These molecules sense ER Ca^{2+} depletion and induce a conformational change of the ER to increase the availability of membrane contact sites and subsequently form tight phagosomal-ER junctions (Nunes et al., 2012; Stendahl et al., 1994). STIM1 also interacts with store-operated Ca^{2+} entry (SOCE) channels on the phagosome membrane which results in highly localized Ca^{2+} signals necessary to sustain phagocytosis (Lewis, 2007; Nunes et al., 2012; Orci et al., 2009).

The RPE secrete a large array of proteins and growth factors that nourish photoreceptor cells and choroidal vessels. For example, polarized mature RPE cells secret pigment epithelium growth factor (PEDF) from their apical surface providing neurotrophic support to photoreceptors and secret vascular endothelial growth factor (VEGF) from their basal side, which is essential for the maintenance of choriocapillaris (Saint-Geniez et al., 2009; Sonoda et al., 2009). As epithelium, the RPE provides metabolic support to photoreceptors by facilitating the transport of nutrients to these cells. In addition, the RPE is considered an integral part of the metabolic ecosystem within the eye. In this intricate system, glucose derived from the choroid is transported through the RPE to photoreceptors (Swarup et al., 2019). Subsequently, photoreceptors convert glucose into lactate, which serves as a fuel source for the RPE and neighboring retinal cells. Lactate also inhibits glycolysis in the RPE, thereby preserving glucose for utilization by the photoreceptors (Kanow et al., 2017). This intricate metabolic interplay ensures the availability of energy resources and contributes to the overall homeostasis of the retina.

4.2. ER stress signaling in RPE survival

Given its multiple significant roles in supporting the neuroretina, in particular phagocytosis and detoxification of photoreceptor OS, the RPE is equipped with sophisticated systems to reduce chronic physiological and pathological stresses, such as aging, light phototoxicity, cigarette smoke, and so on. These factors with time increase oxidative stress, which triggers ER dysfunction and induces ER stress; sustained ER stress, in turn, exacerbates redox imbalance resulting in oxidative damage. Thus, oxidative stress and ER stress often go hand-in-hand in RPE dysfunction and pathogenesis (Chen et al., 2014a; Huang et al., 2015b; Sreekumar et al., 2016). A recent single-cell transcriptomic study shows that genes associated with cellular response to ER stress and oxidative stress, such as *HERPUD1, HMOX1, MDM2, and XBP1*, are highly enriched in the macular RPE (Xu et al., 2021). These genes are believed to provide great ability to the macula to respond to stresses and injuries. Knockout or inhibition of XBP1 activation leads to increased RPE apoptosis, tight junction damage, and RPE/photoreceptor induced by oxidative stress or ER stress (Chen et al., 2014a; Ma et al., 2016; Zhong et al., 2012b). Reduced expression of PERK has been

observed in the RPE of human donors with early and intermediate AMD (Porter et al., 2019; Saptarshi et al., 2022). Downregulation of PERK increases ER stress, impairs autophagic flux, and reduces antioxidant response in ARPE-19 cells challenged with brefeldin A. This suggests that the PERK pathway, along with the IRE/XBP1 pathway, plays a critical role in the RPE response to ER stress. However, it should be noted that in chronic stress conditions overactivation of the PERK-downstream effectors, ATF4 and CHOP, can lead to ER stress-associated apoptosis and cell death (Chen et al., 2014a; Li et al., 2014b; Ma et al., 2016; Zhong et al., 2012b). Yet, complete silencing of the CHOP gene in the RPE increases cell apoptosis and this effect is associated with a reduction of nuclear factor erythroid 2-related factor 2 (Nrf2), a master regulator of the cell's anti-oxidant and detoxification function, suggesting that an optimal level of CHOP is crucial for Nrf2 activation and cell survival in stressed RPE (Huang et al., 2015b). In addition to CHOP, other ER stress signaling molecules also regulate or interact with Nrf2. Deletion of XBP1 decreases Nrf2 protein levels and its downstream target gene expression while downregulation of PERK reduces Nrf2 phosphorylation in RPE cells (Chen et al., 2018; Saptarshi et al., 2022). Overexpression of Nrf2 reduced ER stress-induced RPE cell death and sufficiently rescued the RPE in mouse models of retinitis pigmentosa (RP) (Huang et al., 2015b; Wu et al., 2021). These results suggest that the oxidative and ER stress signaling may converge on common pathways, such as Nrf2, to regulate RPE cell survival.

Disturbance in the phagocytotic process and/or delayed clearance of the POS in the RPE can cause increased oxidative stress and subsequent ER stress, whereas sustained ER stress can also lead to dysfunctional phagocytosis. For example, excessive accumulation of visual cycle metabolites such as all-trans retinal (atRAL) due to mutations of retinol dehydrogenase 12 (RDH12) leads to increased oxidative and ER stress resulting in apoptotic RPE cell death (Li et al., 2015; Zhu et al., 2016) and disrupted phagocytosis (Gal et al., 2000; Zhang et al., 2020). In a zebrafish *rdh12* mutant model, the POS were not able to penetrate beyond the apical surface of the RPE, indicating an abnormal RPE phagocytosis (Sarkar et al., 2021). The impaired communication between RPE and POS may trigger the activation of chronic ER stress response in photoreceptors causing POS degeneration and eventual cell death. In addition, transmission electron microscopy revealed enlarged, undigested phagosomes in the RPE cells, which suggests an impaired POS recycling and the latter has been linked to the LC3-associated phagocytosis (LAP) pathway involving autophagy proteins (Kim et al., 2013). Regulation of autophagy by the ER stress signaling in RPE pathophysiology will be discussed in Section 9. A recent study shows that tauroursodeoxycholic acid (TUDCA), a bile-derived neuroprotectant, can protect against oxidative stress-induced RPE phagocytic dysfunction through enhancing Mer tyrosine kinase receptor (MerTK) (Murase et al., 2015). While TUDCA has demonstrated an anti-ER stress effect in RPE cells (Chen et al., 2014a), in this study the authors reported that TUDCA did not reduce the increase of ER stress marker and thus concluded that TUDCA may promote the phosphorylation of MerTK through an independent pathway of ER stress. Further studies are needed to determine if inhibition of ER stress can promote phagocytosis via regulation of tyrosine kinase.

4.3. ER stress signaling in RPE barrier function

The integrity of the BRB is essential to maintaining the microenvironmental homeostasis of the neural retinal tissue. Damage to the RPE cell tight junctions and adherens junctions resulting in disruption of the barrier integrity of the outer BRB contributes to the pathogenesis of AMD. Studies have shown that prolonged exposure to cigarette smoke, a most significant environmental risk factor for AMD development, or continuous light can trigger the activation of ER stress signaling, e.g. the PERK pathway, in RPE cells and lead to disruption of the outer BRB (Huang et al., 2015a; Song et al., 2020). Overexpression of ER chaperone ERp29 or treatment with cyanidin-3-glucoside (C3G), a natural water-soluble plant pigment demonstrating anti-oxidant properties, can reduce ER stress and PERK activation, restore tight junction formation, and preserve the barrier function in the RPE (Huang et al., 2015a; Song et al., 2020). While these studies provide indirect evidence supporting the role of PERK activation in RPE tight junction damage, experiments to elucidate the exact role of PERK in RPE barrier formation using loss-of-function and gain-of-function approaches are needed in future research. In addition, both ERp29 and C3G have been found to activate Nrf2 which increases the RPE's antioxidant defense (Chen and Cubillos-Ruiz, 2021; Peng et al., 2022b). Whether their pro-Nrf2 effects are dependent or independent of the PERK pathway remains unclear.

The implication of the IRE1/XBP1 pathway in regulation of the RPE barrier function has been studied using conditional XBP1 knockout animals and RPE cell culture treated with pharmacological inhibitors of XBP1 splicing (Ma et al., 2016). The authors demonstrated that inducing ER stress by thapsigargin, which depletes the ER calcium storage causing calcium dyshomeostasis, is sufficient to damage RPE junctions. Moreover, deletion of the XBP1 gene *in vivo* or inhibition of XBP1 activation in cultured ARPE-19 cells and primary primate RPE cells both result in impaired RPE tight junction formation. Mechanistically, inhibition of XBP1 increases intracellular calcium levels, possibly through dysregulation of the calcium channel protein ryanodine receptors on the ER membrane, resulting in activation of the Rho/Rho kinase signaling pathways (Ma et al., 2016). Activation of the Rho/Rho kinase then causes aberrant cytoskeletal rearrangement resulting in the dissociation of the RPE tight junctions. In mammary epithelial cells, activation of transient receptor potential vanilloid 4 (TRPV4), a major calcium channel protein on the plasma membrane, increases XBP1 splicing and expression of tight junction proteins while knockdown of XBP1 blocks TRPV4-induced increase in tight junction component (Islam et al., 2020). These findings further support the role of XBP1 in the regulation of calcium homeostasis and tight junction formation in epithelial cells including the RPE.

4.4. ER stress signaling in epithelial to mesenchymal transition (EMT)

Recent studies have shed light on an association between ER stress and EMT, a biological process responsible for fibrosis development in various cell types, including RPE cells (Ouyang et al., 2022; Zhou et al., 2020). EMT is present in the later stages of neovascular AMD, whereby RPE cells, which are normally a monolayer of polarized epithelial cells, undergo phenotypic changes and lose their epithelial characteristics and barrier function due to growth factor and cytokine stimulation (Tenbrock et al., 2022). Findings from Ouyang et al. demonstrated that inducing mild ER stress by low doses of tunicamycin

and thapsigargin increases GRP78 expression, enhances tight junction protein level, and reduces fibrotic genes (EMT markers) including fibronectin and a-smooth muscle actin. Moreover, pretreating RPE cells with low doses of ER stress inducers significantly blocks TGF-β-induced upregulation of EMT marker proteins and suppresses migration of RPE cells. These findings provide strong support that activation of the UPR can protect RPE cells from EMT, although the underlying mechanisms are yet to be investigated (Ouyang et al., 2022). In contrast to the protective effect of low-dose ER stress inducers, other studies demonstrate that inducing ER stress with high doses of tunicamycin and thapsigargin disrupts epithelial tight junctions and increases EMT (Ma et al., 2016; Zhou et al., 2020). Inhibition of ER stress by chemical chaperones suppresses EMT suggesting high level or sustained ER stress promotes EMT contributing to human eye diseases such as cataract and AMD.

4.5. ER stress signaling in choroidal neovascularization (CNV)

Choroidal neovascularization (CNV) is the most common type of MNV and a hallmark feature of wet AMD. The mechanisms of CNV are complex involving dysregulation of the VEGF signaling that stimulates choroidal endothelial cell proliferation, migration, and forming aberrant new vessels and non-VEGF dependent pathways associated with a diverse array of processes including increased inflammation, complement activation, enhanced oxidative stress, and ER stress. Activation of the PERK pathway by ER stress contributes to RPE dysfunction and CNV formation in AMD. Evidence from earlier studies revealed a critical role of ATF4 in the upregulation of pro-angiogenic factors such as VEGF in RPE cells under conditions of stress or hypoxia (Oskolkova et al., 2008; Roybal et al., 2004). Inhibition of PERK by GSK2606414 reduces VEGF expression in RPE cells (Jiang et al., 2017). In addition, recent work highlights the important role of microRNAs (miRNAs) in angiogenesis (Suárez and Sessa, 2009). Activation of the PERK-ATF4 pathway in RPE cells inhibits the transcription of the miR-106b-25 cluster resulting in a downregulation of miR-106 b. Decreased miR-106 b level then increases the production of VEGF contributing to pathological angiogenesis in retina and choroid in animal models of laser-induced CNV and OIR (Menard et al., 2020). In addition to the PERK-ATF4 pathway, activation of the IRE1/XBP1 pathway and the ATF6 pathway also participates in CNV pathogenesis (Arjunan et al., 2021). Knockdown of IRE1a or ATF6 partially inhibits VEGF-induced *in vitro* angiogenesis and potentiates the anti-angiogenic effect of the anti-VEGF treatment in an animal model of CNV, suggesting that the IRE1a and ATF6 pathways may regulate angiogenesis through VEGF-independent mechanisms (Liu et al., 2013b). In addition to RPE cells, activation of the UPR in macrophages promotes their polarization toward a pro-angiogenic M2 phenotype (Li et al., 2021b). Treatment of choroidal endothelial cells with conditioned medium from M2 macrophages promotes cell proliferation and tube formation and this pro-angiogenic effect was blocked by inhibition of XBP1 splicing in macrophages. These results suggest that XBP1 activation promotes M2 macrophage differentiation and potentially contributes to CNV formation.

5. ER stress signaling in inherited retinal degeneration

Inherited retinal degeneration (IRD) refers to the heterogeneous group of retinal disorders affecting both rod and cone photoreceptors, leading to severe vision loss and blindness in some cases. One example of an IRD is retinitis pigmentosa (RP), which primarily affects rod photoreceptor viability, leading to the subsequent loss of cone photoreceptors, while cone-rod dystrophy (CORD), another example, is characterized by impaired color vision, blind spots in the center of the visual field, and peripheral vision loss. Overall, mutations in more than 300 genes that eventually lead to visual impairment have been identified either in rods or cones. The presence of similar clinical phenotypes resulting from mutations in different genes can pose challenges to the diagnosis of IRDs (Gorbatyuk et al., 2020; Hu et al., 2021a). Moreover, no available treatment to prevent irreversible vision loss exists for the majority of IRDs. However, ongoing research in gene therapy holds great promise in addressing this critical demand, thus supporting the hope of improving vision loss in individuals with IRD. It is important to note that future advancements in retinal gene therapy rely strongly on the identification of feasible therapeutic targets. Moreover, the success of gene therapy is determined based on two critical factors: the ability to effectively target specific cell types in the retina, and the ability to achieve adequate levels of therapeutic transgene expression. Therefore, advancements in our understanding of the molecular mechanisms involved in IRD would not only significantly improve the diagnostic assessment of patients through genetic testing, but also facilitate the development of gene and/or cell therapy.

RP is the most common form of IRD associated with vision loss, which ranges from mild to severe. Human RP is classified based on its syndromic or non-syndromic nature, as well as the mode of inheritance (Daiger et al., 2013). Syndromic RP includes conditions such as Usher syndrome and Bardet–Biedl syndrome. In contrast, non-syndromic RP encompasses all modes of inheritance, including autosomal dominant, autosomal recessive, X-linked, and the remaining forms that are yet to be determined. Non-syndromic types account for approximately 70–80% of all cases of RP (Dias et al., 2018; Verbakel et al., 2018).

A typical manifestation of RP is night vision loss accompanied by a progressive decline in the visual field. Fundus abnormalities in RP patients commonly include bone spicule pigmentation. Diagnosis can further be supported by an electroretinogram, which typically reveals the characteristic loss of photoreceptor function, which predominantly affects rod photoreceptors in the early stages of the disease, as opposed to cones (Verbakel et al., 2018). The molecular mechanism of photoreceptor degeneration has been linked to changes in retinal metabolism, receptor expression, and neuronal network remodeling, which eventually lead to photoreceptor cell death. The latter can be observed through the distinct IRD phases ranging from photoreceptor stress to photoreceptor degeneration, and the occurrence of this phenomenon is expected to influence the effectiveness of therapeutic approaches aimed at restoring or preserving vision (Pfeiffer et al., 2020). The 2007 study by Lin et al. was one of the first to introduce UPR signaling into vision research as a molecular mechanism of IRD, reporting that the degenerating retinas of P23H RHO transgenic rats exhibited the activation of UPR signaling (Lin et al., 2007). This activation was evidenced by an increase in CHOP and GRP78 mRNA levels. Furthermore, P23H RHO knock-in mice crossed with ERAI mice

(carrying a GFP reporter of UPR activity) or Ub-GFP mice (carrying a GFP reporter of proteasome activity) showed selective GFP induction in rods expressing P23H rhodopsin providing evidence of proteostatic activation in diseased rods (Alavi et al., 2015; Chiang et al., 2015; Lobanova et al., 2013). Since then, mounting evidence of UPR's contribution to the mechanism of IRD has accumulated. However, the question of whether the sustained activation of UPR is beneficial or harmful for degenerating photoreceptors is still under investigation due to existing discrepancies in the impact of individual UPR mediators on photoreceptor homeostasis. These discrepancies include the use of different animal models of IRD and the analysis of different time points of disease progression.

The role of PERK has been investigated in rat and mouse models of IRD. A study conducted by Cheetham's lab with P23H RHO transgenic rats demonstrated that PERK inhibition with GSK2606414 A, which led to an inhibition of eIF2α phosphorylation, was correlated with reduced ERG retinal function (Athanasiou et al., 2017). A similar effect of PERK inhibition has been reported in P23H RHO knock-in mice, where it led to a significant increase in photoreceptor cell death (Comitato et al., 2020). Moreover, the authors reported that long-term stimulation of PERK has a protective effect by phosphorylating the nuclear factor erythroid 2-related factor 2 (NRF2) transcription factor, which is associated with antioxidant responses. In Chiang et al.'s study, it was revealed that in cells expressing T17M, P23H, Y178C, C185R, D190G, K296E, and S334ter rhodopsin proteins, selective activation of PERK prevents mutant rhodopsin from accumulating in cells (Chiang et al., 2012). In our study with rd16 mice manifesting severe retinal degeneration, we also manipulated the level of PERK mediators in the retinas using GSK2606414 and a genetic approach to knockout PERK in the photoreceptors by employing the PERK floxed and iCre mice. We found that while these manipulations modulated the p-eIF2α level, they did not lead to a complete recovery in translation or affect further retinal function loss (Starr and Gorbatyuk, 2019a). Specifically, neither an increase nor a decrease in the scotopic A- and B-wave ERG amplitudes were detected in the PERK-deficient photoreceptors. Therefore, we concluded that in rd16 mice with rapid retinal degeneration, the PERK deficit does not play a dramatic role in IRD progression, as it may in other models (Athanasiou et al., 2017). Another study conducted with rd1 mice suggested that the time-dependent upregulation of p-PERK coincided with preceded photoreceptor apoptosis (Yang et al., 2007). At the peak of apoptosis, p-PERK was primarily located in the photoreceptor's inner segments, the outer nuclear layer, or both. The authors thus proposed that ER stress modulators may be strong candidates as therapeutic agents in the treatment of retinal degenerative diseases.

Recently, it has been suggested that the PERK mediator could be responsible for thapsigargin (TG)-induced CXCL10 and CCL2 mRNA expression in photoreceptors (Zhu et al., 2017). In this particular study, the knockdown of PERK-attenuated CXCL10 and CCL2 mRNA elevation was associated with significant decreases in p–NF–κB RelA and STAT3. In contrast to PERK, knockdown of XBP1 robustly enhanced TG-induced CXCL10 and CCL2 expression and the associated p—NF–κB RelA and STAT3 levels. The authors further investigated the role of PERK in diseased photoreceptors by treating them with advanced glycation end products and high glucose and found that PERK is a positive regulator of CXCL10 and CCL2 expression, while XBP1 negatively regulates these chemokines (Zhu et al., 2017).

The role of ATF4 in the progression of IRD has also been elucidated. Elevated ATF4 expression has been found in retinal protein fractions isolated from different models of IRD (Bhootada et al., 2016; Starr et al., 2018). Thus, in T17M RHO transgenic retinas manifesting severe retinal degeneration, the overexpressed ATF4 turned out to have a pro-death role (Bhootada et al., 2016). Consequently, in these mice, we observed ATF4 overexpression concomitantly with an increase in CHOP and caspase-3/7 activity. In this particular study, we proposed that ATF4 possibly contributed to the mechanism of photoreceptor cell loss, since ATF4 knockdown in the T17M RHO retinas retarded retinal degeneration and promoted photoreceptor survival, as measured by scotopic and photopic ERGs and photoreceptor cell counting. The conclusion of the study was confirmed by experiments conducted in C57BL6 retinas overexpressing ATF4 by means of AAV delivery (Rana et al., 2014). Therefore, we concluded that future ADRP therapy that regulates ATF4 expression could be developed to treat retinal degenerative disorders associated with activated UPR.

In contrast, a protective role for ER stress-induced ATF4 has recently been proposed (Huang et al., 2021). In ER stress-manifesting cone-derived 661 W cells and mouse retinas of CH3 and C57BL6 mice, researchers found that treatment with 2, 3, 5, 6-tetramethylpyrazine (TMP) not only ameliorates retinal photoreceptor function loss and alleviates ER stress, but also enhances ATF4 expression. Further examination allowed the investigators to determine that the proportion of insoluble prion protein (PRP) versus soluble PRP was reduced both *in vitro* and *in vivo*. The intrinsic mechanism of the TMP therapeutic effect was proposed to be associated with the ATF4-mediated inhibition of PRP aggregation (Huang et al., 2021). In addition, the protective role of ATF4 in the induction of XBP1 expression has been recently highlighted, specifically in a study in which ATF4-mediated control of IRE/XBP1 pathway has been proposed as a novel mechanism (Tsuru et al., 2016).

The role of TRIB3, a downstream ATF4 mediator, in retinal degeneration has been studied to a lesser extent. In a retinal detachment (RD) model, it has been found that the number of TRIB3-positive photoreceptor cells was significantly induced after RD and peaked at 3 days post-RD. The knockdown of TRIB3 protects photoreceptors against ER stress-induced apoptosis. The authors concluded that TRIB3 may be a crucial molecule in photoreceptor apoptosis induced by ER stress (Yan et al., 2016). In a study conducted with rd16 mice, we investigated the role of TRIB3-mediated regulation of AKT/mTOR (Saltykova et al., 2021). We previously showed that the AKT/mTOR axis is inhibited in rd16 mice (Starr et al., 2018). Knowing that TRIB3 is a pseudokinase that inhibits AKT and mTOR, we genetically ablated TRIB3 in rd16 retinas, which resulted in preservation of photoreceptor function in degenerating retinas, associated with restoration of the p-AKT/p-mTOR activity and photoreceptor homeostasis in TRB3−/−, rd16 retinas. Based on these findings, we propose that TRIB3 may retard retinal degeneration and be a promising therapeutic target for treating retinal degenerative disorders (Saltykova et al., 2021).

CHOP is known to be a pro-apoptotic protein. Therefore, this fact served as a reason to test its role in retinal degeneration, which is known to manifest photoreceptor apoptotic cell death. In degenerating retinas, we and other investigators found that the ablation of CHOP in mice with IRD surprisingly resulted in no rescue of degenerating photoreceptors

(Adekeye et al., 2014; Chiang et al., 2016; Nashine et al., 2013). The T17M RHO and P23H RHO mice did not obtain any benefits for the protection of vision loss from CHOP ablation in their retinas. Moreover, in T17M RHO CHOP−/− photoreceptors, we found a 22–24% decline in the thickness of the outer nuclear layer, which was associated with a 70% reduction in the a-wave ERG amplitude (Nashine et al., 2013). However, another study has shown that CHOP may regulate pathological responses, such as inflammation, that are upregulated during later stages of disease progression (Adekeye et al., 2014). The investigators found a regional protective effect from CHOP ablation in severely degenerated central retina in older P23H RHO mice. Indeed, our study with CHOP knockout mice manifesting Tn-induced ER stress demonstrated significantly lower IL-1b expression as compared to the C57BL6 retina overall, suggesting that CHOP controls this cytokine expression (Rana et al., 2014).

GADD34 is another pro-apoptotic protein known to be a subunit of a protein phosphatase 1-GADD34 complex, providing a feedback loop to dephosphorylate p-eif2α upon activation of PERK signaling. We recently studied its role in two animal models of IRD: rd16 and P23H RHO mice (Saltykova et al., 2022; Starr and Gorbatyuk, 2019a). These mice differ in terms of the rate of retinal degeneration (rapid vs. relatively slow), the affected proteins (CEP290 vs. RHO), and possibly even the molecular mechanisms of retinal pathogenesis. Despite these facts, UPR activation is a common signaling in their retinas. We found that the ablation of GADD34 exacerbated retinal degeneration in both models by increasing the number of apoptotic photoreceptor cells. Moreover, in P23H RHO retinas, GADD34 ablation caused a decline in the scotopic a-wave ERG amplitudes. In this particular study, we also found that, similar to CHOP, GADD34 controls *Il-6* cytokine expression, and its ablation enhances the *Tnfα* mRNA expression in P23H RHO retinas, thus contributing to retinal pathogenesis (Saltykova et al., 2022). These studies have also revealed that future experiments should be conducted to better understand the roles of pro-apoptotic CHOP and GADD34 proteins in degenerating retinas.

6. ER stress signaling in cone photoreceptor disease and achromatopsia

6.1. ATF6 is essential for cone function in people

Achromatopsia is a heritable cone dysfunction disease characterized by loss of color vision, severely impaired visual acuity, photosensitivity, and nystagmus (Zobor et al., 2015). Mutations in cone phototransduction genes account for the majority of achromatopsia cases (Chang et al., 2009; Grau et al., 2011; Kohl et al., 1998, 2000, 2002, 2012), but a fraction of patients with clinical symptoms of achromatopsia lack mutations in cone phototransduction genes, suggesting additional disease genes. In 2015, genetic sequencing of these achromatopsia patients with intact cone phototransduction genes identified the most recent achromatopsia disease gene, ATF6 (Ansar et al., 2015; Kohl et al., 2015; Xu et al., 2015a). ATF6 achromatopsia disease variants carry single-nucleotide changes, small deletions, or duplications that introduce missense mutations, premature stop codons, or damaged splicing sites in ATF6 (Fig. 4). More recently, using advanced sequencing technologies, large multi-exon deletions in the ATF6 gene locus were identified in achromatopsia patients (Lee et al., 2020). By contrast to other achromatopsia disease genes,

ATF6 is not part of the cone phototransduction system and its expression is not restricted to cones. Instead, ATF6 is a key regulator of ER stress signaling and protein homeostasis and is found in all mammalian cells.

Biochemical and computational studies with recombinant proteins, patient fibroblasts and stem cells demonstrated that ATF6 disease alleles were uniformly associated with loss of transcriptional function (Chiang et al., 2017; Kohl et al., 2015; Lee et al., 2020; Skorczyk-Werner et al., 2017). Interestingly, at least 3 different pathomechanisms underlying loss of transcriptional function were identified (Chiang et al., 2017). Class 1 ATF6 achromatopsia mutations prevent ATF6 from exiting the ER to Golgi apparatus, and, therefore, prevent generation of the cytosolic transcription factor fragment (Chiang et al., 2017; Skorczyk-Werner et al., 2017). Class 2 ATF6 mutations introduce premature stop codons that likely trigger nonsense-mediated decay, but for some variants, could also lead to generation of the cytosolic fragment (Chiang et al., 2017). In contrast, class 3 mutations directly damage the bZIP domain, deleting ATF6's transcriptional activity (Chiang et al., 2017; Lee et al., 2020). Patient fibroblasts carrying these ATF6 achromatopsia variants all showed increased vulnerability to ER stress-induced damage and cell death in response to ER toxins, similar to findings with ATF6−/− MEFs (Chiang et al., 2017; Kroeger et al., 2018; Wu et al., 2007; Yamamoto et al., 2007). However, the different pathomechanisms that impair ATF6 transcriptional activity raise the possibility that there could be phenotype differences linked to different ATF6 achromatopsia alleles. Indeed, patients carrying the Class 1 ATF6 D564G variant reported rod dysfunction in addition to cone dysfunction, while patients with other ATF6 variants were limited to cone disease (Skorczyk-Werner et al., 2017).

6.2. Cones fail to develop outer segments in ATF6 mutant retinal organoids

Retinal organoids generated from achromatopsia patients' iPSCs carrying ATF6 variants have shed insight into cellular and molecular pathomechanisms underlying cone dysfunction (Kroeger et al., 2021; Lee et al., 2022). The pace of differentiation and morphology/size of retinal organoids showed no differences in ATF6 defective retinal organoids compared to controls. But, microscopic inspection of ATF6 mutant organoids revealed a "smooth" surface throughout differentiation whereas control retinal organoids developed bulbous projections consistent with formation and extension of cone inner/outer segment (Kroeger et al., 2021). Confocal immunohistochemical examination with cone markers, peanut agglutin and red/green cone opsin, confirmed severe defects in cone IS/OS extension in ATF6 mutant retinal organoids (Kroeger et al., 2021). Sequencing of ATF6 mutant retinal organoids also identified a significant loss of cone phototransduction apparatus genes and pathways. By contrast, cell death/apoptosis was not a significant process in ATF6 mutant organoids. Failure in cone IS/OS extension was observed using multiple different ATF6 disease variant iPSCs (Kroeger et al., 2021). Furthermore, isogenic gene-edited ATF6−/− hESCs also generated retinal organoids with the same morphologic defect (Kroeger et al., 2021). Together, these findings identify a robust sub-cellular phenotype in developing cones on retinal organoids that account for photopic vision loss: defective cone IS/OS formation and extension. These retinal organoid findings are also congruent with adaptive optics imaging of ATF6 patients' fovea showing an absence of cone IS/OS (Kroeger et al., 2021; Mastey et al., 2019).

ATF6 mutant retinal organoids also revealed additional subcellular and genetic defects besides cone IS/OS mal-development that may also contribute to cone dysfunction in people. Ultrastructural and transcriptomic analysis revealed extensive mitochondria damage (malformed cristae, enlarged/dilated mitochondria) coupled with significant induction of oxidative phosphorylation genes (Lee et al., 2022). These mitochondria defects likely impact rods and cones because they were widely found in superficial ultrastructural sections of ATF6 mutant retinal organoids (Lee et al., 2022). Also, Müller glia showed activated gene signatures in transcriptomic data from ATF6 mutant retinal organoids (Lee et al., 2022). Since ATF6 is expressed in all retinal cells (Lee et al., 2020), these mitochondria defects and Müller glia activation could be a direct consequence of ATF6 dysfunction. These defects may also reflect secondary pathology due to primary dysfunction of the developing cones in the ATF6 mutant retinal organoids.

6.3. ATF6 is dispensable for cone development but protects retina from aging and proteotoxicity in mice

While clinical and retinal organoid findings show that ATF6 is essential for cone development in people, ATF6 is dispensable for cone development in mice (Kohl et al., 2015; Lee et al., 2021). ATF6−/− mice carry exon deletions that prevent generation of ATF6 protein (Wu et al., 2007), similar to patient ATF6 disease multi-exon deletion alleles (Lee et al., 2020). However, by contrast to the congenital photopic cone dysfunction seen in people, at all mouse ages <18 months, no defects in retinal lamina thickness, cone photoreceptor numbers by PNA staining, and cone opsin protein expression were found in ATF6−/− mice (Kohl et al., 2015). Consistent with this, no defects in ERG responses (photopic and scotopic) were observed in ATF6−/− mice. However, in aged mice (>18 months), photopic and scotopic ERG responses declined in ATF6−/− mice along with retinal thinning by histology (Kohl et al., 2015). Interestingly, when crossed with P23H rhodopsin knock-in mice, earlier retinal dysfunction accompanied by reduced rhodopsin protein turnover was seen (Lee et al., 2021). Our study reveals that the loss of ATF6 leads to a significant accumulation of P23H rhodopsin. This accumulation is accompanied by hyperactivation of the IRE1 pathway, as a compensatory response to the absence of ATF6. However, as P23H rhodopsin mice age, we find that loss of ATF6 accelerates retinal degeneration (Lee et al., 2021). Thus, our findings provide direct *in vivo* evidence that ATF6 is important in rod photoreceptors to maintain rhodopsin protein quality in a mouse model of retinitis pigmentosa, and its absence worsens retinal degeneration. These findings indicate that ATF6 does protect murine retina from aging and genetic ER/oxidative stressors like the misfolded P23H rhodopsin protein. These data support that ATF6 supports retinal homeostasis – especially protection from ER/oxidative stress and misfolded proteins - throughout life. In people, ATF6 supports another essential function – promoting cone subcellular structural formation during retinal development.

6.4. ER stress and cone disease arising from CNGA3, CNGB3, and cone opsin mutations

In addition to ATF6's direct role in the pathogenesis and progression of cone disease in people, ER stress and UPR activation are also implicated in many other human cone diseases linked to misfolded ER client proteins (secreted and transmembrane proteins). For instance, hundreds of mutations in the CNGA3 and CNGB3 transmembrane channel proteins lead to

cone dysfunction and achromatopsia (Michalakis et al., 2022). Missense mutations in the S-opsin transmembrane protein cause S-cone dysfunction and tritanopia (Weitz et al., 1992). These and many other mutations linked to cone disease damage protein structure leading to retention of the misfolded receptor or channel protein in the endoplasmic reticulum. ER protein misfolding elicits ER stress and triggers UPR activation (Walter and Ron, 2011). However, the consequences of ER stress and UPR activation in these cones carrying misfolded proteins remain to be determined.

7. ER stress signaling in diabetic retinopathy and angiogenesis

As one of the most common complications of diabetes, diabetic retinopathy (DR) poses a significant risk for the development of visual impairment or even severe blindness in patients. Approximately one-third of diabetic patients experience some degree of DR, and around 10% of affected individuals progress to more advanced forms, including diabetic macular edema (DME) and proliferative DR (PDR) (Yau et al., 2012). Recent investigations suggest that DR is a neurovascular disorder characterized by neural retina deterioration and accompanying microvascular abnormalities (Simo et al., 2018). The molecular mechanisms underlying DR are complex, and the specific pathophysiological processes driving the progression from diabetes mellitus to DR are not yet fully understood. Various factors have been linked to the development of DR, including abnormal glucose and lipid metabolism, oxidative stress, inflammatory cytokine exudation, and autophagy. Moreover, all these factors are known to regulate the ER stress response.

7.1. Activation of the PERK signaling in DR

Studies on diabetic mice and rats have revealed that persistent increase or fluctuations in hyperglycemia result in the upregulation of the PERK/eIF2α/ATF4/CHOP signaling in retinal cells ((Chen et al., 2012; Zhong et al., 2012a)Kong et al., 2018; Li et al., 2009c; Ma et al., 2017; Ma et al., 2014; Zhang et al., 2014). Meanwhile, the damage to retinal cells is primarily associated with dysregulation of the PERK/CHOP and IRE1 pathways, which may exert opposite effects (Elmasry et al., 2018; Kong et al., 2018; Li et al., 2011, 2014a; McLaughlin et al., 2019; Yang et al., 2019). It has been proposed that dyslipidemia, a biomarker of diabetes, and lipid oxidation activate UPR signaling in diabetic retinas (Fu et al., 2014). Indeed, we and other groups reported increased UPR activation in the retina in db/db mice, a type 2 diabetes model (Ma et al., 2017; Tang et al., 2011), and in human retinas from donors with type 2 diabetes (Du et al., 2013). In pancreatic β cells, excessive accumulation of free fatty acids (FFAs) observed in the serum of type 2 diabetic patients triggers apoptosis through activation of the PERK/eIF2α/ATF4/CHOP pathway while suppressing both the IRE1 and ATF6 pathways (Cnop et al., 2007). These findings on apoptosis and β-cell dysfunction were confirmed by another study on diabetic liver cells conducted by Cao and colleagues (Cao et al., 2012). In the diabetic retina, lipid peroxidation can alter the phospholipid composition and fluidity of the ER membrane, leading to ER stress, accumulation of fatty acid metabolites, increased mitochondrial beta-oxidation, and subsequent stimulation of ROS production. This could in turn activate the UPR and trigger apoptosis. Understanding the role of ER stress signaling in lipid peroxidation induced retinal cell death holds great promise in identifying new pathways in the pathogenesis of DR.

In the early stage of DR, circulating inflammatory cytokines, such as VEGF, TNFα, and IL-1β, damage the retinal microvessels in diabetic eyes. For example, TNF-α, IL-1β and/or IL-6 have been shown to induce ER stress in hepatocytes (Zhang et al., 2006) and the T-cell-derived cytokine interferon-γ (IFN-γ) activates PERK and PERK-associated apoptosis in oligodendrocytes (Lin et al., 2005). The mechanism underlying this activation is likely associated with the release of calcium from the ER and the generation of ER stress. All these events can occur in cells when metabolic factors, such as cholesterol, nonesterified fatty acids, glucose, and homocysteine, induce the ER stress response and the inflammatory response simultaneously (Zhang and Kaufman, 2008). Regarding the latter, the inflammatory response could be directly triggered by UPR signaling. Indeed, in the last decade, our labs have shown that activated UPR causes cytokine and chemokine overproduction in the retina (Chen et al., 2012; Huang et al., 2015c; Li et al., 2009b; Rana et al., 2014; Wang et al., 2013; Zhong et al., 2012c). In one study, we found that IL-1β and IL-6 expression was responsive to the treatment of C57BL6 retinas with tunicamycin, a UPR inducer, or subretinal injection with AAV2/5 overexpressing ATF4, in C57BL6 mice (Rana et al., 2014). In our other studies, we demonstrated that treatment of C57BL6 mice with periocular injections of tunicamycin-induced retinal TNFα and VEGF expression (Li et al., 2009b) and moreover, intravitreal injection of adenovirus overexpressing ATF4 significantly increase retinal levels of monocyte chemoattractant protein 1 (MCP1) and inflammatory cell infiltration (Huang et al., 2015c). We further demonstrated that ATF4 and its downstream network are directly responsible for the regulation of pro-inflammatory cytokine gene expression. This series of experiments confirmed that ATF4 is the transcriptional factor controlling the expression of both cytokines and chemokines.

7.2. The PERK signaling in regulation of vascular function and angiogenesis

We previously reported high glucose treatment induces the activation of UPR with enhanced GRP78 expression, PERK and eIF2a phosphorylation, and ATF4 expression in cultured human retinal microvascular endothelial cells (RMECs). In human pericytes, fluctuations in glucose concentration, but not constantly high glucose, increases ATF4 and CHOP expression with a concomitant elevation of MCP-1 production (Zhong et al., 2012c). Treatment of the cells chemical chaperone TUDCA suppresses MCP-1 secretion, suggesting a role of ER stress-mediated ATF4/CHOP activation in MCP-1 production. In agreement with these findings, it was reported that advanced glycation end products (AGE) and modified low-density lipoprotein activate the PERK pathway in human retinal pericytes, which was ameliorated by chemical chaperone UDCA (Chung et al., 2017). Our *in vivo* studies support a role of the activated PERK signaling in retinal angiogenesis, a hallmark pathological feature of PDR. We found that retinal levels of p-PERK, p-eIF2α, ATF4, and CHOP are significantly increased in mice with oxygen-induced retinopathy (OIR) (Chen et al., 2012; Li et al., 2009c; Wang et al., 2013). Heterozygous knockout of ATF4 or inhibition of ATF4 function decreased VEGF expression, reduced retinal inflammation, and ameliorated BRB breakdown and vascular leakage in diabetic mice (Chen et al., 2012; Zhong et al., 2012a). We further showed that ATF4 deficiency reduced the rate of retinal neovascularization and angiogenic gene expression (*Flt1*, *Vegf1, Hif1*, and *Tgb1*) in OIR mice (Wang et al., 2013). Mechanistically, we found that overexpression of ATF4 enhanced, while inhibition of ATF4 attenuated, the basal and LPS-stimulated phosphorylation of NF-

κB, P38, and JNK and pharmacological inhibition of NF-κB, P38, or JNK significantly reduced ATF4-stimulated MCP-1 secretion in endothelial cells (Huang et al., 2015c). Recently, we expanded the search of ATF4 downstream targets regulating the pericyte and endothelial cell loss in DR and found that TRIB3 activation is responsible for the increase in acellular capillary area and the decrease in pericytes in the retina in a mouse model of type 1 diabetes (Pitale et al., 2021). The retinal neovascular area was also dramatically reduced in TRIB3$^{-/-}$ mice with OIR. We proposed that the mechanism underlying TRIB3-mediated vascular cell control is most likely linked to the control of cytokine and pro-inflammatory gene expression. Taken together, the results from our studies over the past decade suggest a critical role of PERK signaling in the regulation of vascular endothelial and pericyte damage and pathological angiogenesis in DR.

7.3. The PERK signaling in retinal ganglion cell homeostasis in DR

Mounting evidence suggests that the degeneration of retinal neurons can occur before clinical manifestation as typical microvascular alterations in DR and retinal cell death is often first detected RGCs (Simo et al., 2022). Oshotari and colleagues reported that RGC apoptosis in diabetic retinas exposed to high levels of glucose *in vitro* correlated with the activation of the PERK pathway and increased levels of CHOP (Oshitari et al., 2011). In STZ-induced diabetic rats, activation of PERK UPR mediators (e.g., CHOP), JNK, and caspase 12 protein were found increased and associated with apoptosis (Yang et al., 2013). In a study using a transformed mouse RGC cell line, Zhang and colleagues reported that RGC apoptosis occurs due to activation of ATF4 and CHOP mediators of PERK signaling under conditions mimicking diabetes (Zhang et al., 2018). Finally, our lab demonstrated that human and mouse diabetic RGCs overexpress TRIB3 protein and that the retinal ablation of ATF4-regulated TRIB3 proteins increases RGC survival in the diabetic retina (Pitale et al., 2021). Intriguingly, a recent study shows that increased ER stress in retinal neurons, especially RGCs, in OIR suppresses reparative angiogenesis through reducing neuron-derived angiogenic guidance cue neutrin-1 (Binet et al., 2013). Thus, targeting neuronal ER stress may also improve retinal vascular function in ischemic retinopathy including DR.

7.4. The PERK signaling in glia activation in DR

There are three types of glial cells, including astrocytes, microglia, and Müller cells, in the retina. These cells, in particular Müller cells, are highly responsive to metabolic changes, injuries, or stressors that may cause neuronal and vascular dysfunction [reviewed in (Coughlin et al., 2017; Kelly et al., 2018)]. Increased activation of Müller glial cells or reactive gliosis has been reported in diabetic retinas (Coughlin et al., 2017; Simo et al., 2022). In our previous studies, we investigated the role of the PERK signaling in Müller glial activation in conditions mimicking diabetes (Zhong et al., 2012a). We have shown increased expression of p-eIF2α, ATF4, and CHOP in retinal Müller cells in STZ-diabetic mice. In cultured Müller cells, high glucose is sufficient to induce ER stress and PERK pathway activation and inhibition of ER stress inhibits high glucose-induced ATF4 and CHOP upregulation. Further, we demonstrated that ATF4 interacts with hypoxia inducible factor 1α (HIF-1α) and JNK pathways, playing a critical role in the regulation of inflammatory factor expression and secretion from Müller cells. We also showed that

ATF4 is required for VEGF secretion from Müller cells in diabetic conditions (Zhong et al., 2012a). These findings collectively indicate an important role of the PERK pathway in Müller glial activation in DR. Relative to Müller cells, the role of the PERK signaling in microglia and astrocytes is less well explored in the diabetic retina. In one study, Wang and associates showed increased ATF4 expression in astrocytes of optic nerves but not in the retina of STZ-diabetic rats (Wang et al., 2020). In another study, Lind et al. examined the UPR activation in cultured astrocytes and rat brain during experimental diabetes (Lind et al., 2013). They found no alterations in p-eIF2α, ATF4, and CHOP in astrocytes with extended high glucose treatment for up to 4 weeks or in STZ-treated rats with up to 7 months of diabetes. The authors concluded that in sharp contrast to retinal Muller cells and diabetic retina, the astrocytes and STZ-diabetic brain are relatively resistant to diabetes-induced ER stress. Future research should elucidate if the PERK and other UPR pathways regulate the function of astrocytes and microglia in DR.

7.5. Activation of the IRE1/XBP1 signaling in DR

Like the PERK signaling but to a less extent, studies have shown that the IRE1/XBP1 pathway is activated in diabetic retinal tissue and actively involved in the regulation of oxidative stress, inflammation, and energy metabolism in retinal cells (Li et al., 2011; McLaughlin et al., 2018, 2019; Yang et al., 2019). Activation of the IRE1/XBP1 pathway, demonstrated by increased levels of p-IRE1a and spliced XBP1, has been observed in the retina of Akita mice and STZ-induced diabetic mice, both of which are common animal models of type 1 diabetes, and db/db mice, a model of type 2 diabetes (Li et al., 2011; Ma et al., 2014, 2017). In cultured human retinal microvascular endothelial cells and Müller cells, the IRE1/XBP1 pathway can be activated by hypoxia and hyperglycemia, two major insults pertinent to the pathogenesis of DR (Li et al., 2011; Yang et al., 2019). Exposure of retinal endothelial cells to hypoxia or inflammatory cytokine TNF-α increases the expression of adhesion molecules ICAM-1 and VCAM-1, resulting in enhanced endothelial inflammation, tight junction damage, and vascular leakage. Using transcriptomic analysis, a recent study identified that XBP1 is downregulated in retinal pericytes isolated from 3-month-diabetic animals (Rangasamy et al., 2020). The exact role of XBP1 in pericyte dysfunction and pericyte loss during diabetes remains to be investigated.

7.6. The IRE/XBP1 signaling in retinal inflammation

Activation of the IRE1/XBP1 pathway has been implicated in regulation of retinal inflammation. In an earlier study, we demonstrate that preconditioning with mild ER stress induces a transient activation of the IRE1/XBP1 pathway resulting in increased expression of XBP1s in retinal endothelial cells. ER stress preconditioning protects the cells from TNF-a-induced endothelial inflammation and retinal vascular leakage and this protective effect is mediated by XBP1 (Li et al., 2011). We showed that overexpression of spliced XBP1 negatively regulates the activation of IRE1α and inhibits NF-kB-mediated ICAM-1 and VCAM-1 expression, suggesting a protective role of spliced XBP1 against endothelial inflammation (Li et al., 2011). Interestingly, a recent study using next-generation sequencing and bioinformatic analysis of XBP1-binding motifs identified XBP1 as a repressor of IRE1 mRNA expression during the UPR in HeLa cells (Gebert et al., 2021). The negative regulation of the IRE1 activity by XBP1s needs further in-depth study in retinal cells.

In a recent study, we determine the role of XBP1 in regulation of Müller cell activation and cytokine production. We found that conditional knockout of the XBP1 gene in Müller cells leads to a substantial increase in VEGF and TNF-a production resulting in enhanced retinal inflammation and vascular leakage in diabetic animals (Yang et al., 2019). Consist with these findings, as discussed earlier, inhibition of XBP1 in 661w cells leads to increased inflammatory cytokine production while deletion of PERK reduces ER stress-induced inflammation, suggesting a differential role of the XBP1 and PERK pathways in photoreceptor-derived inflammatory factor production (Zhu et al., 2017).

7.7. The IRE/XBP1 signaling in retinal neurodegeneration in DR

Neuronal dysfunction and degeneration are considered integral components in DR pathogenesis, ultimately resulting in vision impairment and blindness. To determine the role of XBP1 in retinal neuronal survival and function, we generated retina-specific conditional XBP1 knockout mice. We found that XBP1 deficiency does not affect retinal development but causes a significant reduction in retinal function and degeneration of retinal neurons with aging (McLaughlin et al., 2018). These findings are consistent with previous observations in Drosophila that mutations of IRE1, but not mutations of XBP1, cause defective rhodopsin delivery in photoreceptor development and degeneration of rhabdomeres (Coelho et al., 2013). The latter is the light-sensing organelle in drosophila functionally equivalent to the photoreceptor OS in vertebrates. Furthermore, IRE1 is required for rough ER differentiation and expansion in developing drosophila photoreceptors (Xu et al., 2016). In contrast, mice with selective deletion of the IRE1 gene in photoreceptors show normal photoreceptor development but lead to reduced outer nuclear layer thickness after 6 months of age (Massoudi et al., 2023). The results from these studies strongly suggest that the IRE1/XBP1 pathway is dispensable for photoreceptor/retinal neuronal development but is important for maintaining ER homeostasis, cellular survival, and function in retinal neurons.

In a later study, we determined the effect of XBP1 deficiency on diabetes-induced retinal dysfunction and neurodegeneration. We found that loss of XBP1 increases the susceptibility of retinal neurons to diabetic metabolic stress resulting in accelerated photoreceptor degeneration, RGC loss, and increased glial activation (McLaughlin et al., 2019). The number of photoreceptor ribbon synapses was also significantly reduced in XBP1 knockout mice during diabetes, suggesting a role of XBP1 in regulation of photoreceptor synaptic integrity (McLaughlin et al., 2019)(McLaughlin et al., 2023). In line with these observations, Massoudi et al. showed that loss of IRE1 in photoreceptors leads to accelerated photoreceptor degeneration in a *RhoP23H* mutation-induced RP model (Massoudi et al., 2023). These findings support an important role of the IRE1/XBP1 pathway in maintaining retinal neuronal function and structural integrity during normal and stress conditions. Further discussion can be found in our recent review article (McLaughlin et al., 2022). More recently, UPR dysregulation was identified during 1-deoxyspingolipid induced toxicity to retinal organoids, and this finding may shed insight into macular telangiectasia (Rosarda et al., 2023).

8. The ER-mitochondria crosstalk

The ER is involved in the regulation of multiple vital cellular processes, namely protein synthesis and folding, lipid biosynthesis, and calcium metabolism (Schwarz and Blower, 2016). To achieve homeostasis within such a functionally multifaceted organelle, the ER acts in part with the mitochondria through a protein-and-membrane complex called the mitochondria-associated ER membrane (MAM) to orchestrate many of the signaling pathways involved in ER function (Fig. 5) (Hayashi et al., 2009). Before the advent of advanced biochemical techniques, the MAM was first described in 1958 b y Copeland and Dalton as a unique association between the ER and mitochondria after examining pseudobranch glands of teleosts (Copeland and Dalton, 1959). It was not until 1990 that it was highly purified from rat liver by Vance as “Fraction X,” which was further described as a mitochondrial membrane fraction that was suspected to take part in the transfer of lipids between the ER and mitochondria (Vance, 1990). The most recent liquid chromatography (LC)-mass spectrometry (MS)-based proteomic analyses in rat retinas have now revealed the MAM to be a scaffold consisting of as many as >2660 proteins that serve as the physical interface for biochemical crosstalk between the ER and mitochondria (Wang et al., 2022b). A smaller and simpler structure analogous to the mammalian cell MAM has also been discovered in yeast as well, termed the ER-mitochondria encounter structure (ERMES) (Kundu and Pasrija, 2020). Similar to the MAM in mammalian cells, the ERMES has also been deemed crucial for lipid exchange between the ER and mitochondria (Kawano et al., 2018). Evidence of such ER-mitochondrial associations across eukaryotic cells of varying complexities suggests that these associations are basic and vital to normal cell function as well as to the maintenance of both ER and mitochondrial homeostasis.

Structurally, the MAM tethers the ER to the mitochondria so that they may crosstalk at an approximate distance of 10–25 nm, though this range may vary based on cell condition and spatial occupancy by ER ribosomes (Csordas et al., 2006; Wang et al., 2021a). While some tethering proteins solely act to physically link the ER to the mitochondria (e. g., the MOSPD2-PTPIP51 complex (Di Mattia et al., 2018)), other tethering proteins (e.g., the IP3Rs-Grp75-VDACs complex (Tubbs et al., 2014), VAPB-PTPIP51 complex (Qiao et al., 2017; Stoica et al., 2014), and REEP1 (Lim et al., 2015)) may play a more dynamic role in maintaining and/or adjusting the morphology of the ER and mitochondrial membrane surfaces (Wang et al., 2021a). According to electron microscopy studies, MAM tethering proteins tend to connect the ER to the mitochondria at (1) a single site that covers roughly 10% of the outer mitochondrial membrane (OMM) surface, (2) at multiple sites covering 50% of the OMM, or (3) at nearly all sites along the OMM covering nearly 100% of the mitochondrial surface area (Fujimoto and Hayashi, 2011).

Largely a function of structure, the MAM coordinates numerous processes such as calcium regulation, mitochondrial remodeling, inflammation, reactive oxygen species (ROS) production, apoptosis, and lipid transfer based on the composition of its proteome located within and between the ER and OMM (Fig. 5) (Lee and Min, 2018). For example, PERK is an important ER stress sensor protein that is heavily embedded within the MAM. The loss of PERK in MAM has been shown to not only weaken the ER-mitochondrial tethering by the MAM but also disrupt ER morphology, impair calcium signaling, and dysregulate the

ER-mitochondrial crosstalk necessary for ROS-induced cell death (Verfaillie et al., 2012). The MAM interface also serves as an important site for inflammasome formation as it houses NOD-like receptor protein 3 (NLRP3) in its activated state (Missiroli et al., 2018; Zhou et al., 2011). It is even involved in the antiviral response via Gp78, an E3 ubiquitin ligase involved in the ERAD pathway that also localizes to the MAM (Jacobs et al., 2014). Hence, the MAM's diverse proteomic composition allows it to serve as a key crossroad site for a variety of ER-mitochondrial signaling.

Given the MAM's intricate involvement in key signaling pathways contributing to ER and cellular homeostasis, disturbances in the MAM proteome can lead to impairment of ER-mitochondrial communication, further resulting in calcium dysregulation, aberrant metabolism, mitochondrial damage, and oxidative stress. Such consequences have been linked to the pathogeneses of diseases including but not limited to insulin resistance (Cheng et al., 2020a; Tubbs et al., 2014), atherosclerosis (Wang et al., 2021b), cancer (Yang et al., 2023a), and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Hedskog et al., 2013; Liu and Yang, 2022). Although more studies are needed to elucidate the exact scale of the MAM's impact on regulating systemic health, growing evidence has made it clear that there is indeed an association between MAM dysfunction and disease on a macro level. As such, the MAM proteome may offer additional avenues for the study of potential therapeutic targets.

8.1. MAM and calcium regulation

The MAM plays an indispensable role in regulating calcium signaling between the ER and mitochondria. The ER is the primary site of intracellular calcium storage. In the healthy state, a low constitutive level of calcium is transmitted from the ER to mitochondria to regulate essential cellular processes such as apoptosis, ATP production, and metabolism (Marchi et al., 2018). Numerous MAM proteins involved in the direct supply of calcium from the ER to mitochondria have been discovered, the most well-studied of which has been the inositol 1,4,5-trisphosphate receptor (IP3R)-75 kDa glucose-regulated protein (GRP75)-voltage-dependent anion channel (VDAC) MAM tethering complex (Bononi et al., 2012). IP3Rs located on the ER membrane are physically attached to GRP75 within the MAM and facilitate the release of ER calcium into the cytoplasm. Once released, the cytoplasmic calcium is shuttled into the mitochondrial intermembrane space (MIMS) via VDAC porins. Impaired calcium signaling is critically involved in the process of cell death, as calcium overload within the mitochondrial matrix disrupts normal metabolism and triggers apoptosis (Giorgi et al., 2012; Zhivotovsky and Orrenius, 2011). Interestingly, the distance and surface area at which the MAM tethers the ER to the mitochondria are not trivial in the context of calcium signaling and cell death; in one study, large ER-mitochondrial contacts as created by the MAM (i.e. contacts covering 20% of the mitochondrial surface) have been associated with higher concentrations of IP3R-mediated calcium release and greater saturation of calcium binding to aequorin chimeras in the MIMS (Rizzuto et al., 1998). Another study found that mitochondria were exposed to much higher levels of calcium when in close contact with the ER than with the rest of the cytoplasm, lending significance to the fact that the physical ER-mitochondria interface plays an integral role in calcium homeostasis (Rizzuto et al., 1993).

Several studies have sought to investigate other protein targets associated with the IP3R-GRP75-VDAC complex in the MAM that, when impaired, may also influence normal ER calcium trafficking. One such protein is mammalian target of rapamycin complex 2 (mTORC2), a kinase involved in pathways of cell proliferation, growth, and metabolism that also phosphorylates kinases linked to the pathogenesis of cancer and diabetes (Oh and Jacinto, 2011). One study found that mTORC2 localizes to the MAM in a growth factor-dependent manner and modulates calcium flux through Akt-dependent IP3R phosphorylation (Betz et al., 2013). The same study also showed that an mTORC2 knockout significantly compromises MAM integrity by reducing the number of ER-mitochondrial contact sites by about 40%. Cyclophilin D (CYPD) is another protein closely linked to the IP3R-GRP75-VDAC complex that, when downregulated in mice, similarly disrupts MAM integrity and blunts IP3R-mediated calcium transfer, which further induces hepatic insulin resistance downstream (Rieusset et al., 2016). The IP3R complex in the MAM additionally interacts with phosphatase and tensin homolog deleted on chromosome 10 (PTEN), a tumor suppressor protein that also localizes to the signaling domains in the MAM involved in ER-mitochondria calcium transfers (Bononi et al., 2013). When silenced, PTEN was found to impair calcium release from the ER and diminish cellular sensitivity to apoptosis. Through proteins associated with the IP3R-GRP75-VDAC trimeric complex alone, the MAM offers multiple insights into the mechanism of calcium regulation between the ER and mitochondria.

8.2. MAM and mitochondrial remodeling

Mitochondrial remodeling refers to the dynamic events that shape and alter mitochondrial morphology, including but not limited to mitochondrial fusion and fission, mitophagy, and mitochondrial biogenesis (Gottlieb and Bernstein, 2016). Proper mitochondrial remodeling is crucial to normal cell function as studies have shown that inhibition of fission, fusion, and mitophagy events leads to the accumulation of dysfunctional mitochondria and macro-level consequences. In mouse hearts, for example, cardiomyocyte-specific knockout of Dynamin-related protein (Drp)-1, which is an inducer of mitochondrial fission, resulted in a generalized loss of mitochondria and full-blown heart failure after six to seven weeks (Song et al., 2015). Other prominent proteins in mitochondrial remodeling include mitofusin (Mfn), a mitochondrial fusion factor attached to the OMM, Opa1, a dynamin-related GTPase in the MIMS that controls fusion and fission events, Mff, an OMM protein that mediates fission, and mitochondrial elongation factor 1 (Mief1), also another fusion factor (Gottlieb and Bernstein, 2016).

Though the mechanisms are not always clear, the MAM has been shown to house a few of the above proteins and serve as a key entity in regulating mitochondrial remodeling dynamics. In mouse embryonic fibroblasts, the loss of MFN2 was associated with a MAM deficiency (Hu et al., 2021b). Moreover, during mitochondrial fission induced by energy stress, the cellular energy sensor AMP-activated protein kinase (AMPK) translocated from the cytosol to the MAM and mitochondria, highlighting the MAM's role in mediating energy stress-induced fission. In retinal precursor cells, an *Mfn2* knockdown exacerbated MAM dysregulation and mitochondrial dysfunction under both normal and oxidative stress conditions, again highlighting the role of Mfn2 in mitochondrial maintenance (Yang et al.,

2023b). During apoptosis, DRP1 is recruited to the MAM by C1q/TNF-related protein 1 (CTRP1), which itself partly localizes to the MAM based on electron microscopy studies (Sonn et al., 2021). Podocytes exhibit an abundance of MAMs when undergoing excessive mitochondrial fission mediated by A-kinase anchoring protein 1 (AKAP1)-DRP1 signaling in diabetic nephropathy (Li et al., 2023). In another study, levels of DRP1 in the MAM were also found to increase in response to hypoxia, which can trigger mitophagy (Wu et al., 2016).

Several other MAM proteins involved in mitochondrial fission, mitophagy, and biogenesis have also been discovered. siRNA silencing of FUN14 domain containing1 (FUNDC1), a novel MAM protein that functions as a mitophagy receptor, resulted in mitochondrial elongation and prevention of mitophagy in HeLa cells under hypoxic conditions (Wu et al., 2016). Phosphofurin acidic cluster sorting protein 2 (PACS2) is an important regulator of MAM formation that has been studied in human kidney 2 (HK-2) cells (Li et al., 2022). In addition to restoring MAM integrity, PACS2 was also suggested to play a role in decreasing high glucose-induced mitochondrial fission by inhibiting the recruitment of DRP1. The MAM may also participate in mitochondrial biogenesis via the transport of ER cholesterol to mitochondria; one study reported the presence of dihydroceramide desaturase Δ4-dihydroceramide desaturase 1 (DEGS1) not only in the ER but also in the MAM (Planas-Serra et al., 2023). By inducing a DEGS1 deficiency in patient fibroblasts, the authors observed aberrant mitochondrial morphology and consequent defects in oxidative phosphorylation, disruption of lipid droplet biogenesis, and abnormal lipid and phospholipid metabolism. Accumulating evidence thus suggests that MAM-associated proteins, both those that are resident in the MAM and others that may regulate the MAM remotely, are involved in the maintenance and life cycle of mitochondria. Further studies are needed to explore the exact extent to which other remodeling proteins localize to and interact with the MAM during remodeling events.

8.3. MAM and inflammation

Inflammation is an overarching term that refers to a host's protective immune response mounted against pathogenic microbes on both a systemic and intracellular level. On an intracellular level, the activation of inflammasomes as the gateway to systemic inflammation has been of great interest, especially because it reveals further information regarding the mechanistic origins of inflammation. Additionally, inflammasomes have been linked to numerous ailments—neurodegenerative disorders, autoimmune diseases, cancers, and metabolic disorders—and may therefore offer possibilities for therapeutic targets if understood thoroughly (Heneka et al., 2018; Sharma and Kanneganti, 2021; Wilson and Cassel, 2010). The inflammasome itself is a protein complex consisting of a sensor protein, an adaptor called apoptosis-associated speck-like protein (ASC), and a zymogen procaspase-1 protein. The most well-studied subfamilies of inflammasome, differentiated by their sensor proteins, include NLRP3, NLRP1, NLRC4, and AIM2. Given that mitochondria are a major source of ROS, which can trigger the activation of the NLRP3 inflammasome (Latz et al., 2013), it is no surprise that MAMs have been found to participate in the inflammatory process via inflammasome activation (Zhou et al., 2011). To date, the only inflammasome known to interact with the MAM is NLRP3 (Missiroli et al., 2018), which

localizes to the MAM with its adaptor ASC in the presence of NLRP3 inflammasome activators (Zhou et al., 2011).

There are several stress pathways through which the MAM may trigger inflammasome activation, such as hypoxia, mitochondrial fission, autophagy, and calcium overload (Thoudam et al., 2016). Hypoxia is known to cause mitochondrial dysfunction by depriving the mitochondria of oxygen needed for ATP generation, ultimately leading to superoxide formation, oxidative stress, and eventual mitochondrial damage (Jassim et al., 2021). The damaged mitochondrial components can then be recognized as damage-associated molecular patterns (DAMPs) by inflammasome components, instigating inflammasome complex formation (Thoudam et al., 2016). Interestingly, in some cases hypoxia and mitochondrial turnover via mitophagy have actually provided a context for the prevention of inflammation; one study found that the mitophagy receptor FUNDC1 works to inhibit NLRP3 inflammasome activation by promoting mitophagy in the setting of hypoxia (Zheng et al., 2021). Mitochondrial fission has been associated with inflammation as well in lipopolysaccharide (LPS)-stimulated microglial cells (Park et al., 2013); LPS was found to induce the translocation of Drp1 from the cytosol to the MAM, where it would not only promote fission by cleaving mitochondria but also coincide with the expression of pro-inflammatory cytokines. Overload of mitochondrial matrix calcium caused by abnormal ER-mitochondrial calcium transfer by the MAM is another cause of mitochondrial ROS generation, leading to mitochondrial collapse and apoptosis. Here again, the mitochondrial contents released during apoptosis are detected as inflammasome-inducing DAMPs, triggering inflammation (Thoudam et al., 2016). Given the association between inflammasome activation and various diseases, it is evident that many studies have sought to identify targets in MAM-associated inflammation to discover avenues for therapy. Though inflammasome formation can be harmful with overactivation, future research in therapeutics should always be mindful of the potential negative consequences of quelling what is otherwise a necessary step in the development of the inflammatory response against pathogens.

8.4. MAM in diabetic retinopathy

The study of the MAM's role in the pathogenesis of DR is a relatively new field, but one that warrants exploration. DR is a common and serious but preventable complication of diabetes that affects over a third of diabetic adults worldwide (Lee et al., 2015). Though DR is often understood to be a primarily microvascular disease, growing evidence supports the notion that it may be caused first by neurodegenerative changes and retinal inflammation prior to the manifestation of vascular changes (Joltikov et al., 2018; Lee et al., 2018; Simo et al., 2018). As disturbances in MAM activity are associated with pathways of inflammation (Missiroli et al., 2018) and neurodegenerative disorders (Raeisossadati and Ferrari, 2022), it is reasonable to investigate whether the MAM may play a contributive role in DR. Thus far, studies have highlighted the importance of MAM formation and proper ER-mitochondrial communication in insulin signaling as a whole (Cheng et al., 2020a; Tubbs et al., 2014; Wang et al., 2022a), but relatively few have delved into their effect in DR.

An initial study of rat retinal MAM in diabetes has examined whether the diabetic condition is associated with changes in the MAM proteome (Wang et al., 2022b). Interestingly, in rats with STZ-induced long-term Type 1 diabetes, 179 out of 2664 MAM proteins (6.72%) discovered in the retina were significantly altered in concentration, many of which were found to be involved in key processes of cell survival, inflammation, calcium regulation, and protein synthesis and trafficking. Of note, the identified altered MAM proteins were linked to several non-MAM major protein regulators of inflammation, diabetes, and/or DR, illustrating the extent of the MAM's indirect involvement in a diverse array of signaling pathways. These preliminary data hint at the likely possibility that aberrations in the MAM proteome contribute to the development of DR, but further studies are needed to gauge the degree and mechanisms of its involvement. Differences in the MAM proteome may also exist depending on whether a Type 1 or Type 2 model of diabetes is utilized.

While abnormal concentrations of MAM proteins may potentially feed into DR pathology, normal concentrations of functioning MAM proteins may also instigate DR in the presence of triggers such as ER stress. For example, PERK, as a key ER stress sensor, is activated in DR given that ER stress is implicated in DR pathogenesis (Li et al., 2009b). When activated, PERK transmits ROS signals between the ER and mitochondria via its tethering function at the MAM and thereby promotes ROS-mediated apoptosis (Verfaillie et al., 2012). As long as ER stress is involved in the manifestation of DR, the MAM is equally likely to be involved as well due to its importance in maintaining ER homeostasis.

8.5. Sigma-1R, a MAM protein in retinal protection and disease

Sigma-1R is an ER-resident MAM protein that is classified as a non-opioid receptor. It has been well established that Sigma-1R is a necessary modulatory protein in calcium and lipid exchange between the ER and mitochondria, though there is also growing evidence of its involvement in autophagy, ER stress response, and protein folding (Hayashi and Su, 2007). Much is also known regarding its role in neuroprotection, making Sigma-1R a common protein of interest as a therapeutic target for disorders such as Alzheimer's disease, dementia, and Parkinson's disease (Lachance et al., 2023). Thus, it is not surprising that studies have also begun to investigate the potential therapeutic effects of this protein in the retina. Recent data from a study have suggested that Sigma-1R also serves a protective role in an optic nerve crush (ONC) model of glaucoma (Li et al., 2021a); transgenic expression of Sigma-1R in RGCs from Sigma-1R knockout mice resulted in higher RGC counts, attenuated apoptosis, and increased RGC activity following ONC. Similar results could also be seen when Sigma-1R was activated via pentazocine. These study findings associate well with previous data revealing the restorative role that Sigma-1R plays towards mitochondrial function when Sigma-1R is overexpressed and/or activated in RGCs (Ellis et al., 2017). Specifically, administration of Sigma-1R agonists and transgenic overexpression of Sigma-1R in rat RGCs that were oxygen- and glucose-deprived led to restoration of the mitochondrial membrane potential, restoration of cytochrome c activity, and decreased caspase activity. There have also been several other studies correlating accelerated RGC dysfunction and death with a Sigma-1R deficiency in mice, further underscoring the relevance of this protein in the prevention of retinal neurodegeneration (Ha et al., 2012; Mavlyutov et al., 2011).

9. ER stress signaling and autophagy

Autophagy is a self-digested pathway and a major catabolic process activated to protect cells against certain pathological conditions. The last few decades have been important for the cell biology field in establishing a link between UPR and autophagy. The link between UPR and autophagy, however, seems to be more complicated than originally thought. These two systems may act independently, or the induction of one system may interfere with the other. Autophagy can be classified into three subtypes: macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy (here referred to as autophagy) is accompanied by the process of formation of double-membrane vesicles, autophagosomes that sequester cytosolic proteins and organelles and serve as cargo degradation machinery. Later, these autophagosomes fuse with lysosomes, and as a result, intracellular components are degraded as a part of macromolecule recycling (Maiuri et al., 2007). Activation of autophagy occurs under two different stress conditions: starvation when the activation is aimed at promoting survival and accumulation of misfolded proteins leading to ER stress response when autophagy acts to eliminate damaged intracellular components (Levine and Klionsky, 2004; Martinez-Vicente and Cuervo, 2007; Matus et al., 2008). Among the 30 recently identified mammalian autophagy genes (Gallagher et al., 2016), the most common autophagy marker LC3 (Atg8) and the first identified mammalian gene Beclin-1 (Atg6) are regulated by BCL-2 protein members at the ER membrane.

During UPR, autophagy activation may be necessary to serve as a mechanism for eliminating damaged ER organelles or controlling ER expansion. For instance, the cellular process aimed at the timely removal of damaged ER is known as ER-phagy (He et al., 2021; Reggiori and Molinari, 2022; Yang et al., 2021) ER-phagy is a selective form of autophagy that safeguards cells from the damage caused by excessive ER stress and maintains ER homeostasis. ER-phagy is a multistep process that requires specific receptors and the core autophagic machinery to promote the degradation of ER components. These receptors can be found in the ER or cytosol and are subsequently recruited to the ER membrane. To date, eleven ER-phagy receptors have been identified from various species (He et al., 2021). Among them, six exist in mammals (FAM134B, RTN3L, TEX264, ATL3, SEC62, and CCPG1) and two in budding yeasts (Atg40 and Atg39), which are directly anchored on the ER membrane by their reticulon domains or transmembrane domains. The remaining identified receptors (CALCOCO1, C53, and Epr1) are located within the ER by binding to resident ER membrane proteins. Cells employ various mechanisms to tightly control ER-phagy, including the regulation of the expression of key ER-phagy players. Transcription factors play a pivotal role in controlling the expression levels of these proteins. Notable among these transcription factors are Transcription Factor EB/E3, CCAAT/Enhancer-Binding Protein β, Histone Deacetylase Large Complex, and Regulatory Protein Mig 1 and 2. Dysfunctional ER-phagy may be related to several neurodegenerative diseases, such as Hereditary Sensory and Autonomic Neuropathy (HSAN), Niemann-Pick Type C Disease, autosomal dominant hereditary spastic paraplegia, Alzheimer Disease, and Parkinson Disease (He et al., 2021) (PMID: 34571977). Although several studies have suggested a connection between ER-phagy receptors and these diseases, these associations

remain speculative at this point. It's worth noting that, as of the current knowledge, no retina-associated diseases related to ER-phagy have been described.

Many laboratories have shown that ER stress triggers autophagy, and this effect is regulated by UPR stress sensors, such as IRE1α and PERK signaling (Fig. 6) (Ding et al., 2007; Kouroku et al., 2007; Maiuri et al., 2007; Vicencio et al., 2008). Thus, ATG5 and ATG7 have been proposed to connect autophagy with ER stress through PERK signaling (Zheng et al., 2019). The protective effect of ATG5/7 overexpression on chondrocyte survival has been found to rely strongly on PERK signaling. Herewith siRNA-mediated PERK or Nrf2 knockdown reduced expressions of ATG5, ATG7, and LC3-I/LC3-II while expression of p62 was oppositely increased. Meantime, knockdown of ATF4 manifests an antagonistic effect suggesting that the overall PERK signal is the pivot for autophagy, ER homeostasis, and ER-phagy. Interestingly, overexpression of ATG5 and ATG7 in turn not only enhances autophagy but also inhibits ER stress in chondrocytes (Zheng et al., 2019). Together, ATF4 and its transcriptional target CHOP, have been proposed to regulate more than a dozen different ATG genes (B'Chir et al., 2013). Three classes of autophagy genes were distinguished recently according to their dependence on ATF4 and/or CHOP binding to specific promoter cis-elements. It was found that CHOP and ATF4 together are essential for the transcriptional activation of p62, NB1, and ATG7. The CHOP protein alone activates ATG10, Gabarap, and ATG5, while ATF4 by itself regulates the expression of Atg16l1, Map1lc3b, Atg12, Atg3, Beclin1, and Gabarap12 genes (B'Chir et al., 2013). Overall, this study reveals a novel regulatory role of the eIF2a–ATF4 pathway activated as a result of different stresses, amino acid starvation, and ER stress in tuning the autophagy gene transcription program.

Another UPR signaling pathway, the IRE1 pathway, is also known to activate autophagy. However, the mode of this activation is indirect. The IRE1 interaction with adapter proteins, such as tumor necrosis factor (TNF), receptor-associated factor 2 (TRAF2), and apoptosis signal-regulating kinase 1 (ASK1), results in the formation of the IRE1/TRAF2/ASK1 complex that activates c-Jun N-terminal kinase (JNK) (Prestes et al., 2021). In turn, JNK phosphorylates transcription factor c-Jun, inducing expression of Beclin1 (Liu et al., 2020). Moreover, this effect could be as protective against cell death, depending on the duration of ER stress (Lindner et al., 2020; Liu et al., 2020).

Approaches to investigate the role of ATF6 signaling in the regulation of autophagy have been taken as well. However, how ATF6 mediates ERS-induced autophagy remains unclear. It has been reported that silencing ATF6 inhibits autophagy and affects LC3 conversion in fibroblasts treated with hydroxycamptothecin, an antineoplastic drug, overall suggesting a role of ATF6 in autophagy activation (Tao et al., 2021). Another potential mode of ATF6-mediated regulation of autophagy is an increase in the expression of death-associated protein kinase1 (DAPK1), which in turn phosphorylates Beclin1 (Gade et al., 2014; Zhou et al., 2016). Additionally, it is known that mAtg9 trafficking, which is critical for autophagosome formation, also occurs via the ATF6-regulated expression of DAPK1 (Zhou et al., 2016). In this study, the authors found that generation of a HepG2 cell line with a stable ATF6 and DAPK1 knockdown results in a decrease in the conversion ratio of LC3 upon the treatment of quinocetone, a potent synthetic antimicrobial agent used for improving feed efficiency

and controlling dysentery in food-producing animals (Zhou et al., 2016). The UPR signaling has also been linked to autophagy in the vision research field.

9.1. Inherited retinal degeneration

A study conducted by Yamoah et al. demonstrated that the retina of rd10 mice mimicking retinitis pigmentosa (RP) in humans caused by mutant PDE6b manifests RNA binding protein (RBP) aggregation (Yamoah et al., 2023). Moreover, this accumulation takes place as an early pathogenic event, damaging non-photoreceptor retinal cell types and is independent of Pde6b gene defects. The authors also revealed that robust increases in levels of the protective ER calcium (Ca^{2+}) buffering chaperone Sigma-1R, together with other ER-Ca^{2+} buffering proteins in photoreceptors and non-photoreceptor neuronal cells, occur before any noticeable photoreceptor degeneration in these mouse retinas. In addition, the changes in the ER resident proteins were accompanied by altered expression of autophagy proteins p62 and LC3, abnormal ER widening, large autophagic vacuole formation detected by EM, and stress granule formation. The authors concluded that progressive neurodegeneration in the rd10 mouse retina is associated with early disturbances of proteostasis and autophagy, along with abnormal cytoplasmic RBP aggregation (Yamoah et al., 2023).

The human rod photoreceptor-specific rhodopsin protein was the first gene identified to cause causative RP (Dryja et al., 1990a, 1990b; Thiagalingam et al., 2007). More than 150 different mutations in RHO are associated with 25% autosomal dominant (ad) inherited RP (Meng et al., 2022). For this disease, two classes of RHO mutations have been described. Class A mutations (R135G, R135L, R135W, V345L, and P347L) trigger loss of rod function in the entire retina, with an early onset of blindness (Cideciyan et al., 1998). Class B mutations, in turn, can be divided into two subclasses: B1 and B2. The subclass B1 mutations (T17M, P23H, T58R, V87D, G106R, and D190G) lead to a milder phenotype characterized by normal rod activation kinetics and preserved rod outer segment length, although mutation-specific abnormalities in the rod visual cycle are detected. Subclass B2 mutations (G51A, Q64ter, and Q344ter) show no regional retinal predisposition for disease (Meng et al., 2022).

The P23H RHO mutation is the most prevalent RHO mutation in North America, accounting for 10% of cases of adRP. Models expressing the P23H RHO mutations include mice and rats. Moreover, both transgenic and knock-in animals have been generated, although fine mechanisms of P23H RHO aggregation and degradation have been explored *in vitro*. For example, genetic and proteomic analysis of P23H rhodopsin mouse retinas demonstrated induction of ER-associated protein degradation *in vivo* (Chiang et al., 2015; Kim et al., 2022), and Intartaglia et al. demonstrated that induction of autophagy causes clearance of the P23H RHO aggregates *in vitro* (Intartaglia et al., 2022). Previously, this group identified the ezrin protein as an inhibitor of autophagy and lysosomal functions in the retina. To identify potential pharmacological targets, the investigators inhibited ezrin and treated the P23H RHO mice with NSC668394 inhibitor daily and followed the treated mice with electrophysiological recording and molecular biological assessment of the retinal proteins. The authors revealed that the approach inhibiting ezrin promotes lysosomal clearance of diseased-linked P23H RHO agglomerates, which in turn reduced ER stress, provided robust

decreases in photoreceptor cell death, and ameliorated both retinal morphology and function. For example, reductions in PERK, XBP1s, ATF6, and CHOP and an increase in BIP were associated with a decline in LAMP1, p62, and LC3II in the treated mouse group. Therefore, a better understanding of how the therapeutic use of autophagy inducers could be applied in the degenerating retina is necessary to move the field forward in clinical studies or to evaluate the therapeutic efficacy of autophagy inducers (Intartaglia et al., 2022).

A group led by David Zacks recently reported that knock-in P23H RHO mice demonstrate elevated levels of autophagy flux, and that the pharmacological stimulation of autophagy in these mice accelerates retinal degeneration (Qiu et al., 2019). Overall, the P23H RHO mouse retinas manifested the activation of UPR markers concomitantly with increases in Beclin1, p-p62, p62, and GFP-LC3 puncta. In this study, the authors found that genetic deletion of Atg5 gene improved photoreceptor structure and function, while mTOR inhibition by CCI-779 resulted in increased autophagy and accelerated retinal degeneration in P23H RHO mice (Intartaglia et al., 2022). Contrary to the study led by Conte (Intartaglia et al., 2022), the study by Zacks lab proposed autophagy-induced cell death as a contributing factor in retinal degeneration caused by P23H RHO. Later, this group also revealed that the ratio of autophagy to proteosome (A:P) in P23H RHO is an overall important marker defining photoreceptor cell homeostasis and that shifting the A:P ratio is key to reducing proteotoxic cell death (Qiu et al., 2019). In the referred study, the P23H mice were treated with a chemical chaperone (4-phenylbutyric acid) to improve rhodopsin folding or with a selective phosphodiesterase-4 inhibitor (rolipram) to increase proteasome activity. Both treated P23H RHO mouse groups exhibited a reduced ER stress response, decreased autophagy flux, increased proteasome activity, and decreased activation of cell death pathways (Qiu et al., 2019).

Using transgenic T17M RHO mice modeling adRP in humans, our group also detected aberrant autophagy in the retina (Bhootada et al., 2016). We found that at P30, the T17M RHO retinas show increased ER stress markers, such as PERK, p-eIF2α, ATF4, and p-ATF6, in addition to a reduction in LC3 conversion and beclin1 and p62 levels. Conversely, ATF4 knockdown significantly reduced retinal degeneration in T17M RHO mice, leading to photoreceptor survival as measured by scotopic and photopic ERGs and photoreceptor nuclei row counts. This delay was accompanied by a dramatic decrease in UPR signaling, restoration of LC3 conversion, and levels of Beclin1 and p62. We therefore proposed that an increase in autophagy genes may also manifest temporal protection in T17M RHO ATF4 ± mice and this strategy may contribute to photoreceptor health at early time points through increasing a clearance of intracellular cargo; however, this approach may not be sufficient to maintain cellular homeostasis at later time points (Bhootada et al., 2016).

Recently, in an $Rh1^{P23H}$ *Drosophila* model of adRP, it was proposed that degradation of wild-type rhodopsin is mediated by selective autophagy induced by IRE1/XBP1 signaling and insufficient proteasome activities (Zhao et al., 2023). The authors revealed that the upregulation of PERK signaling during ER stress prevents autophagy and suppresses retinal degeneration in the fly adRP model. Thus, by comparing the $Rh1^{P37H–GFP}$, $PERK^{RNAi}$, and $Rh1^{P37H}$-GFP of flies' retinas, the authors found that deficiency in the PERK pathway overactivates IRE1, leading to the accumulation of $Rh1^{P37H}$ due to insufficient

proteasome activity and degradation of wild-type Rh1 by autophagy, ultimately causing neuron dysfunction and degeneration. The authors proposed a pathological role of autophagy under these neurodegenerative conditions and indicated that promoting PERK activity could be used to treat ER stress-related neuropathies, including adRP (Zhao et al., 2023).

Not only animal models of adRP manifest concomitant upregulation of UPR markers and autophagy. We examined rd16 mice, which mimics Leber congenital amaurosis and manifest severe and rapid ciliopathy due to expression of the mutant gene encoding CEP290 (Collin and Garanto, 2017). In these animals, we found persistent activation of the integrated stress response (p-eIF2α, ATF4, TRIB3, GADD34, and CHOP) and compromised activities of AKT and mTOR at P15 and P20 (Starr et al., 2018). We also found an increase in beclin1, LC3 conversion (I to II), and p62 accumulation, suggesting an increase in autophagy flux (Saltykova et al., 2021). However, when we visualized the rd16 retina expressing the RGP-eGFP-LC3 transgene driven by the control of the CAG promoter under fluorescence microscopy, we found a decrease in the number of red puncta (RFP and acid insensitive) localized in the IS of rd16 photoreceptors. The latest suggests that the conversion from autophagosome (neutral pH) to autolysosome (acidic pH) in rd16 photoreceptors could be reduced. We then decided to investigate the consequences of reduced mTOR activation and ablated TRIB3 in the rd16 retina. The TRIB3 protein serves as a pseudokinase to prevent phosphorylation of AKT and mTOR (Borsting et al., 2014; Salazar et al., 2015). Therefore, in rd16 TRIB3$^{-/-}$ retinas, in addition to restored p-AKT and p-mTOR levels, we found reduction in Beclin1, reduced LCA3II/I ratio, and diminished p62 accumulation, which together with an increased number of red puncta, a marker of healthy autolysosomes, are evidence of the restoration of autophagolysosome function (Saltykova et al., 2021). However, at this point, we do not know whether improvement of autophagolysosome flux is an mTOR dependent event. Independently of mTOR, TRIB3 could interact with autophagic receptor p62 and abrogate the binding of LC3 and ubiquitinated substrates to P62, which induces the blockage of autophagic flux and subsequent ubiquitin proteasomal system (UPS) defects, leading to p62 accumulation (Fig. 6) (Hua et al., 2015). Therefore, interrupting TRIB3-p62 interaction could be a potential novel strategy against different retinopathies associated with p62 depositions and defective UPS.

9.2. Age-related macular degeneration (AMD)

AMD is a disease with a special need for the efficient removal of cellular waste in RPE cells due to elevated oxidative stress causing protein misfolding and ER stress. Waste clearing in the RPE includes UPS and the autophagosome-lysosomal system (ALS). Compared to UPS, ALS could degrade damaged organelles in addition to the degradation of proteins. Studies on RPE cells from AMD donors and mice with AMD-like phenotypes suggest that autophagy increases during aging and AMD (Mitter et al., 2014). Various environmental risk factors (cigarette smoke and light exposure) have been linked to AMD pathology. Thus, in a study conducted with mice exposed to cigarette smoke, we found dysregulated ER stress-dependent antioxidant responses associated with incidents of apoptosis and activation of autophagy in the RPE/choroid samples (Chen et al., 2014a). In this study, we employed strategies aimed at suppressing ER stress or inhibiting CHOP activation by either pharmacological chaperones or genetic ablation. These approaches were found to attenuate

apoptosis in RPE cells exposed to hydroquinone, causing oxidative stress. In a study by Zhang et al. using RPE-specific deletion of Atg5 and Atg7 in the mouse retina, the authors found an accumulation of p62 in the RPE, suggesting autophagy deficiency and disrupted autophagy flux (Zhang et al., 2017). The $Atg5^{\Delta RPE}$ and $Atg7^{\Delta RPE}$ mice occasionally manifested retinal degeneration (35% and 45% of the entire group, respectively), which gradually increased with age. In addition, RPE atrophy and choroidal neovascularization were occasionally observed in mice of advanced age. Therefore, the authors concluded that autophagy deficiency induced by RPE-specific deletion of Atg5 or Atg7 predisposes, but does not necessarily drive, the development of AMD-like phenotypes or retinal degeneration (Zhang et al., 2017).

Overall, the lack of animal models truly reflecting all aspects of AMD retinal pathology in humans most likely significantly impedes the investigation of crosstalk between UPR and autophagy. Therefore, the majority of the studies have been conducted in cell models; one that is of particular importance in this field is the study by Porter et al., which showed significant dysregulation of *EIF2AK3 (PERK)* gene expression in the RPE of human donors with early and intermediate AMD (Porter et al., 2019). In ARPE-19 cells exposed to brefeldin A, the authors found that PERK downregulation results in increased ER stress and impaired apoptosis induction, antioxidant responses, and autophagic flux (Saptarshi et al., 2022). They also showed that PERK regulates the rate of autophagy induction in a time-dependent manner and that PERK downregulation is an integrative event leading to reduced RPE cell survival in AMD development (Saptarshi et al., 2022). Finally, the authors proposed PERK as a potential future therapeutic target for AMD (Saptarshi et al., 2022).

Accumulated unfolded proteins activate UPR and are targeted for degradation by UPS or autophagy, the two major proteolytic systems for clearance of misfolded or damaged proteins. The study conducted by Zhan et al. investigated how these two systems communicate and coordinate with each other in RPE cells to eliminate intracellular misfolded and damaged proteins (Zhan et al., 2016). The authors employed ARPE-19 cells treated with proteasome inhibitors MG132 and chloroquine and found that when the level of ubiquitinated protein aggregations is significantly increased after the treatment of MG132, the RPE cells also manifest an increase in the levels of LC3-I, LC3-II, and LAMP1. Moreover, the levels of γ-tubulin and p62 were also increased in MG132-treated cells. Alternatively, the inhibition of lysosomal activity with chloroquine increases the levels of ubiquitin conjugates, LC3-II, and p62. In this study, the authors concluded that UPS and ALS are interrelated and that dysfunction of the ALS results in dysfunction of the UPS and severely compromises the capacity to eliminate misfolded and other forms of damaged proteins.

9.3. Diabetic retinopathy

Compared to the nondiabetic retina, the human diabetic retina manifests activation of the UPR markers (Du et al., 2013; Pitale et al., 2021) and an increase in autophagy proteins ATG5, Beclin1, and LC3-II (Fu et al., 2016). Interestingly, a literature review suggests that autophagy may play a dual role either protecting or damaging retinal cells in DR pathogenesis (Gong et al., 2021). For example, in human pericytes, heavily

oxidized glycated low-density lipoprotein (HOG-LDL) at low doses induces mild ER stress triggering protective autophagy while at higher concentrations increases ER stress leading to autophagic and apoptotic death, suggesting the impacts of ER stress and autophagy on cell viability are similar and dose-dependent (Fu et al., 2016). Another study demonstrated the protective role of autophagy in the context of activated UPR. In this study, the authors found an increase in ER stress markers, including p-PERK, p-eIF2a, and CHOP, and a concomitant inhibition of autophagy in ARPE-19 cells cultured under high glucose (25 mM) or hypoxia (1% oxygen) (Miranda et al., 2012). Treatment with fenofibrate protected the cells by upregulating LC3-II and thus increasing autophagy flux associated with inhibition of stress-mediated signaling and improvement of tight junction (Miranda et al., 2012). By contrast, a study by Devi et al. found that high glucose induced pro-inflammatory factor TXNIP expression in retinal Müller cells, which evokes a process of cellular defense, ultimately leading to the activation of ER stress, inflammation, apoptosis, and autophagy, contributing to the development of DR (Devi et al., 2012).

Overall, currently published studies pointed out existing crosstalk between ER stress and autophagy, and in many cases, the inhibition of ER stress is linked to alteration of autophagy flux. It is also worth mentioning that autophagy in the retina manifesting in different retinal degenerative conditions may play distinct roles. This most likely explain the fact that different strategies inducing or inhibiting autophagy flux benefit the degenerating retina. Moreover, not only degenerative conditions, but also experimental conditions, such as time points and doses of pharmacological treatments, may contribute to the results of the study. Nevertheless, manipulation with autophagy, either ER stress-mediated or direct, could be effective strategies to slow down inherited or age- and diabetes-related retinal pathogenesis.

10. ER stress signaling in mitochondrial regulation

Because of the close functional and physical inter-connections between ER and mitochondria (described in detail in Section 8), ER stress impacts morphology and function of mitochondria. A growing body of data supports that the UPR – in addition regulating ER homeostasis – also regulates mitochondria in response to ER stress (Malhotra and Kaufman, 2011; Rainbolt et al., 2014; Vannuvel et al., 2013). The PERK signal transduction cascade is especially important in regulating mitochondria function and morphology in response to ER stress. PERK signaling promotes mitochondria elongation and fusion in cell culture studies through its translational and transcriptional programs (Lebeau et al., 2018; Perea et al., 2023). The PERK-regulated ATF4 transcription factor also induces many mitochondria quality control genes (Han et al., 2013); mitochondrial respiratory chain assembly and activity (Balsa et al., 2019); mitochondria membrane phospholipid composition (Perea et al., 2023). In cell culture, sustained PERK signaling also triggers cell death through multiple pro-apoptotic pathomechanisms including induction of CHOP (Marciniak et al., 2004); attenuation of anti-apoptotic IAPs (Hiramatsu et al., 2014); and disruption of ATP levels (Hiramatsu et al., 2020).

In retina, the link between ER stress and mitochondria morphology and function has not been as extensively examined as *in vitro*. Interestingly, ATF6 mutant retinal organoids from achromatopsia patients showed excessive ER stress, as to be expected with disruption of a

UPR signaling pathway, but also showed extensive mitochondria structural abnormalities by ultrastructural analyses and significant induction of oxidative phosphorylation pathways in developing photoreceptors (Lee et al., 2022). These mitochondria abnormalities in retinal organoids suggest that ER stress may also lead to morphologic and functional consequences on mitochondria in specialized retinal cell types. In turn, disruption of mitochondria could also contribute to pathogenesis and progression of retinal diseases due to ER stress.

11. The integrated stress response (ISR)

As mentioned in the PERK section, the UPR results in the phosphorylation of eIF2α by PERK. However, a multitude of cellular stresses lead to elevation in p-eIF2α levels. In addition to PERK, there are at least three other kinases — heme-regulated kinase (HRI), protein kinase double-stranded RNA-dependent (protein kinase R or PKR) and general control nonderepressible 2 (GCN2) — in vertebrates that phosphorylate eIF2α at Serine 51 in response to a variety of stresses (Costa-Mattioli and Walter, 2020; Hinnebusch, 1984). HRI is mainly activated in blood cells due to heme deprivation. PKR is activated during viral infection and GCN2 is activated in amino acid starvation. Interestingly, Wu et al. recently published their exciting findings on a fifth eIF2α kinase, FAM69C, which acts on eIF2α and promotes stress granule formation in primary microglia (Wu et al., 2023). Additional work will need to be carried out to determine what the primary triggers of FAM69C as well as its role in other cell types and tissues including the retina. Each of these pathways converge on and phosphorylate eIF2α to stop conventional protein synthesis and enabling translation of ATF4. ATF4 promotes transcription of many genes involved in a variety of cellular processes ranging from development to apoptosis. The most studied targets of ATF4 are the ones that ATF4 promotes following a cellular stress resulting in elevated p-eIF2α levels. Together, this translational inhibition, the subsequent activation of an altered translational program and stress-induced gene targeting by ATF4 is the ISR (Donnelly et al., 2013; Harding et al., 2003).

Aside from PERK, very little research has been conducted to assess the role of eIF2α kinases in IRD. This is mainly because many IRDs have misfolded proteins (Gorbatyuk et al., 2010; Kunte et al., 2012; Murray et al., 2015), meaning the ISR in these retinas should be dependent on PERK. However, we cannot definitively exclude the possibility that other eIF2α kinases are active in these diseases. We previously attempted to answer this question using a small molecule inhibitor of PERK, GSK2606414, and while inhibition of PERK led to normalized levels of p-eIF2α (S51), it only marginally increased translation rates, which could possibly indicate activity of other eIF2α kinases (Starr et al., 2018). Given the inhibition of PERK results in diminished eIF2α phosphorylation without affecting translation rates, we then investigated whether an increase in p-eIF2α more prominently arrests protein synthesis. Knocking out *Gadd34*—one of the two known PP1 regulatory subunits that facilitates the dephosphorylation of eIF2α, in two different models of IRD, *rd16* and P23H *RHO* mice—we learned there was also no significant difference in the levels of protein synthesis associated with p-eIF2a increase (Saltykova et al., 2022; Starr and Gorbatyuk, 2019b). Altogether this series of experiments indicated that either during chronic ER stress, translational regulation could occur through other mechanisms (Starr et al., 2018, 2019) or p-eIF2 inhibition reaches a threshold in degenerating photoreceptors.

Due to the nature of the ISR's alleged role in various neurodegenerative diseases, groups have worked on targeting this signaling for therapeutics. The ideal pharmacological compound would be one that targets the ISR effectively without destroying the tissues that rely on it so heavily. The small molecule ISRIB was developed for this purpose. ISRIB inhibits the ISR by preventing the interaction with p-eIF2α(S51) and eIF2B (Zyryanova et al., 2021). Though ISRIB has had promising results in studies of various diseases (Chang et al., 2022; Hosoi et al., 2016; Wong et al., 2018) and retinal disorders related to wet AMD (Yasuda et al., 2021) and glaucomatous RGC loss (Larhammar et al., 2017), no reports on a benefit for IRD has been published to date.

12. Emerging pharmacological regulators of the UPR

The elucidation of the molecules and mechanisms regulating UPR lead to development of small molecule screens to identify chemicals that selectively modulate the IRE1, PERK, and ATF6 signal transduction pathways in the absence of ER stress or protein misfolding. These small molecules provide tools to harness the activities of specific UPR signaling molecules and test consequences in different disease settings, and those compounds that show beneficial effects in disease models have been advanced into additional preclinical studies to potentially develop into pharmaceutical agents to treat disease in people. Here, we discuss several of the most robust small molecule regulators of UPR signaling and highlight interesting biologic effects in disease models.

For the IRE1 pathway, a small molecule activator, IXA4, has been identified that promotes generation of the XBP1s transcription factor and selective upregulation of XBP1s target genes but not transcriptional programs regulated by other arms of the UPR (e.g., PERK/ATF4 and ATF6) (Grandjean et al., 2020). This small molecule IRE1 pathway activator was effective *in vivo* in a mouse model of obesity where intraperitoneal injections of IXA4 improved systemic glucose levels and reduced hepatic steatosis (Madhavan et al., 2022). A small molecule aldehyde compound, 4u8c, covalently modifies and inactivates that RNase domain of IRE1, thereby inhibiting this UPR signaling pathway (Cross et al., 2012) (Fig. 7).

For the PERK pathway, small molecules including salubrinal,guanabenz, sephin1, and raphin1 have been identified that enhance PERK signaling by inhibiting intracellular phosphatases that normally counteract the kinase activity of PERK and related eIF2a kinases (Boyce et al., 2005; Das et al., 2015; Krzyzosiak et al., 2018; Tsaytler et al., 2011). The specificity of these compounds for target phosphatases as well as the molecular mechanisms of phosphatase inhibition are incompletely understood. However, in experimental neurodegeneration disease models, extension of phosphorylated eIF2a levels (and thereby extension of PERK signaling by application of these molecules has prevented neuropathology (Das et al., 2015; Park et al., 2023). The GSK2606414 and related GSK2656157 small molecules bind the PERK kinase and thereby inhibit the PERK pathway (Axten et al., 2012, 2013). These compounds are not PERK-specific as they can also inhibit other kinases (Mahameed et al., 2019; Rojas-Rivera et al., 2017), but administration of these compounds prevented neurodegeneration in mouse prion disease model (Moreno et al., 2013). The ISRIB compound interferes with PERK signaling via binding and stabilizing the active form of eIF2B which is normally rendered inactive by PERK signaling (Zyryanova et

al., 2021) (Fig. 7). The autosomal recessive Vanishing White Matter demyelination disease arises in people carrying destabilizing eIF2B missense mutations, and ISRIB has been effective in rescuing eIF2B activity and preventing neuropathology for some of these disease mutations in animal studies (Wong et al., 2018). A second generation ISRIB derivative has advanced into early-stage clinical safety trial (ClinicalTrials.gov Identifier: NCT05740813) and, if successful, may offer a pharmacologic treatment particularly suited to Vanishing White Matter patients carrying disease eIF2B mutations.

For the ATF6 pathway, a small molecule activator of this pathway has been identified, AA147 (Plate et al., 2016). AA147 covalently targets protein disulfide isomerases (Paxman et al., 2018) that in turn, lead to increase in the pool of monomeric reduced full-length ATF6 available to traffic to Golgi for generation of the ATF6 transcription factor fragment. AA147 has been effective in activating ATF6's transcriptional program in cell culture and mouse disease models (Blackwood et al., 2019; Kroeger et al., 2018; Wang et al., 2022c). Ceapins are selective ATF6 inhibitors that tether ATF6 protein in the ER with ABCD3 protein in peroxisome, and in doing so, prevent the generation of the ATF6 transcription factor fragment at the Golgi (Torres et al., 2019) (Fig. 7).

AA147 Restores Transcriptional Activity of ATF6 Achromatopsia Disease Mutations.

AA147 enhances ATF6 signaling by promoting ATF6 trafficking from ER to Golgi. This raised the possibility that AA147 may be well tailored to restore function of the Class 1 ATF6 disease variants found in achromatopsia patients, where ATF6 is retained in ER. In cells expressing recombinant ATF6 bearing Class 1 luminal domain variant proteins, AA147 addition restored generation of the ATF6 transcription factor fragment (Chiang et al., 2017; Kroeger et al., 2021), and in retinal organoids derived from achromatopsia patients carrying Class 1 mutations, AA147 increased ATF6 transcriptional output and most intriguingly, restored development of cone photoreceptors, specifically growth of the IS/OS structure (Kroeger et al., 2021). These findings demonstrate that chemical restoration of ATF6 function in developing ATF6-mutant retinal organoids restores cone growth, specifically the extension of IS/OS structure and cone gene expression. Based on these results, ATF6 activators like AA147 are particularly well-suited for ATF6 Class 1 disease variants, and more broadly may offer benefits for photoreceptor growth, viability, and structure in other vision loss diseases.

13. Conclusions and future directions

Studies from nearly over two decades have provided compelling evidence for the important roles of ER stress signaling in maintaining the cellular homeostasis of retinal neurons during development, maintenance, and aging. Loss and/or reduced functional UPR pathways mediated by IRE1/XBP1 and ATF6 contribute to retinal degeneration associated with aging and age-related diseases (Kohl et al., 2015; Massoudi et al., 2023; McLaughlin et al., 2018). Paradoxical results have been reported in the context of the impacts and consequences of defective PERK pathway, in part due to the great diversity of the downstream effector of this UPR branch (Athanasiou et al., 2017; Starr and Gorbatyuk, 2019a; Zhu et al., 2017). The close interactions and overlapping between the UPR signaling and other cellular stress

response pathways mediated by autophagy, ISR, mitochondria, calcium regulation, etc. further add to the complexity of the biological and functional outcome of UPR activation or inactivation. Moreover, even the same UPR molecule can demonstrate distinct functions in different cell types, animal models, and treatments. Therefore, the interpretation of the findings should be carefully justified based on the experimental systems and conditions. Nevertheless, research to uncover the structural and functional characteristics of the ER and ER stress signaling would provide insightful information to improve our understanding of the fundamental mechanisms underlying the survival and function of retinal neurons and vascular cells. More importantly, it would help the discovery of signaling pathways of cellular response by which retinal cells adapt to physiological and pathological environments and identify molecular targets for the development of new treatments for retinal diseases. Interestingly, many variants of UPR, ISR, and protein quality control genes are found in the human population and linked to human diseases (Table 1). Patients carrying loss-of-function ATF6 and WFS1 gene variants develop vision loss, but it is unknown how disease variants in other protein quality control genes affect the retina. Given the importance of UPR, ISR, and protein quality control mechanisms in photoreceptor disease, diabetic retinopathy, retinal inflammation, and the many other ocular diseases highlighted in this review, future studies should investigate if human genetic variation in ER and protein quality control genes directly causes vision loss diseases (as demonstrated with WFS1 and ATF6) or acts as risk factors and genetic modifiers for the pathogenesis or progression of retinal diseases.

As discussed in Sections 4 - 7, activation of the UPR has been implicated in both inherited and age-related retinal degenerative diseases as well as in diabetes-induced neurovascular damage and angiogenesis. In animal models of inherited retinal degeneration, improving protein homeostasis by overexpressing GRP78 or enhancing ATF6 activation using pharmacological activators reduces photoreceptor loss, improves retinal function, and restores cone photoreceptor growth. Treatment of P23H RHO mice with pharmacological chaperones that promote the production and correct localization of rhodopsin protein also reduces retinal inflammation and ameliorates photoreceptor degeneration (Vats et al., 2022). These findings suggest that restoring protein homeostasis is a promising approach for the treatment of photoreceptor degeneration in certain inherited retinal diseases. In parallel with the influence of genetic factors on protein dyshomeostasis, environmental factors also lead to chronic stress that disrupts protein homeostasis in retinal cells. For instance, accumulation of ubiquitinated protein aggregation and tau-like proteins was observed in both the retina tissue and the RPE, which is believed to contribute to RPE degeneration in AMD (Leger et al., 2011). Overexpression of the UPR regulators, ATF6 and XBP1, has shown great beneficial effects on neuroprotection *in vivo* in preclinical models of Parkinson's disease and Huntington's disease (Vidal et al., 2021). Thus, enhancing the function of the adaptive UPR by genetic or pharmacological approach (discussed in Section 12) may provide new hope for age-related degenerative retinal disease.

In addition to protein homeostasis, maintaining a well-balanced lipid content and composition is critical for retinal development, neuronal survival, synapse formation, and function. For example, lack of cholesterol, the major sterol component of the lipid bilayer of the cell member, causes progressive retinal degeneration in Smith-Lemli-Opitz syndrome (SLOS), whilst aberrant accumulation of cholesterol increases oxidative stress

and inflammation contributing to retinal degeneration in multiple diseases, such as DR and AMD (Dasari et al., 2010; Elmasry et al., 2018; Fliesler et al., 2004; Wu et al., 2012). Emerging evidence suggests dysregulation of lipid metabolism, in addition to protein dyshomeostasis, is an important cause of ER stress. Several studies have demonstrated oxidative cholesterol metabolites such as 27-hydroxycholesterol (Dasari et al., 2010), highly oxidized glycated LDL (Wu et al., 2012), 12/15-lipoxygenase (Elmasry et al., 2018), and 7-Ketocholesterol (Pariente et al., 2023), can increase ER stress in cultured retinal cells. However, the exact mechanism by which lipid dysregulation activates the UPR signaling and the role of the UPR pathways in lipid-mediated retinal cell damage and dysfunction in disease development remains largely unknown. Related to lipid and protein homeostasis, the ER plays an important role in assisting and regulating the biogenesis, remodeling, and function of intracellular organelles. For example, as discussed in Section 8, the ER closely interact with the mitochondria via MAM, which plays a significant role in calcium homeostasis, mitochondrial remodeling and function, as well as regulation of oxidative stress and inflammatory signaling. Recent proteomic studies identified a number of differentially expressed retinal MAM proteins to be involved in key pathogenic pathways of DR, such as glucose metabolism, retinal degeneration, fibrosis, and angiogenesis. However, the implication and regulation of these MAM proteins in DR pathogenesis remain to be explored. In macrophages and neutrophils, the ER has been shown to form close contact with the plasma membrane and participate in the process of phagocytosis. To our knowledge, whether the ER-phagosome contact sites exist in the RPE and are implicated in POS phagocytosis and clearance have not been studied and warrant investigation. Understanding the molecular pathways of the ER and ER stress signaling that regulate protein and lipid homeostasis in each specific retinal cell type, and in the retina as an integrated neural tissue involving active neuron-glia-vascular interactions, and developing novel therapeutics targeting these pathways will likely lead to new approaches for the prevention and treatment of retinal disease.

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Data availability

Data will be made available on request.

Abbreviations

ACC	acetyl-coenzyme carboxylase
AdRP	autosomal dominant retinitis pigmentosa
AGE	advanced glycation end products

AKAP1	A-kinase anchoring protein 1
ALS	autophagosome-lysosomal system
AMD	age-related macular degeneration
AMPK	AMP-activated protein kinase
ASC	apoptosis-associated speck-like protein
ASK1	apoptosis signal-regulating kinase 1
ATF4	activating transcription factor 4
ATF6	activating transcription factor-6
BCL-2	B-cell lymphoma 2
BRB	blood-retinal barrier
bZIP	basic leucine zipper
C/EBP	CCAAT box/enhancer-binding protein b
C3G	Cyanidin-3-glucoside
CEP290	centrosomal protein of 290 kD
CHOP	C/EBP homologous protein
CNS	central nervous system
CNV	choroidal neovascularization
CORD	cone-rod dystrophy
CRE	cAMP response element
CTRP1	C1q/TNF-related protein 1
CYPD	Cyclophilin D
DAMPs	damage-associated molecular patterns
DAPK1	death-associated protein kinase 1
DEGS1	dihydroceramide desaturase Δ4-dihydroceramide desaturase 1
DME	diabetic macular edema
DR	diabetic retinopathy
DR5	death receptor 5
Drp-1	Dynamin related protein 1
EIF2AK3	eukaryotic translation initiation factor 2-alpha kinase 3

eIF2α	-subunit of the eukaryotic translation initiation factor 2 complex
EMT	epithelial to mesenchymal transition
ER	endoplasmic reticulum
ERAD	ER-associated degradation
ERMES	ER-mitochondria encounter structure
FFAs	free fatty acids
FUNDC1	FUN14 domain containing 1
GA	geographic atrophy
GADD34	growth arrest and DNA-damage inducible 34
GCN2	general control nondepressible 2
GRP75	75-kDa glucose-regulated protein
GTP	guanosine tri-phosphate
HK-2	human kidney 2
HRI	heme-regulated kinase
HSP	hereditary spastic paraplegia
IFN-γ	interferon-γ
IP3R	inositol 1,4,5-triphosphate receptor
IRD	inherited retinal degeneration
IRE1	inositol-requiring protein-1
IRES	internal ribosome entry site
IS	inner segments (of photoreceptors)
ISR	integrated stress response
JNK	c-Jun N-terminal kinase
LC	liquid chromatography
LCA	Leber congenital amaurosis
LDL	low-density lipoprotein
LPS	lipopolysaccharide
LRAT	lecithin:retinol acyltransferase
MAM	mitochondria-associated ER membrane

Mfn	mitofusin
Mief1	mitochondrial elongation factor 1
MIMS	mitochondrial intermembrane space
miRNA	micro ribonucleic acid
MNV	macular neovascularization
mRNA	messenger ribonucleic acid
mTORC2	mammalian target of rapamycin complex 2
nAMD	neovascular AMD
NLRP3	NOD-like receptor protein 3
NRF2	nuclear factor erythroid 2-related factor 2
OIR	oxygen-induced retinopathy
OMM	outer mitochondrial membrane
ONC	optic nerve crush
OS	outer segments (of photoreceptors)
PACS2	phosphofurin acidic cluster sorting protein 2
PDR	proliferative DR
PEDF	pigment epithelium growth factor
PERK	protein kinase RNA-like endoplasmic reticulum kinase
PEST	proline, glutamic acid, serine, and threonine rich region
PIC	pre-initiation complex
PKR	protein kinase RNA
POS	photoreceptor outer segment-
PP1	protein phosphatase 1
PRP	prion protein
PTEN	phosphatase and tensin homolog deleted on chromosome 10
RAV	ribosome-associated vesicles
RBP	RNA binding protein
RD	retinal detachment
RGC	retinal ganglion cell

RIDD	regulated IRE-1 dependent decay
RIDDLE	RIDD lacking endomotif
RMECs	retinal microvascular endothelial cells
ROS	reactive oxygen species
RP	retinitis pigmentosa
RPE	retinal pigment epithelium
SLOS	Smith-Lemli-Opitz Syndrome
STZ	streptozotocin
TC	ternary complex
TMP	tetramethylpyrazine
TNF	tumor necrosis factor
TRAF2	receptor-associated factor 2
TRIB3	tribbles homolog 3 or tribbles pseudokinase 3
TRPV4	transient receptor potential vanilloid 4
uoRF	upstream open reading frames
UPR	unfolded protein response
VDAC	voltage dependent anion channel
VEGF	vascular endothelial growth factor
XBP1	X-box binding protein 1
XBP1s	spliced X-box binding protein 1
XBP1u	unspliced X-box binding protein 1

References

Adachi Y, Yamamoto K, Okada T, Yoshida H, Harada A, Mori K, 2008. ATF6 is a transcription factor specializing in the regulation of quality control proteins in the endoplasmic reticulum. Cell Struct. Funct 33, 75–89. [PubMed: 18360008]

Adekeye A, Haeri M, Solessio E, Knox BE, 2014. Ablation of the proapoptotic genes CHOP or Ask1 does not prevent or delay loss of visual function in a P23H transgenic mouse model of retinitis pigmentosa. PLoS One 9, e83871. [PubMed: 24523853]

Agosto MA, Anastassov IA, Robichaux MA, Wensel TG, 2018. A large endoplasmic reticulum-resident pool of TRPM1 in retinal ON-bipolar cells. eNeuro 5. ENEURO.0143-18.2018.

Alavi MV, Chiang WC, Kroeger H, Yasumura D, Matthes MT, Iwawaki T, LaVail MM, Gould DB, Lin JH, 2015. In vivo visualization of endoplasmic reticulum stress in the retina using the ERAI reporter mouse. Invest. Ophthalmol. Vis. Sci 56, 6961–6970. [PubMed: 26513501]

Almanza A, Mnich K, Blomme A, Robinson CM, Rodriguez-Blanco G, Kierszniowska S, McGrath EP, Le Gallo M, Pilalis E, Swinnen JV, Chatziioannou A, Chevet E, Gorman AM, Samali A, 2022. Regulated IRE1α-dependent decay (RIDD)-mediated reprograming of lipid metabolism in cancer. Nat. Commun 13, 2493. [PubMed: 35524156]

Alone PV, Dever TE, 2006. Direct binding of translation initiation factor eIF2gamma-G domain to its GTPase-activating and GDP-GTP exchange factors eIF5 and eIF2B epsilon. a 281, 12636–12644.

Altman BJ, Wofford JA, Zhao Y, Coloff JL, Ferguson EC, Wieman HL, Day AE, Ilkayeva O, Rathmell JC, 2009. Autophagy provides nutrients but can lead to Chop-dependent induction of Bim to sensitize growth factor-deprived cells to apoptosis. Mol. Biol. Cell 20, 1180–1191. [PubMed: 19109422]

Ambati J, Fowler BJ, 2012. Mechanisms of age-related macular degeneration. Neuron 75, 26–39. [PubMed: 22794258]

Ameri K, Harris AL, 2008. Activating transcription factor 4. Int. J. Biochem. Cell Biol 40, 14–21. [PubMed: 17466566]

Amini R, Rocha-Martins M, Norden C, 2018. Neuronal Migration and Lamination in the Vertebrate Retina, vol. 11.

Ansar M, Santos-Cortez RL, Saqib MA, Zulfiqar F, Lee K, Ashraf NM, Ullah E, Wang X, Sajid S, Khan FS, Amin-ud-Din M, University of Washington Center for Mendelian Genomics (UW-CMG), Smith JD, Shendure J, Bamshad MJ, Nickerson DA, Hameed A, Riazuddin S, Ahmed ZM, Ahmad W, Leal SM, 2015. Mutation of ATF6 causes autosomal recessive achromatopsia. Hum. Genet 134, 941–950. [PubMed: 26063662]

Anttonen AK, Mahjneh I, Hämäläinen RH, Lagier-Tourenne C, Kopra O, Waris L, Anttonen M, Joensuu T, Kalimo H, Paetau A, Tranebjaerg L, Chaigne D, Koenig M, Eeg-Olofsson O, Udd B, Somer M, Somer H, Lehesjoki AE, 2005. The gene disrupted in Marinesco-Sjögren syndrome encodes SIL1, an HSPA5 cochaperone. Nat. Genet 37, 1309–1311. [PubMed: 16282978]

Arjunan P, Swaminathan R, Yuan J, Elashiry M, Tawfik A, Al-Shabrawey M, Martin PM, Muthusamy T, Cutler CW, 2021. Exacerbation of AMD phenotype in lasered CNV murine model by dysbiotic oral pathogens. Antioxidants 10.

Athanasiou D, Aguila M, Bellingham J, Kanuga N, Adamson P, Cheetham ME, 2017. The role of the ER stress-response protein PERK in rhodopsin retinitis pigmentosa. Hum. Mol. Genet 26, 4896–4905. [PubMed: 29036441]

Axten JM, Medina JR, Feng Y, Shu A, Romeril SP, Grant SW, Li WH, Heerding DA, Minthorn E, Mencken T, Atkins C, Liu Q, Rabindran S, Kumar R, Hong X, Goetz A, Stanley T, Taylor JD, Sigethy SD, Tomberlin GH, Hassell AM, Kahler KM, Shewchuk LM, Gampe RT, 2012. Discovery of 7-methyl-5-(1-{[3-(trifluoromethyl)phenyl]acetyl}-2,3-dihydro-1H-indol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (GSK2606414), a potent and selective first-in-class inhibitor of protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK). J. Med. Chem 55, 7193–7207. [PubMed: 22827572]

Axten JM, Romeril SP, Shu A, Ralph J, Medina JR, Feng Y, Li WH, Grant SW, Heerding DA, Minthorn E, Mencken T, Gaul N, Goetz A, Stanley T, Hassell AM, Gampe RT, Atkins C, Kumar R, 2013. Discovery of GSK2656157: an optimized PERK inhibitor selected for preclinical development. ACS Med. Chem. Lett 4, 964–968. [PubMed: 24900593]

B'Chir W, Maurin AC, Carraro V, Averous J, Jousse C, Muranishi Y, Parry L, Stepien G, Fafournoux P, Bruhat A, 2013. The eIF2alpha/ATF4 pathway is essential for stress-induced autophagy gene expression. Nucleic Acids Res. 41, 7683–7699. [PubMed: 23804767]

Back SH, Scheuner D, Han J, Song B, Ribick M, Wang J, Gildersleeve RD, Pennathur S, Kaufman RJ, 2009. Translation attenuation through eIF2alpha phosphorylation prevents oxidative stress and maintains the differentiated state in beta cells. Cell Metabol. 10, 13–26.

Baird TD, Wek RC, 2012. Eukaryotic initiation factor 2 phosphorylation and translational control in metabolism. Adv. Nutr 3, 307–321. [PubMed: 22585904]

Balsa E, Soustek MS, Thomas A, Cogliati S, García-Poyatos C, Martín-García E, Jedrychowski M, Gygi SP, Enriquez JA, Puigserver P, 2019. ER and nutrient stress promote assembly of respiratory chain supercomplexes through the PERK-eIF2α Axis. Mol. Cell 74, 877–890.e876. [PubMed: 31023583]

Bertolotti A, Wang X, Novoa I, Jungreis R, Schlessinger K, Cho JH, West AB, Ron D, 2001. Increased sensitivity to dextran sodium sulfate colitis in IRE1beta-deficient mice. J. Clin. Invest 107, 585–593. [PubMed: 11238559]

Bertolotti A, Zhang Y, Hendershot LM, Harding HP, Ron D, 2000. Dynamic interaction of BiP and ER stress transducers in the unfolded-protein response. Nat. Cell Biol 2, 326–332. [PubMed: 10854322]

Betz C, Stracka D, Prescianotto-Baschong C, Frieden M, Demaurex N, Hall MN, 2013. Feature Article: mTOR complex 2-Akt signaling at mitochondria-associated endoplasmic reticulum membranes (MAM) regulates mitochondrial physiology. Proc. Natl. Acad. Sci. U.S.A 110, 12526–12534. [PubMed: 23852728]

Bhootada Y, Kotla P, Zolotukhin S, Gorbatyuk O, Bebok Z, Athar M, Gorbatyuk M, 2016. Limited ATF4 expression in degenerating retinas with ongoing ER stress promotes photoreceptor survival in a mouse model of autosomal dominant retinitis pigmentosa. PLoS One 11, e0154779. [PubMed: 27144303]

Binet F, Mawambo G, Sitaras N, Tetreault N, Lapalme E, Favret S, Cerani A, Leboeuf D, Tremblay S, Rezende F, Juan AM, Stahl A, Joyal JS, Milot E, Kaufman RJ, Guimond M, Kennedy TE, Sapieha P, 2013. Neuronal ER stress impedes myeloid-cell-induced vascular regeneration through IRE1α degradation of netrin-1. Cell Metabol. 17, 353–371.

Bird A, 2021. Role of retinal pigment epithelium in age-related macular disease: a systematic review. Br. J. Ophthalmol 105, 1469–1474. [PubMed: 32950958]

Blackwood EA, Azizi K, Thuerauf DJ, Paxman RJ, Plate L, Kelly JW, Wiseman RL, Glembotski CC, 2019. Pharmacologic ATF6 activation confers global protection in widespread disease models by reprograming cellular proteostasis. Nat. Commun 10, 187. [PubMed: 30643122]

Bommiasamy H, Back SH, Fagone P, Lee K, Meshinchi S, Vink E, Sriburi R, Frank M, Jackowski S, Kaufman RJ, Brewer JW, 2009. ATF6alpha induces XBP1-independent expansion of the endoplasmic reticulum. J. Cell Sci 122, 1626–1636. [PubMed: 19420237]

Bonilha VL, Rayborn ME, Bhattacharya SK, Gu X, Crabb JS, Crabb JW, Hollyfield JG, 2006. The retinal pigment epithelium apical microvilli and retinal function. Adv. Exp. Med. Biol 572, 519–524. [PubMed: 17249618]

Bononi A, Bonora M, Marchi S, Missiroli S, Poletti F, Giorgi C, Pandolfi PP, Pinton P, 2013. Identification of PTEN at the ER and MAMs and its regulation of Ca (2+) signaling and apoptosis in a protein phosphatase-dependent manner. Cell Death Differ. 20, 1631–1643. [PubMed: 23811847]

Bononi A, Missiroli S, Poletti F, Suski JM, Agnoletto C, Bonora M, De Marchi E, Giorgi C, Marchi S, Patergnani S, Rimessi A, Wieckowski MR, Pinton P, 2012. Mitochondria-associated membranes (MAMs) as hotspot Ca(2+) signaling units. Adv. Exp. Med. Biol 740, 411–437. [PubMed: 22453952]

Borsting E, Patel SV, Decleves AE, Lee SJ, Rahman QM, Akira S, Satriano J, Sharma K, Vallon V, Cunard R, 2014. Tribbles homolog 3 attenuates mammalian target of rapamycin complex-2 signaling and inflammation in the diabetic kidney. J. Am. Soc. Nephrol 25, 2067–2078. [PubMed: 24676635]

Boyce M, Bryant KF, Jousse C, Long K, Harding HP, Scheuner D, Kaufman RJ, Ma D, Coen DM, Ron D, Yuan J, 2005. A selective inhibitor of eIF2alpha dephosphorylation protects cells from ER stress. Science (New York, N.Y.) 307, 935–939. [PubMed: 15705855]

Brush MH, Weiser DC, Shenolikar S, 2003. Growth arrest and DNA damage-inducible protein GADD34 targets protein phosphatase 1 alpha to the endoplasmic reticulum and promotes dephosphorylation of the alpha subunit of eukaryotic translation initiation factor 2. Mol. Cell Biol 23, 1292–1303. [PubMed: 12556489]

Cai X, Conley SM, Naash MI, 2009. RPE65: role in the visual cycle, human retinal disease, and gene therapy. Ophthalmic Genet. 30, 57–62. [PubMed: 19373675]

Calame DG, Hainlen M, Takacs D, Ferrante L, Pence K, Emrick LT, Chao HT, 2021. EIF2AK2-related neurodevelopmental disorder with leukoencephalopathy, developmental delay, and episodic neurologic regression mimics pelizaeus-merzbacher disease. Neurology. Genetics 7, e539. [PubMed: 33553620]

Cao J, Dai DL, Yao L, Yu HH, Ning B, Zhang Q, Chen J, Cheng WH, Shen W, Yang ZX, 2012. Saturated fatty acid induction of endoplasmic reticulum stress and apoptosis in human liver cells via the PERK/ATF4/CHOP signaling pathway. Mol. Cell. Biochem 364, 115–129. [PubMed: 22246806]

Carter SD, Hampton CM, Langlois R, Melero R, Farino ZJ, Calderon MJ, Li W, Wallace CT, Tran NH, Grassucci RA, Siegmund SE, Pemberton J, Morgenstern TJ, Eisenman L, Aguilar JI, Greenberg NL, Levy ES, Yi E, Mitchell WG, Rice WJ, Wigge C, Pilli J, George EW, Aslanoglou D, Courel M, Freyberg RJ, Javitch JA, Wills ZP, Area-Gomez E, Shiva S, Bartolini F, Volchuk A, Murray SA, Aridor M, Fish KN, Walter P, Balla T, Fass D, Wolf SG, Watkins SC, Carazo JM, Jensen GJ, Frank J, Freyberg Z, 2020. Ribosome-associated vesicles: a dynamic subcompartment of the endoplasmic reticulum in secretory cells, 6, eaay9572.

Chan CP, Kok KH, Tang HM, Wong CM, Jin DY, 2013. Internal ribosome entry site-mediated translational regulation of ATF4 splice variant in mammalian unfolded protein response. Biochim. Biophys. Acta 1833, 2165–2175. [PubMed: 23665047]

Chang B, Grau T, Dangel S, Hurd R, Jurklies B, Sener EC, Andreasson S, Dollfus H, Baumann B, Bolz S, Artemyev N, Kohl S, Heckenlively J, Wissinger B, 2009. A homologous genetic basis of the murine cpfl1 mutant and human achromatopsia linked to mutations in the PDE6C gene. Proc. Natl. Acad. Sci. U. S. A 106, 19581–19586. [PubMed: 19887631]

Chang L, Liu X, Chen J, Liu H, Wang G, Wang G, Liao X, Shen X, 2022. Attenuation of activated eIF2α signaling by ISRIB treatment after spinal cord injury improves locomotor function. J. Mol. Neurosci 72, 585–597. [PubMed: 34647267]

Chen C, Cano M, Wang JJ, Li J, Huang C, Yu Q, Herbert TP, Handa JT, Zhang SX, 2014a. Role of unfolded protein response dysregulation in oxidative injury of retinal pigment epithelial cells. Antioxidants Redox Signal. 20, 2091–2106.

Chen C, Zhong Y, Wang JJ, Yu Q, Plafker K, Plafker S, Zhang SX, 2018. Regulation of Nrf2 by X box-binding protein 1 in retinal pigment epithelium. Front. Genet 9.

Chen CY, Malchus NS, Hehn B, Stelzer W, Avci D, Langosch D, Lemberg MK, 2014b. Signal peptide peptidase functions in ERAD to cleave the unfolded protein response regulator XBP1u. EMBO J. 33, 2492–2506. [PubMed: 25239945]

Chen L, Li M, Messinger JD, Ferrara D, Curcio CA, Freund KB, 2020. Recognizing atrophy and mixed-type neovascularization in age-related macular degeneration via clinicopathologic correlation. Transl Vis Sci Technol 9, 8.

Chen X, Cubillos-Ruiz JR, 2021. Endoplasmic reticulum stress signals in the tumour and its microenvironment. Nat. Rev. Cancer 21, 71–88. [PubMed: 33214692]

Chen X, Shen J, Prywes R, 2002. The luminal domain of ATF6 senses endoplasmic reticulum (ER) stress and causes translocation of ATF6 from the ER to the Golgi. J. Biol. Chem 277, 13045–13052. [PubMed: 11821395]

Chen X, Shi C, He M, Xiong S, Xia X, 2023. Endoplasmic reticulum stress: molecular mechanism and therapeutic targets. Signal Transduct. Targeted Ther 8, 352.

Chen Y, Wang JJ, Li J, Hosoya KI, Ratan R, Townes T, Zhang SX, 2012. Activating transcription factor 4 mediates hyperglycaemia-induced endothelial inflammation and retinal vascular leakage through activation of STAT3 in a mouse model of type 1 diabetes. Diabetologia 55, 2533–2545. [PubMed: 22660795]

Cheng H, Gang X, He G, Liu Y, Wang Y, Zhao X, Wang G, 2020a. The molecular mechanisms underlying mitochondria-associated endoplasmic reticulum membrane-induced insulin resistance. Front. Endocrinol 11, 592129.

Cheng SY, Cipi J, Ma S, Hafler BP, Kanadia RN, Brush RS, Agbaga MP, Punzo C, 2020b. Altered photoreceptor metabolism in mouse causes late stage age-related macular degeneration-like pathologies. Proc. Natl. Acad. Sci. U. S. A 117, 13094–13104. [PubMed: 32434914]

Chiang WC, Chan P, Wissinger B, Vincent A, Skorczyk-Werner A, Krawczyński MR, Kaufman RJ, Tsang SH, Héon E, Kohl S, Lin JH, 2017. Achromatopsia mutations target sequential steps of ATF6 activation. Proc. Natl. Acad. Sci. U. S. A 114, 400–405. [PubMed: 28028229]

Chiang WC, Hiramatsu N, Messah C, Kroeger H, Lin JH, 2012. Selective activation of ATF6 and PERK endoplasmic reticulum stress signaling pathways prevent mutant rhodopsin accumulation. Invest. Ophthalmol. Vis. Sci 53, 7159–7166. [PubMed: 22956602]

Chiang WC, Joseph V, Yasumura D, Matthes MT, Lewin AS, Gorbatyuk MS, Ahern K, LaVail MM, Lin JH, 2016. Ablation of chop transiently enhances photoreceptor survival but does not prevent retinal degeneration in transgenic mice expressing human P23H rhodopsin. Adv. Exp. Med. Biol 854, 185–191. [PubMed: 26427410]

Chiang WC, Kroeger H, Sakami S, Messah C, Yasumura D, Matthes MT, Coppinger JA, Palczewski K, LaVail MM, Lin JH, 2015. Robust endoplasmic reticulum-associated degradation of rhodopsin precedes retinal degeneration. Mol. Neurobiol 52, 679–695. [PubMed: 25270370]

Chu WS, Das SK, Wang H, Chan JC, Deloukas P, Froguel P, Baier LJ, Jia W, McCarthy MI, Ng MC, Damcott C, Shuldiner AR, Zeggini E, Elbein SC, 2007. Activating transcription factor 6 (ATF6) sequence polymorphisms in type 2 diabetes and pre-diabetic traits. Diabetes 56, 856–862. [PubMed: 17327457]

Chung YR, Choi JA, Koh JY, Yoon YH, 2017. Ursodeoxycholic acid attenuates endoplasmic reticulum stress-related retinal pericyte loss in streptozotocin-induced diabetic mice. J. Diabetes Res 2017, 1763292. [PubMed: 28127564]

Cideciyan AV, Hood DC, Huang Y, Banin E, Li ZY, Stone EM, Milam AH, Jacobson SG, 1998. Disease sequence from mutant rhodopsin allele to rod and cone photoreceptor degeneration in man. Proc. Natl. Acad. Sci. U. S. A 95, 7103–7108. [PubMed: 9618546]

Cnop M, Ladriere L, Hekerman P, Ortis F, Cardozo AK, Dogusan Z, Flamez D, Boyce M, Yuan J, Eizirik DL, 2007. Selective inhibition of eukaryotic translation initiation factor 2 alpha dephosphorylation potentiates fatty acid-induced endoplasmic reticulum stress and causes pancreatic beta-cell dysfunction and apoptosis. J. Biol. Chem 282, 3989–3997. [PubMed: 17158450]

Coelho Dina S., Cairrão F, Zeng X, Pires E, Coelho Ana V., Ron D, Ryoo Hyung D., Domingos Pedro M., 2013. Xbp1-Independent Ire1 signaling is required for photoreceptor differentiation and rhabdomere morphogenesis in Drosophila. Cell Rep. 5, 791–801. [PubMed: 24183663]

Collin RW, Garanto A, 2017. Applications of antisense oligonucleotides for the treatment of inherited retinal diseases. Curr. Opin. Ophthalmol 28, 260–266. [PubMed: 28151748]

Comitato A, Schiroli D, Montanari M, Marigo V, 2020. Calpain activation is the major cause of cell death in photoreceptors expressing a rhodopsin misfolding mutation. Mol. Neurobiol 57, 589–599. [PubMed: 31401765]

Connor JH, Weiser DC, Li S, Hallenbeck JM, Shenolikar S, 2001. Growth arrest and DNA damage-inducible protein GADD34 assembles a novel signaling complex containing protein phosphatase 1 and inhibitor 1. Mol. Cell Biol 21, 6841–6850. [PubMed: 11564868]

Copeland DE, Dalton AJ, 1959. An association between mitochondria and the endoplasmic reticulum in cells of the pseudobranch gland of a teleost. J. Biophys. Biochem. Cytol 5, 393–396. [PubMed: 13664679]

Costa-Mattioli M, Walter P, 2020. The Integrated Stress Response: from Mechanism to Disease, vol. 368. Science, New York, N.Y.

Coughlin BA, Feenstra DJ, Mohr S, 2017. Müller cells and diabetic retinopathy. Vis. Res 139, 93–100. [PubMed: 28866025]

Cross BC, Bond PJ, Sadowski PG, Jha BK, Zak J, Goodman JM, Silverman RH, Neubert TA, Baxendale IR, Ron D, Harding HP, 2012. The molecular basis for selective inhibition of unconventional mRNA splicing by an IRE1-binding small molecule. Proc. Natl. Acad. Sci. U. S. A 109, E869–E878. [PubMed: 22315414]

Csordas G, Renken C, Varnai P, Walter L, Weaver D, Buttle KF, Balla T, Mannella CA, Hajnoczky G, 2006. Structural and functional features and significance of the physical linkage between ER and mitochondria. J. Cell Biol 174, 915–921. [PubMed: 16982799]

Cui W, Li J, Ron D, Sha B, 2011. The structure of the PERK kinase domain suggests the mechanism for its activation. Acta Crystallogr. Sect. D Biol. Crystallogr 67, 423–428. [PubMed: 21543844]

Daiger SP, Sullivan LS, Bowne SJ, 2013. Genes and mutations causing retinitis pigmentosa. Clin. Genet 84, 132–141. [PubMed: 23701314]

Das I, Krzyzosiak A, Schneider K, Wrabetz L, D'Antonio M, Barry N, Sigurdardottir A, Bertolotti A, 2015. Preventing proteostasis diseases by selective inhibition of a phosphatase regulatory subunit. Science (New York, N.Y.) 348, 239–242. [PubMed: 25859045]

Dasari B, Prasanthi JR, Marwarha G, Singh BB, Ghribi O, 2010. The oxysterol 27-hydroxycholesterol increases β-amyloid and oxidative stress in retinal pigment epithelial cells. BMC Ophthalmol. 10, 22. [PubMed: 20836858]

Dedigama-Arachchige PM, Acharige NPN, Pflum MKH, 2018. Identification of PP1-Gadd34 substrates involved in the unfolded protein response using K-BIPS, a method for phosphatase substrate identification. Molecular omics 14, 121–133. [PubMed: 29623310]

Delépine M, Nicolino M, Barrett T, Golamaully M, Lathrop GM, Julier C, 2000. EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. Nat. Genet 25, 406–409. [PubMed: 10932183]

Devi TS, Lee I, Huttemann M, Kumar A, Nantwi KD, Singh LP, 2012. TXNIP links innate host defense mechanisms to oxidative stress and inflammation in retinal Muller glia under chronic hyperglycemia: implications for diabetic retinopathy. Exp. Diabetes Res 2012, 438238. [PubMed: 22474421]

Di Mattia T, Wilhelm LP, Ikhlef S, Wendling C, Spehner D, Nomine Y, Giordano F, Mathelin C, Drin G, Tomasetto C, Alpy F, 2018. Identification of MOSPD2, a novel scaffold for endoplasmic reticulum membrane contact sites. EMBO Rep. 19.

Dias MF, Joo K, Kemp JA, Fialho SL, da Silva Cunha A Jr., Woo SJ, Kwon YJ, 2018. Molecular genetics and emerging therapies for retinitis pigmentosa: basic research and clinical perspectives. Prog. Retin. Eye Res 63, 107–131. [PubMed: 29097191]

Ding WX, Ni HM, Gao W, Hou YF, Melan MA, Chen X, Stolz DB, Shao ZM, Yin XM, 2007. Differential effects of endoplasmic reticulum stress-induced autophagy on cell survival. J. Biol. Chem 282, 4702–4710. [PubMed: 17135238]

Donnelly N, Gorman AM, Gupta S, Samali A, 2013. The eIF2α kinases: their structures and functions. Cell. Mol. Life Sci. : CM 70, 3493–3511.

Dryja TP, McGee TL, Hahn LB, Cowley GS, Olsson JE, Reichel E, Sandberg MA, Berson EL, 1990a. Mutations within the rhodopsin gene in patients with autosomal dominant retinitis pigmentosa. N. Engl. J. Med 323, 1302–1307. [PubMed: 2215617]

Dryja TP, McGee TL, Reichel E, Hahn LB, Cowley GS, Yandell DW, Sandberg MA, Berson EL, 1990b. A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. Nature 343, 364–366. [PubMed: 2137202]

Du K, Herzig S, Kulkarni RN, Montminy M, 2003. TRB3: a tribbles homolog that inhibits Akt/PKB activation by insulin in liver. Science (New York, N.Y.) 300, 1574–1577. [PubMed: 12791994]

Du M, Wu M, Fu D, Yang S, Chen J, Wilson K, Lyons TJ, 2013. Effects of modified LDL and HDL on retinal pigment epithelial cells: a role in diabetic retinopathy? Diabetologia 56, 2318–2328. [PubMed: 23842729]

Ebert SM, Rasmussen BB, Judge AR, Judge SM, Larsson L, Wek RC, Anthony TG, Marcotte GR, Miller MJ, Yorek MA, Vella A, Volpi E, Stern JI, Strub MD, Ryan Z, Talley JJ, Adams CM, 2022. Biology of activating transcription factor 4 (ATF4) and its role in skeletal muscle atrophy. J. Nutr 152, 926–938. [PubMed: 34958390]

Egawa N, Yamamoto K, Inoue H, Hikawa R, Nishi K, Mori K, Takahashi R, 2011. The endoplasmic reticulum stress sensor, ATF6α, protects against neurotoxin-induced dopaminergic neuronal death. J. Biol. Chem 286, 7947–7957. [PubMed: 21131360]

Ellis DZ, Li L, Park Y, He S, Mueller B, Yorio T, 2017. Sigma-1 receptor regulates mitochondrial function in glucose- and oxygen-deprived retinal ganglion cells. Invest. Ophthalmol. Vis. Sci 58, 2755–2764. [PubMed: 28549090]

Elmasry K, Ibrahim AS, Saleh H, Elsherbiny N, Elshafey S, Hussein KA, Al-Shabrawey M, 2018. Role of endoplasmic reticulum stress in 12/15-lipoxygenase-induced retinal microvascular dysfunction in a mouse model of diabetic retinopathy. Diabetologia 61, 1220–1232. [PubMed: 29468369]

Eyers PA, Keeshan K, Kannan N, 2017. Tribbles in the 21st century: the evolving roles of tribbles pseudokinases in biology and disease. Trends Cell Biol. 27, 284–298. [PubMed: 27908682]

Eyries M, Montani D, Girerd B, Perret C, Leroy A, Lonjou C, Chelghoum N, Coulet F, Bonnet D, Dorfmüller P, Fadel E, Sitbon O, Simonneau G, Tregouët DA, Humbert M, Soubrier F, 2014. EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. Nat. Genet 46, 65–69. [PubMed: 24292273]

Farook JM, Shields J, Tawfik A, Markand S, Sen T, Smith SB, Brann D, Dhandapani KM, Sen N, 2013. GADD34 induces cell death through inactivation of Akt following traumatic brain injury. Cell Death Dis. 4, e754. [PubMed: 23907468]

Fawcett TW, Martindale JL, Guyton KZ, Hai T, Holbrook NJ, 1999. Complexes containing activating transcription factor (ATF)/cAMP-responsive-element-binding protein (CREB) interact with the CCAAT/enhancer-binding protein (C/EBP)-ATF composite site to regulate Gadd153 expression during the stress response. Biochem. J 339 (Pt 1), 135–141. [PubMed: 10085237]

Ferrari R, Ryten M, Simone R, Trabzuni D, Nicolaou N, Hondhamuni G, Ramasamy A, Vandrovcova J, Weale ME, Lees AJ, Momeni P, Hardy J, de Silva R, Consortium, U.B.E., 2014. Assessment of common variability and expression quantitative trait loci for genome-wide associations for progressive supranuclear palsy. Neurobiol. Aging 35, 1514.e1511–1512.

Fields MA, Del Priore LV, Adelman RA, Rizzolo LJ, 2020. Interactions of the choroid, Bruch's membrane, retinal pigment epithelium, and neurosensory retina collaborate to form the outer blood-retinal-barrier. Prog. Retin. Eye Res 76, 100803. [PubMed: 31704339]

Fisher CR, Ferrington DA, 2018. Perspective on AMD pathobiology: a bioenergetic crisis in the RPE. Invest. Ophthalmol. Vis. Sci 59, AMD41–AMD47. [PubMed: 30025108]

Fleckenstein M, Keenan TDL, Guymer RH, Chakravarthy U, Schmitz-Valckenberg S, Klaver CC, Wong WT, Chew EY, 2021. Age-related macular degeneration. Nat. Rev. Dis. Prim 7, 31. [PubMed: 33958600]

Fletcher EL, Downie LE, Ly A, Ward MM, Batcha AH, Puthussery T, Yee P, Hatzopoulos KM, 2008. A review of the role of glial cells in understanding retinal disease, 91, 67–77.

Fliesler SJ, Peachey NS, Richards MJ, Nagel BA, Vaughan DK, 2004. Retinal degeneration in a rodent model of Smith-Lemli-Opitz syndrome: electrophysiologic, biochemical, and morphologic features. Arch. Ophthalmol 122, 1190–1200. [PubMed: 15302661]

Fu D, Yu JY, Wu M, Du M, Chen Y, Abdelsamie SA, Li Y, Chen J, Boulton ME, Ma JX, Lopes-Virella MF, Virella G, Lyons TJ, 2014. Immune complex formation in human diabetic retina enhances toxicity of oxidized LDL towards retinal capillary pericytes. J. Lipid Res 55, 860–869. [PubMed: 24616481]

Fu D, Yu JY, Yang S, Wu M, Hammad SM, Connell AR, Du M, Chen J, Lyons TJ, 2016. Survival or death: a dual role for autophagy in stress-induced pericyte loss in diabetic retinopathy. Diabetologia 59, 2251–2261. [PubMed: 27475954]

Fujimoto M, Hayashi T, 2011. New insights into the role of mitochondria-associated endoplasmic reticulum membrane. Int Rev Cell Mol Biol 292, 73–117. [PubMed: 22078959]

Gade P, Manjegowda SB, Nallar SC, Maachani UB, Cross AS, Kalvakolanu DV, 2014.Regulation of the death-associated protein kinase 1 expression and autophagy via ATF6 requires apoptosis signal-regulating kinase 1. Mol. Cell Biol 34, 4033–4048. [PubMed: 25135476]

Gagnon E, Duclos S, Rondeau C, Chevet E, Cameron PH, Steele-Mortimer O, Paiement J, Bergeron JJ, Desjardins M, 2002. Endoplasmic reticulum-mediated phagocytosis is a mechanism of entry into macrophages. Cell 110, 119–131. [PubMed: 12151002]

Gal A, Li Y, Thompson DA, Weir J, Orth U, Jacobson SG, Apfelstedt-Sylla E, Vollrath D, 2000. Mutations in MERTK, the human orthologue of the RCS rat retinal dystrophy gene, cause retinitis pigmentosa. Nat. Genet 26, 270–271. [PubMed: 11062461]

Gallagher LE, Williamson LE, Chan EY, 2016. Advances in autophagy regulatory mechanisms. Cells 5.

Gass JN, Gunn KE, Sriburi R, Brewer JW, 2004. Stressed-out B cells? Plasma-cell differentiation and the unfolded protein response. Trends Immunol. 25, 17–24. [PubMed: 14698280]

Gebert M, Sobolewska A, Bartoszewska S, Cabaj A, Crossman DK, Króliczewski J, Madanecki P, Dąbrowski M, Collawn JF, Bartoszewski R, 2021. Genome-wide mRNA profiling identifies X-box-binding protein 1 (XBP1) as an IRE1 and PUMA repressor. Cell. Mol. Life Sci. : CM 78, 7061–7080.

Ghavami M, Fairn GD, 2022. Endoplasmic reticulum-Phagosome contact sites from the cradle to the grave. Front. Cell Dev. Biol 10, 1074443. [PubMed: 36619860]

Giorgi C, Baldassari F, Bononi A, Bonora M, De Marchi E, Marchi S, Missiroli S, Patergnani S, Rimessi A, Suski JM, Wieckowski MR, Pinton P, 2012. Mitochondrial Ca(2+) and apoptosis. Cell Calcium 52, 36–43. [PubMed: 22480931]

Gong Q, Wang H, Yu P, Qian T, Xu X, 2021. Protective or harmful: the dual roles of autophagy in diabetic retinopathy. Front. Med 8, 644121.

Gorbatyuk MS, Knox T, LaVail MM, Gorbatyuk OS, Noorwez SM, Hauswirth WW, Lin JH, Muzyczka N, Lewin AS, 2010. Restoration of visual function in P23H rhodopsin transgenic rats by gene delivery of BiP/Grp78. Proc. Natl. Acad. Sci. U. S. A 107, 5961–5966. [PubMed: 20231467]

Gorbatyuk MS, Starr CR, Gorbatyuk OS, 2020. Endoplasmic reticulum stress: new insights into the pathogenesis and treatment of retinal degenerative diseases. Prog. Retin. Eye Res 79, 100860. [PubMed: 32272207]

Gottlieb RA, Bernstein D, 2016. Mitochondrial remodeling: rearranging, recycling, and reprogramming. Cell Calcium 60, 88–101. [PubMed: 27130902]

Goyal U, Blackstone C, 2013. Untangling the web: mechanisms underlying ER network formation. Biochim. Biophys. Acta 1833, 2492–2498. [PubMed: 23602970]

Grandjean JMD, Madhavan A, Cech L, Seguinot BO, Paxman RJ, Smith E, Scampavia L, Powers ET, Cooley CB, Plate L, Spicer TP, Kelly JW, Wiseman RL, 2020. Pharmacologic IRE1/XBP1s activation confers targeted ER proteostasis reprogramming. Nat. Chem. Biol 16, 1052–1061. [PubMed: 32690944]

Grau T, Artemyev NO, Rosenberg T, Dollfus H, Haugen OH, Cumhur Sener E, Jurklies B, Andreasson S, Kernstock C, Larsen M, Zrenner E, Wissinger B, Kohl S, 2011. Decreased catalytic activity and altered activation properties of PDE6C mutants associated with autosomal recessive achromatopsia. Hum. Mol. Genet 20, 719–730. [PubMed: 21127010]

Gross M, Wing M, Rundquist C, Rubino MS, 1987. Evidence that phosphorylation of eIF-2(alpha) prevents the eIF-2B-mediated dissociation of eIF-2 X GDP from the 60 S subunit of complete initiation complexes. J. Biol. Chem 262, 6899–6907. [PubMed: 3646234]

Ha Y, Saul A, Tawfik A, Zorrilla EP, Ganapathy V, Smith SB, 2012. Diabetes accelerates retinal ganglion cell dysfunction in mice lacking sigma receptor 1. Mol. Vis 18, 2860–2870. [PubMed: 23233788]

Hadziahmetovic M, Malek G, 2020. Age-related macular degeneration revisited: from pathology and cellular stress to potential therapies. Front. Cell Dev. Biol 8, 612812. [PubMed: 33569380]

Han J, Back SH, Hur J, Lin YH, Gildersleeve R, Shan J, Yuan CL, Krokowski D, Wang S, Hatzoglou M, Kilberg MS, Sartor MA, Kaufman RJ, 2013. ER-stress-induced transcriptional regulation increases protein synthesis leading to cell death. Nat. Cell Biol 15, 481–490. [PubMed: 23624402]

Hanks SK, Hunter T, 1995. Protein kinases 6. The eukaryotic protein kinase superfamily: kinase (catalytic) domain structure and classification. Faseb. J 9, 576–596. [PubMed: 7768349]

Harding HP, Novoa I, Zhang Y, Zeng H, Wek R, Schapira M, Ron D, 2000. Regulated translation initiation controls stress-induced gene expression in mammalian cells. Mol. Cell 6, 1099–1108. [PubMed: 11106749]

Harding HP, Zhang Y, Zeng H, Novoa I, Lu PD, Calfon M, Sadri N, Yun C, Popko B, Paules R, Stojdl DF, Bell JC, Hettmann T, Leiden JM, Ron D, 2003. An integrated stress response regulates amino acid metabolism and resistance to oxidative stress. Mol. Cell 11, 619–633. [PubMed: 12667446]

Hayashi T, Rizzuto R, Hajnoczky G, Su TP, 2009. MAM: more than just a housekeeper. Trends Cell Biol. 19, 81–88. [PubMed: 19144519]

Hayashi T, Su TP, 2007. Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca(2+) signaling and cell survival. Cell 131, 596–610. [PubMed: 17981125]

Haze K, Yoshida H, Yanagi H, Yura T, Mori K, 1999. Mammalian transcription factor ATF6 is synthesized as a transmembrane protein and activated by proteolysis in response to endoplasmic reticulum stress. Mol. Biol. Cell 10, 3787–3799. [PubMed: 10564271]

He L, Qian X, Cui Y, 2021. Advances in ER-phagy and its diseases relevance. Cells 10.

Hedskog L, Pinho CM, Filadi R, Ronnback A, Hertwig L, Wiehager B, Larssen P, Gellhaar S, Sandebring A, Westerlund M, Graff C, Winblad B, Galter D, Behbahani H, Pizzo P, Glaser E, Ankarcrona M, 2013. Modulation of the endoplasmic reticulum-mitochondria interface in Alzheimer's disease and related models. Proc. Natl. Acad. Sci. U. S. A 110, 7916–7921. [PubMed: 23620518]

Hegedus Z, Czibula A, Kiss-Toth E, 2007. Tribbles: a family of kinase-like proteins with potent signalling regulatory function. Cell. Signal 19, 238–250. [PubMed: 16963228]

Heneka MT, McManus RM, Latz E, 2018. Inflammasome signalling in brain function and neurodegenerative disease. Nat. Rev. Neurosci 19, 610–621. [PubMed: 30206330]

Hernandez-Quiles M, Baak R, Borgman A, den Haan S, Sobrevals Alcaraz P, van Es R, Kiss-Toth E, Vos H, Kalkhoven E, 2021. Comprehensive profiling of mammalian tribbles interactomes implicates TRIB3 in gene repression. Cancers 13.

Hinnebusch AG, 1984. Evidence for translational regulation of the activator of general amino acid control in yeast. Proc. Natl. Acad. Sci. U. S. A 81, 6442–6446. [PubMed: 6387704]

Hinnebusch AG, 2005. Translational regulation of GCN4 and the general amino acid control of yeast. Annu. Rev. Microbiol 59, 407–450. [PubMed: 16153175]

Hinnebusch AG, Ivanov IP, Sonenberg N, 2016. Translational control by 5'-untranslated regions of eukaryotic mRNAs. Science (New York, N.Y.) 352, 1413–1416. [PubMed: 27313038]

Hiramatsu N, Chiang K, Aivati C, Rodvold JJ, Lee JM, Han J, Chea L, Zanetti M, Koo EH, Lin JH, 2020. PERK-mediated induction of microRNA-483 disrupts cellular ATP homeostasis during the unfolded protein response. J. Biol. Chem 295, 237–249. [PubMed: 31792031]

Hiramatsu N, Messah C, Han J, LaVail MM, Kaufman RJ, Lin JH, 2014. Translational and posttranslational regulation of XIAP by eIF2α and ATF4 promotes ER stress-induced cell death during the unfolded protein response. Mol. Biol. Cell 25, 1411–1420. [PubMed: 24623724]

Höglinger GU, Melhem NM, Dickson DW, Sleiman PM, Wang LS, Klei L, Rademakers R, de Silva R, Litvan I, Riley DE, van Swieten JC, Heutink P, Wszolek ZK, Uitti RJ, Vandrovcova J, Hurtig HI, Gross RG, Maetzler W, Goldwurm S, Tolosa E, Borroni B, Pastor P, Cantwell LB, Han MR, Dillman A, van der Brug MP, Gibbs JR, Cookson MR, Hernandez DG, Singleton AB, Farrer MJ, Yu CE, Golbe LI, Revesz T, Hardy J, Lees AJ, Devlin B, Hakonarson H, Müller U, Schellenberg GD, 2011a. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat. Genet 43, 699–705. [PubMed: 21685912]

Höglinger GU, Melhem NM, Dickson DW, Sleiman PM, Wang LS, Klei L, Rademakers R, de Silva R, Litvan I, Riley DE, van Swieten JC, Heutink P, Wszolek ZK, Uitti RJ, Vandrovcova J, Hurtig HI, Gross RG, Maetzler W, Goldwurm S, Tolosa E, Borroni B, Pastor P, Cantwell LB, Han MR, Dillman A, van der Brug MP, Gibbs JR, Cookson MR, Hernandez DG, Singleton AB, Farrer MJ, Yu CE, Golbe LI, Revesz T, Hardy J, Lees AJ, Devlin B, Hakonarson H, Müller U, Schellenberg GD, Group, P.G.S., 2011b. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat. Genet 43, 699–705. [PubMed: 21685912]

Hosoi T, Kakimoto M, Tanaka K, Nomura J, Ozawa K, 2016. Unique pharmacological property of ISRIB in inhibition of Aβ-induced neuronal cell death. J. Pharmacol. Sci 131, 292–295. [PubMed: 27569458]

Hu ML, Edwards TL, O'Hare F, Hickey DG, Wang JH, Liu Z, Ayton LN, 2021a. Gene therapy for inherited retinal diseases: progress and possibilities. Clin. Exp. Optom 104, 444–454. [PubMed: 33689657]

Hu Y, Chen H, Zhang L, Lin X, Li X, Zhuang H, Fan H, Meng T, He Z, Huang H, Gong Q, Zhu D, Xu Y, He P, Li L, Feng D, 2021b. The AMPK-MFN2 axis regulates MAM dynamics and autophagy induced by energy stresses. Autophagy 17, 1142–1156. [PubMed: 32249716]

Hua F, Li K, Yu JJ, Lv XX, Yan J, Zhang XW, Sun W, Lin H, Shang S, Wang F, Cui B, Mu R, Huang B, Jiang JD, Hu ZW, 2015. TRB3 links insulin/IGF to tumour promotion by interacting with p62 and impeding autophagic/proteasomal degradations. Nat. Commun 6, 7951. [PubMed: 26268733]

Huang C, Wang JJ, Jing G, Li J, Jin C, Yu Q, Falkowski MW, Zhang SX, 2015a. Erp29 attenuates cigarette smoke extract–induced endoplasmic reticulum stress and mitigates tight junction

damage in retinal pigment epithelial CellsProtective role of ERp29 in RPE cells. Invest. Ophthalmol. Vis. Sci 56, 6196–6207. [PubMed: 26431474]

Huang C, Wang JJ, Ma JH, Jin C, Yu Q, Zhang SX, 2015b. Activation of the UPR protects against cigarette smoke-induced RPE apoptosis through up-regulation of Nrf2. J. Biol. Chem

Huang H, Jing G, Wang JJ, Sheibani N, Zhang SX, 2015c. ATF4 is a novel regulator of MCP-1 in microvascular endothelial cells. J. Inflamm 12, 31.

Huang H, Zhu X, Cheng H, Kuang X, Long C, Deng X, Zou Y, Zhang H, Xing Y, Ling X, Wang R, Tang H, Du H, Shi K, Wang L, Yan J, Shen H, 2021. 2,3,5,6-Tetramethylpyrazine protects retinal photoreceptors against endoplasmic reticulum stress by modulating ATF4-mediated inhibition of PRP aggregation. J. Mol. Med. (Berl.) 99, 383–402. [PubMed: 33409554]

Humphrey RK, Newcomb CJ, Yu SM, Hao E, Yu D, Krajewski S, Du K, Jhala US, 2010. Mixed lineage kinase-3 stabilizes and functionally cooperates with TRIBBLES-3 to compromise mitochondrial integrity in cytokine-induced death of pancreatic beta cells. J. Biol. Chem 285, 22426–22436. [PubMed: 20421299]

Hurley JB, 2021. Retina metabolism and metabolism in the pigmented epithelium: a busy intersection. Annual review of vision science 7, 665–692.

Hutmacher F, 2019. Why is there so much more research on vision than on any other sensory modality? Front. Psychol 10, 2246. [PubMed: 31636589]

Inoue H, Tanizawa Y, Wasson J, Behn P, Kalidas K, Bernal-Mizrachi E, Mueckler M, Marshall H, Donis-Keller H, Crock P, Rogers D, Mikuni M, Kumashiro H, Higashi K, Sobue G, Oka Y, Permutt MA, 1998. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). Nat. Genet 20, 143–148. [PubMed: 9771706]

Intartaglia D, Giamundo G, Naso F, Nusco E, Di Giulio S, Salierno FG, Polishchuk E, Conte I, 2022. Induction of autophagy promotes clearance of RHO (P23H) aggregates and protects from retinal degeneration. Front. Aging Neurosci 14, 878958. [PubMed: 35847673]

Islam MA, Mizusawa M, Sharmin MM, Hayashi S, Yonekura S, 2020. TRPV4 increases the expression of tight junction protein-encoding genes via XBP1 in mammary epithelial cells. Animals : an open access journal from MDPI 10.

Iwakoshi NN, Lee AH, Vallabhajosyula P, Otipoby KL, Rajewsky K, Glimcher LH, 2003. Plasma cell differentiation and the unfolded protein response intersect at the transcription factor XBP-1. Nat. Immunol 4, 321–329. [PubMed: 12612580]

Iwawaki T, Akai R, Yamanaka S, Kohno K, 2009. Function of IRE1 alpha in the placenta is essential for placental development and embryonic viability. Proc. Natl. Acad. Sci. USA 106, 16657–16662. [PubMed: 19805353]

Jacobs JL, Zhu J, Sarkar SN, Coyne CB, 2014. Regulation of mitochondrial antiviral signaling (MAVS) expression and signaling by the mitochondria-associated endoplasmic reticulum membrane (MAM) protein Gp78. J. Biol. Chem 289, 1604–1616. [PubMed: 24285545]

Jassim AH, Inman DM, Mitchell CH, 2021. Crosstalk between dysfunctional mitochondria and inflammation in glaucomatous neurodegeneration. Front. Pharmacol 12, 699623. [PubMed: 34366851]

Jiang HY, Wek RC, 2005. Phosphorylation of the alpha-subunit of the eukaryotic initiation factor-2 (eIF2alpha) reduces protein synthesis and enhances apoptosis in response to proteasome inhibition. J. Biol. Chem 280, 14189–14202. [PubMed: 15684420]

Jiang X, Wei Y, Zhang T, Zhang Z, Qiu S, Zhou X, Zhang S, 2017. Effects of GSK2606414 on cell proliferation and endoplasmic reticulum stress-associated gene expression in retinal pigment epithelial cells. Mol. Med. Rep 15, 3105–3110. [PubMed: 28358434]

Joltikov KA, Sesi CA, de Castro VM, Davila JR, Anand R, Khan SM, Farbman N, Jackson GR, Johnson CA, Gardner TW, 2018. Disorganization of retinal inner layers (DRIL) and neuroretinal dysfunction in early diabetic retinopathy. Invest. Ophthalmol. Vis. Sci 59, 5481–5486. [PubMed: 30452602]

Kakiuchi C, Iwamoto K, Ishiwata M, Bundo M, Kasahara T, Kusumi I, Tsujita T, Okazaki Y, Nanko S, Kunugi H, Sasaki T, Kato T, 2003. Impaired feedback regulation of XBP1 as a genetic risk factor for bipolar disorder. Nat. Genet 35, 171–175. [PubMed: 12949534]

Kang MK, Lee EJ, Kim YH, Kim DY, Oh H, Kim SI, Kang YH, 2018. Chrysin ameliorates malfunction of retinoid visual cycle through blocking activation of AGE-RAGE-ER stress in glucose-stimulated retinal pigment epithelial cells and diabetic eyes. Nutrients 10.

Kanow MA, Giarmarco MM, Jankowski CS, Tsantilas K, Engel AL, Du J, Linton JD, Farnsworth CC, Sloat SR, Rountree A, Sweet IR, Lindsay KJ, Parker ED, Brockerhoff SE, Sadilek M, Chao JR, Hurley JB, 2017. Biochemical adaptations of the retina and retinal pigment epithelium support a metabolic ecosystem in the vertebrate eye. Elife 6.

Kashiwagi K, Ito T, Yokoyama S, 2017. Crystal structure of eIF2B and insights into eIF2-eIF2B interactions. FEBS J. 284, 868–874. [PubMed: 27627185]

Kaufman RJ, 1999. Stress signaling from the lumen of the endoplasmic reticulum: coordination of gene transcriptional and translational controls. Genes Dev. 13, 1211–1233. [PubMed: 10346810]

Kawano S, Tamura Y, Kojima R, Bala S, Asai E, Michel AH, Kornmann B, Riezman I, Riezman H, Sakae Y, Okamoto Y, Endo T, 2018. Structure-function insights into direct lipid transfer between membranes by Mmm1-Mdm12 of ERMES. J. Cell Biol 217, 959–974. [PubMed: 29279306]

Kelly K, Wang JJ, Zhang SX, 2018. The unfolded protein response signaling and retinal Müller cell metabolism. Neural Regen Res 13, 1861–1870. [PubMed: 30233053]

Khan S, 2022. Endoplasmic reticulum in metaplasticity: from information processing to synaptic proteostasis. Mol. Neurobiol 59, 5630–5655. [PubMed: 35739409]

Kim EH, Yoon MJ, Kim SU, Kwon TK, Sohn S, Choi KS, 2008. Arsenic trioxide sensitizes human glioma cells, but not normal astrocytes, to TRAIL-induced apoptosis via CCAAT/enhancer-binding protein homologous protein-dependent DR5 up-regulation. Cancer Res. 68, 266–275. [PubMed: 18172319]

Kim JY, Zhao H, Martinez J, Doggett TA, Kolesnikov AV, Tang PH, Ablonczy Z, Chan CC, Zhou Z, Green DR, Ferguson TA, 2013. Noncanonical autophagy promotes the visual cycle. Cell 154, 365–376. [PubMed: 23870125]

Kim K, Safarta LA, Chiang WJ, Coppinger JA, Lee EJ, Lin JH, 2022. Network biology analysis of P23H rhodopsin interactome identifies protein and mRNA quality control mechanisms. Sci. Rep 12, 17405. [PubMed: 36258031]

Kimball SR, Heinzinger NK, Horetsky RL, Jefferson LS, 1998. Identification of interprotein interactions between the subunits of eukaryotic initiation factors eIF2 and eIF2B. J. Biol. Chem 273, 3039–3044. [PubMed: 9446619]

Kiss-Toth E, Bagstaff SM, Sung HY, Jozsa V, Dempsey C, Caunt JC, Oxley KM, Wyllie DH, Polgar T, Harte M, O'Neill LA, Qwarnstrom EE, Dower SK, 2004. Human tribbles, a protein family controlling mitogen-activated protein kinase cascades. J. Biol. Chem 279, 42703–42708. [PubMed: 15299019]

Koba H, Jin S, Imada N, Ishikawa T, Ninagawa S, Okada T, Sakuma T, Yamamoto T, Mori K, 2020. Reinvestigation of disulfide-bonded oligomeric forms of the unfolded protein response transducer ATF6. Cell Struct. Funct 45, 9–21. [PubMed: 31852864]

Kohl S, Baumann B, Broghammer M, Jägle H, Sieving P, Kellner U, Spegal R, Anastasi M, Zrenner E, Sharpe LT, Wissinger B, 2000. Mutations in the CNGB3 gene encoding the beta-subunit of the cone photoreceptor cGMP-gated channel are responsible for achromatopsia (ACHM3) linked to chromosome 8q21. Hum. Mol. Genet 9, 2107–2116. [PubMed: 10958649]

Kohl S, Baumann B, Rosenberg T, Kellner U, Lorenz B, Vadalà M, Jacobson SG, Wissinger B, 2002. Mutations in the cone photoreceptor G-protein alpha-subunit gene GNAT2 in patients with achromatopsia. Am. J. Hum. Genet 71, 422–425. [PubMed: 12077706]

Kohl S, Coppieters F, Meire F, Schaich S, Roosing S, Brennenstuhl C, Bolz S, van Genderen MM, Riemslag FC, Lukowski R, den Hollander AI, Cremers FP, De Baere E, Hoyng CB, Wissinger B, Consortium, E.R.D., 2012. A nonsense mutation in PDE6H causes autosomal-recessive incomplete achromatopsia. Am. J. Hum. Genet 91, 527–532. [PubMed: 22901948]

Kohl S, Marx T, Giddings I, Jägle H, Jacobson SG, Apfelstedt-Sylla E, Zrenner E, Sharpe LT, Wissinger B, 1998. Total colourblindness is caused by mutations in the gene encoding the alpha-subunit of the cone photoreceptor cGMP-gated cation channel. Nat. Genet 19, 257–259. [PubMed: 9662398]

Kohl S, Zobor D, Chiang WC, Weisschuh N, Staller J, Gonzalez Menendez I, Chang S, Beck SC, Garcia Garrido M, Sothilingam V, Seeliger MW, Stanzial F, Benedicenti F, Inzana F, Héon E, Vincent A, Beis J, Strom TM, Rudolph G, Roosing S, Hollander AI, Cremers FP, Lopez I, Ren H, Moore AT, Webster AR, Michaelides M, Koenekoop RK, Zrenner E, Kaufman RJ, Tsang SH, Wissinger B, Lin JH, 2015. Mutations in the unfolded protein response regulator ATF6 cause the cone dysfunction disorder achromatopsia. Nat. Genet 47, 757–765. [PubMed: 26029869]

Kong DQ, Li L, Liu Y, Zheng GY, 2018. Association between endoplasmic reticulum stress and risk factors of diabetic retinopathy. Int. J. Ophthalmol 11, 1704–1710. [PubMed: 30364130]

Kopp MC, Larburu N, Durairaj V, Adams CJ, Ali MMU, 2019. UPR proteins IRE1 and PERK switch BiP from chaperone to ER stress sensor. Nat. Struct. Mol. Biol 26, 1053–1062. [PubMed: 31695187]

Kouhara J, Yoshida T, Nakata S, Horinaka M, Wakada M, Ueda Y, Yamagishi H, Sakai T, 2007. Fenretinide up-regulates DR5/TRAIL-R2 expression via the induction of the transcription factor CHOP and combined treatment with fenretinide and TRAIL induces synergistic apoptosis in colon cancer cell lines. Int. J. Oncol 30, 679–687. [PubMed: 17273769]

Kouroku Y, Fujita E, Tanida I, Ueno T, Isoai A, Kumagai H, Ogawa S, Kaufman RJ, Kominami E, Momoi T, 2007. ER stress (PERK/eIF2alpha phosphorylation) mediates the polyglutamine-induced LC3 conversion, an essential step for autophagy formation. Cell Death Differ. 14, 230–239. [PubMed: 16794605]

Križaj D, 2012. Calcium stores in vertebrate photoreceptors. Adv. Exp. Med. Biol 740, 873–889. [PubMed: 22453974]

Kroeger H, Grandjean JMD, Chiang WJ, Bindels DD, Mastey R, Okalova J, Nguyen A, Powers ET, Kelly JW, Grimsey NJ, Michaelides M, Carroll J, Wiseman RL, Lin JH, 2021. ATF6 is essential for human cone photoreceptor development. Proc. Natl. Acad. Sci. U. S. A 118.

Kroeger H, Grimsey N, Paxman R, Chiang WC, Plate L, Jones Y, Shaw PX, Trejo J, Tsang SH, Powers E, Kelly JW, Wiseman RL, Lin JH, 2018. The unfolded protein response regulator ATF6 promotes mesodermal differentiation. Sci. Signal 11.

Krokowski D, Guan BJ, Wu J, Zheng Y, Pattabiraman PP, Jobava R, Gao XH, Di XJ, Snider MD, Mu TW, Liu S, Storrie B, Pearlman E, Blumental-Perry A, Hatzoglou M, 2017. GADD34 function in protein trafficking promotes adaptation to hyperosmotic stress in human corneal cells. Cell Rep. 21, 2895–2910. [PubMed: 29212034]

Krzyzosiak A, Sigurdardottir A, Luh L, Carrara M, Das I, Schneider K, Bertolotti A, 2018. Target-based discovery of an inhibitor of the regulatory phosphatase PPP1R15B. Cell 174, 1216–1228.e1219. [PubMed: 30057111]

Kundu D, Pasrija R, 2020. The ERMES (endoplasmic reticulum and mitochondria encounter structures) mediated functions in fungi. Mitochondrion 52, 89–99. [PubMed: 32105794]

Kunte MM, Choudhury S, Manheim JF, Shinde VM, Miura M, Chiodo VA, Hauswirth WW, Gorbatyuk OS, Gorbatyuk MS, 2012. ER stress is involved in T17M rhodopsin-induced retinal degeneration. Invest. Ophthalmol. Vis. Sci 53, 3792–3800. [PubMed: 22589437]

Kwon W, Freeman SA, 2020. Phagocytosis by the Retinal Pigment Epithelium: Recognition, Resolution, Recycling, vol. 11.

Lachance V, Belanger SM, Hay C, Le Corvec V, Banouvong V, Lapalme M, Tarmoun K, Beaucaire G, Lussier MP, Kourrich S, 2023. Overview of sigma-1R subcellular specific biological functions and role in neuroprotection. Int. J. Mol. Sci 24.

Larhammar M, Huntwork-Rodriguez S, Jiang Z, Solanoy H, Sengupta Ghosh A, Wang B, Kaminker JS, Huang K, Eastham-Anderson J, Siu M, Modrusan Z, Farley MM, Tessier-Lavigne M, Lewcock JW, Watkins TA, 2017. Dual leucine zipper kinase-dependent PERK activation contributes to neuronal degeneration following insult. Elife 6.

Latz E, Xiao TS, Stutz A, 2013. Activation and regulation of the inflammasomes. Nat. Rev. Immunol 13, 397–411. [PubMed: 23702978]

Le Thomas A, Ferri E, Marsters S, Harnoss JM, Lawrence DA, Zuazo-Gaztelu I, Modrusan Z, Chan S, Solon M, Chalouni C, Li W, Koeppen H, Rudolph J, Wang W, Wu TD, Walter P, Ashkenazi A, 2021. Decoding non-canonical mRNA decay by the endoplasmic-reticulum stress sensor IRE1α. Nat. Commun 12, 7310. [PubMed: 34911951]

Lebeau J, Saunders JM, Moraes VWR, Madhavan A, Madrazo N, Anthony MC, Wiseman RL, 2018. The PERK arm of the unfolded protein response regulates mitochondrial morphology during acute endoplasmic reticulum stress. Cell Rep. 22, 2827–2836. [PubMed: 29539413]

Lee AH, Iwakoshi NN, Glimcher LH, 2003. XBP-1 regulates a subset of endoplasmic reticulum resident chaperone genes in the unfolded protein response. Mol. Cell Biol 23, 7448–7459. [PubMed: 14559994]

Lee EJ, Chan P, Chea L, Kim K, Kaufman RJ, Lin JH, 2021. ATF6 is required for efficient rhodopsin clearance and retinal homeostasis in the P23H rho retinitis pigmentosa mouse model. Sci. Rep 11, 16356. [PubMed: 34381136]

Lee EJ, Chiang WJ, Kroeger H, Bi CX, Chao DL, Skowronska-Krawczyk D, Mastey RR, Tsang SH, Chea L, Kim K, Lambert SR, Grandjean JM, Baumann B, Audo I, Kohl S, Moore AT, Wiseman RL, Carroll J, Lin JH, 2020. Multiexon deletion alleles of ATF6 linked to achromatopsia. JCI Insight 5.

Lee EJ, Diaz-Aguilar MS, Min H, Choi J, Valdez Duran DA, Grandjean JM, Wiseman RL, Kroeger H, Lin JH, 2022. Mitochondria and endoplasmic reticulum stress in retinal organoids from patients with vision loss. Am. J. Pathol

Lee R, Wong TY, Sabanayagam C, 2015. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye Vis (Lond) 2, 17. [PubMed: 26605370]

Lee S, Min KT, 2018. The interface between ER and mitochondria: molecular compositions and functions. Mol. Cell 41, 1000–1007.

Lee VK, Hosking BM, Holeniewska J, Kubala EC, Lundh von Leithner P, Gardner PJ, Foxton RH, Shima DT, 2018. BTBR ob/ob mouse model of type 2 diabetes exhibits early loss of retinal function and retinal inflammation followed by late vascular changes. Diabetologia 61, 2422–2432. [PubMed: 30094465]

Leegwater PA, Vermeulen G, Könst AA, Naidu S, Mulders J, Visser A, Kersbergen P, Mobach D, Fonds D, van Berkel CG, Lemmers RJ, Frants RR, Oudejans CB, Schutgens RB, Pronk JC, van der Knaap MS, 2001. Subunits of the translation initiation factor eIF2B are mutant in leukoencephalopathy with vanishing white matter. Nat. Genet 29, 383–388. [PubMed: 11704758]

Leger F, Fernagut PO, Canron MH, Léoni S, Vital C, Tison F, Bezard E, Vital A, 2011. Protein aggregation in the aging retina. J. Neuropathol. Exp. Neurol 70, 63–68. [PubMed: 21157377]

Levine B, Klionsky DJ, 2004. Development by self-digestion: molecular mechanisms and biological functions of autophagy. Dev. Cell 6, 463–477. [PubMed: 15068787]

Lewis RS, 2007. The molecular choreography of a store-operated calcium channel. Nature 446, 284–287. [PubMed: 17361175]

Li C, Li L, Yang M, Yang J, Zhao C, Han Y, Zhao H, Jiang N, Wei L, Xiao Y, Liu Y, Xiong X, Xi Y, Luo S, Deng F, Chen W, Yuan S, Zhu X, Xiao L, Sun L, 2022. PACS-2 ameliorates tubular injury by facilitating endoplasmic reticulum-mitochondria contact and mitophagy in diabetic nephropathy. Diabetes 71, 1034–1050. [PubMed: 35133431]

Li G, Mongillo M, Chin KT, Harding H, Ron D, Marks AR, Tabas I, 2009a. Role of ERO1-alpha-mediated stimulation of inositol 1,4,5-triphosphate receptor activity in endoplasmic reticulum stress-induced apoptosis. J. Cell Biol 186, 783–792. [PubMed: 19752026]

Li H, Korennykh AV, Behrman SL, Walter P, 2010. Mammalian endoplasmic reticulum stress sensor IRE1 signals by dynamic clustering, 107, 16113–16118.

Li H, Zhu X, Fang F, Jiang D, Tang L, 2014a. Down-regulation of GRP78 enhances apoptosis via CHOP pathway in retinal ischemia-reperfusion injury. Neurosci. Lett 575, 68–73. [PubMed: 24880098]

Li J, Cai X, Xia Q, Yao K, Chen J, Zhang Y, Naranmandura H, Liu X, Wu Y, 2014b. Involvement of endoplasmic reticulum stress in all-trans-retinal-induced retinal pigment epithelium degeneration. Toxicol. Sci 143, 196–208. [PubMed: 25331497]

Li J, Cai X, Xia Q, Yao K, Chen J, Zhang Y, Naranmandura H, Liu X, Wu Y, 2015. Involvement of endoplasmic reticulum stress in all-trans-retinal-induced retinal pigment epithelium degeneration. Toxicol. Sci 143, 196–208. [PubMed: 25331497]

Li J, Wang JJ, Yu Q, Wang M, Zhang SX, 2009b. Endoplasmic reticulum stress is implicated in retinal inflammation and diabetic retinopathy. FEBS Lett. 583, 1521–1527. [PubMed: 19364508]

Li J, Wang JJ, Zhang SX, 2011. Preconditioning with endoplasmic reticulum stress mitigates retinal endothelial inflammation via activation of X-box binding protein 1. J. Biol. Chem 286, 4912–4921. [PubMed: 21138840]

Li L, He S, Liu Y, Yorio T, Ellis DZ, 2021a. Sigma-1R protects retinal ganglion cells in optic nerve crush model for glaucoma. Invest. Ophthalmol. Vis. Sci 62, 17.

Li W, Wang Y, Zhu L, Du S, Mao J, Wang Y, Wang S, Bo Q, Tu Y, Yi Q, 2021b. The P300/XBP1s/Herpud1 axis promotes macrophage M2 polarization and the development of choroidal neovascularization, 25, 6709–6720.

Li X, Yang Q, Liu S, Song S, Wang C, 2023. Mitochondria-associated endoplasmic reticulum membranes promote mitochondrial fission through AKAP1-Drp1 pathway in podocytes under high glucose conditions. Exp. Cell Res 424, 113512. [PubMed: 36775185]

Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY, 2012. Age-related macular degeneration. Lancet 379, 1728–1738. [PubMed: 22559899]

Lim Y, Cho IT, Schoel LJ, Cho G, Golden JA, 2015. Hereditary spastic paraplegia-linked REEP1 modulates endoplasmic reticulum/mitochondria contacts. Ann. Neurol 78, 679–696. [PubMed: 26201691]

Lin JH, Li H, Yasumura D, Cohen HR, Zhang C, Panning B, Shokat KM, Lavail MM, Walter P, 2007. IRE1 signaling affects cell fate during the unfolded protein response. Science 318, 944–949. [PubMed: 17991856]

Lin W, Harding HP, Ron D, Popko B, 2005. Endoplasmic reticulum stress modulates the response of myelinating oligodendrocytes to the immune cytokine interferongamma. J. Cell Biol 169, 603–612. [PubMed: 15911877]

Lind KR, Ball KK, Cruz NF, Dienel GA, 2013. The unfolded protein response to endoplasmic reticulum stress in cultured astrocytes and rat brain during experimental diabetes. Neurochem. Int 62, 784–795. [PubMed: 23411409]

Lindner P, Christensen SB, Nissen P, Moller JV, Engedal N, 2020. Cell death induced by the ER stressor thapsigargin involves death receptor 5, a non-autophagic function of MAP1LC3B, and distinct contributions from unfolded protein response components. Cell Commun. Signal 18, 12. [PubMed: 31987044]

Liu C, Yan DY, Wang C, Ma Z, Deng Y, Liu W, Xu B, 2020. IRE1 signaling pathway mediates protective autophagic response against manganese-induced neuronal apoptosis in vivo and in vitro. Sci. Total Environ 712, 136480. [PubMed: 31931206]

Liu CC, Kanekiyo T, Xu H, Bu G, 2013a. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat. Rev. Neurol 9, 106–118. [PubMed: 23296339]

Liu CY, Schroder M, Kaufman RJ, 2000. Ligand-independent dimerization activates the stress response kinases IRE1 and PERK in the lumen of the endoplasmic reticulum. J. Biol. Chem 275, 24881–24885. [PubMed: 10835430]

Liu J, Yang J, 2022. Mitochondria-associated membranes: a hub for neurodegenerative diseases. Biomed. Pharmacother 149, 112890. [PubMed: 35367757]

Liu L, Qi X, Chen Z, Shaw L, Cai J, Smith LH, Grant MB, Boulton ME, 2013b. Targeting the IRE1alpha/XBP1 and ATF6 arms of the unfolded protein response enhances VEGF blockade to prevent retinal and choroidal neovascularization. Am. J. Pathol 182, 1412–1424. [PubMed: 23395094]

Lobanova ES, Finkelstein S, Skiba NP, Arshavsky VY, 2013. Proteasome overload is a common stress factor in multiple forms of inherited retinal degeneration. Proc. Natl. Acad. Sci. U. S. A 110, 9986–9991. [PubMed: 23716657]

Longo F, Mancini M, Ibraheem PL, Aryal S, Mesini C, Patel JC, Penhos E, Rahman N, Mamcarz M, Santini E, Rice ME, Klann E, 2021. Cell-type-specific disruption of PERK-eIF2α signaling in dopaminergic neurons alters motor and cognitive function. Mol. Psychiatr 26, 6427–6450.

Lu M, van Tartwijk FW, Lin JQ, Nijenhuis W, Parutto P, Fantham M, Christensen CN, Avezov E, Holt CE, Tunnacliffe A, Holcman D, Kapitein L, Schierle GSK, Kaminski CF, 2020. The structure and global distribution of the endoplasmic reticulum network are actively regulated by lysosomes, 6, eabc7209.

Lu PD, Harding HP, Ron D, 2004. Translation reinitiation at alternative open reading frames regulates gene expression in an integrated stress response. J. Cell Biol 167, 27–33. [PubMed: 15479734]

Ma JH, Shen S, Wang JJ, He Z, Poon A, Li J, Qu J, Zhang SX, 2017. Comparative proteomic analysis of the mitochondria-associated ER membrane (MAM) in a long-term type 2 diabetic rodent model. Sci. Rep 7, 2062. [PubMed: 28522876]

Ma JH, Wang JJ, Li J, Pfeffer BA, Zhong Y, Zhang SX, 2016. The role of IRE-XBP1 pathway in regulation of retinal pigment epithelium tight JunctionsXBP1 regulates the RPE tight junctions. Invest. Ophthalmol. Vis. Sci 57, 5244–5252. [PubMed: 27701635]

Ma JH, Wang JJ, Zhang SX, 2014. The unfolded protein response and diabetic retinopathy. J. Diabetes Res 14, 2014.

Ma K, Vattem KM, Wek RC, 2002. Dimerization and release of molecular chaperone inhibition facilitate activation of eukaryotic initiation factor-2 kinase in response to endoplasmic reticulum stress. J. Biol. Chem 277, 18728–18735. [PubMed: 11907036]

Madhavan A, Kok BP, Rius B, Grandjean JMD, Alabi A, Albert V, Sukiasyan A, Powers ET, Galmozzi A, Saez E, Wiseman RL, 2022. Pharmacologic IRE1/XBP1s activation promotes systemic adaptive remodeling in obesity. Nat. Commun 13, 608. [PubMed: 35105890]

Mahameed M, Wilhelm T, Darawshi O, Obiedat A, Tommy WS, Chintha C, Schubert T, Samali A, Chevet E, Eriksson LA, Huber M, Tirosh B, 2019. The unfolded protein response modulators GSK2606414 and KIRA6 are potent KIT inhibitors. Cell Death Dis. 10, 300. [PubMed: 30931942]

Maiuri MC, Zalckvar E, Kimchi A, Kroemer G, 2007. Self-eating and self-killing: crosstalk between autophagy and apoptosis. Nat. Rev. Mol. Cell Biol 8, 741–752. [PubMed: 17717517]

Malhotra JD, Kaufman RJ, 2011. ER stress and its functional link to mitochondria: role in cell survival and death. Cold Spring Harbor Perspect. Biol 3, a004424.

Mao D, Reuter CM, Ruzhnikov MRZ, Beck AE, Farrow EG, Emrick LT, Rosenfeld JA, Mackenzie KM, Robak L, Wheeler MT, Burrage LC, Jain M, Liu P, Calame D, Küry S, Sillesen M, Schmitz-Abe K, Tonduti D, Spaccini L, Iascone M, Genetti CA, Koenig MK, Graf M, Tran A, Alejandro M, Lee BH, Thiffault I, Agrawal PB, Bernstein JA, Bellen HJ, Chao HT, 2020. De novo EIF2AK1 and EIF2AK2 variants are associated with developmental delay, leukoencephalopathy, and neurologic decompensation. Am. J. Hum. Genet 106, 570–583. [PubMed: 32197074]

Marchi S, Patergnani S, Missiroli S, Morciano G, Rimessi A, Wieckowski MR, Giorgi C, Pinton P, 2018. Mitochondrial and endoplasmic reticulum calcium homeostasis and cell death. Cell Calcium 69, 62–72. [PubMed: 28515000]

Marciniak SJ, Yun CY, Oyadomari S, Novoa I, Zhang Y, Jungreis R, Nagata K, Harding HP, Ron D, 2004. CHOP induces death by promoting protein synthesis and oxidation in the stressed endoplasmic reticulum. Gene Dev. 18, 3066–3077. [PubMed: 15601821]

Martinez-Vicente M, Cuervo AM, 2007. Autophagy and neurodegeneration: when the cleaning crew goes on strike. Lancet Neurol. 6, 352–361. [PubMed: 17362839]

Massoudi D, Gorman S, Kuo Y-M, Iwawaki T, Oakes SA, Papa FR, Gould DB, 2023. Deletion of the unfolded protein response transducer IRE1α is detrimental to aging photoreceptors and to ER stress-mediated retinal degeneration. Invest. Ophthalmol. Vis. Sci 64, 30, 30.

Mastey RR, Georgiou M, Langlo CS, Kalitzeos A, Patterson EJ, Kane T, Singh N, Vincent A, Moore AT, Tsang SH, Lin JH, Young MP, Hartnett ME, Héon E, Kohl S, Michaelides M, Carroll J, 2019. Characterization of retinal structure in ATF6-associated achromatopsia. Invest. Ophthalmol. Vis. Sci 60, 2631–2640. [PubMed: 31237654]

Mata J, Curado S, Ephrussi A, Rorth P, 2000. Tribbles coordinates mitosis and morphogenesis in Drosophila by regulating string/CDC25 proteolysis. Cell 101, 511–522. [PubMed: 10850493]

Matus S, Lisbona F, Torres M, Leon C, Thielen P, Hetz C, 2008. The stress rheostat: an interplay between the unfolded protein response (UPR) and autophagy in neurodegeneration. Curr. Mol. Med 8, 157–172. [PubMed: 18473817]

Maurel M, Chevet E, Tavernier J, Gerlo S, 2014. Getting RIDD of RNA: IRE1 in cell fate regulation. Trends Biochem. Sci 39, 245–254. [PubMed: 24657016]

Mavlyutov TA, Nickells RW, Guo LW, 2011. Accelerated retinal ganglion cell death in mice deficient in the Sigma-1 receptor. Mol. Vis 17, 1034–1043. [PubMed: 21541278]

Mayumi-Matsuda K, Kojima S, Suzuki H, Sakata T, 1999. Identification of a novel kinase-like gene induced during neuronal cell death. Biochem. Biophys. Res. Commun 258, 260–264. [PubMed: 10329375]

McCullough KD, Martindale JL, Klotz LO, Aw TY, Holbrook NJ, 2001. Gadd153 sensitizes cells to endoplasmic reticulum stress by down-regulating Bcl2 and perturbing the cellular redox state. Mol. Cell Biol 21, 1249–1259. [PubMed: 11158311]

McLaughlin T, Falkowski M, Park JW, Keegan S, Elliott M, Wang JJ, Zhang SX, 2018. Loss of XBP1 accelerates age-related decline in retinal function and neurodegeneration. Mol. Neurodegener 13, 16. [PubMed: 29615095]

McLaughlin T, Medina A, Perkins J, Yera M, Wang JJ, Zhang SX, 2022. Cellular stress signaling and the unfolded protein response in retinal degeneration: mechanisms and therapeutic implications. Mol. Neurodegener 17, 25. [PubMed: 35346303]

McLaughlin T, Siddiqi M, Wang JJ, Zhang SX, 2019. Loss of XBP1 leads to early-onset retinal neurodegeneration in a mouse model of type I diabetes. J. Clin. Med 8.

McLaughlin T, Wang G, Medina A, Perkins J, Nihlawi R, Seyfried D, Hu Z, Wang JJ, Zhang SX, 2023. Essential Role of XBP1 in Maintaining Photoreceptor Synaptic Integrity in Early Diabetic Retinopathy. Invest Ophthalmol Vis Sci 64, 40.

Meex SJ, van Greevenbroek MM, Ayoubi TA, Vlietinck R, van Vliet-Ostaptchouk JV, Hofker MH, Vermeulen VM, Schalkwijk CG, Feskens EJ, Boer JM, Stehouwer CD, van der Kallen CJ, de Bruin TW, 2007. Activating transcription factor 6 polymorphisms and haplotypes are associated with impaired glucose homeostasis and type 2 diabetes in Dutch Caucasians. J. Clin. Endocrinol. Metab 92, 2720–2725. [PubMed: 17440018]

Meex SJ, Weissglas-Volkov D, van der Kallen CJ, Thuerauf DJ, van Greevenbroek MM, Schalkwijk CG, Stehouwer CD, Feskens EJ, Heldens L, Ayoubi TA, Hofker MH, Wouters BG, Vlietinck R, Sinsheimer JS, Taskinen MR, Kuusisto J, Laakso M, de Bruin TW, Pajukanta P, Glembotski CC, 2009. The ATF6-Met[67]Val substitution is associated with increased plasma cholesterol levels. Arterioscler. Thromb. Vasc. Biol 29, 1322–1327. [PubMed: 19667116]

Menard C, Wilson AM, Dejda A, Miloudi K, Binet F, Crespo-Garcia S, Parinot C, Pilon F, Juneau R, Andriessen EM, Mawambo G, SanGiovanni JP, De Guire V, Sapieha P, 2020. miR-106b suppresses pathological retinal angiogenesis. Aging 12, 24836–24852. [PubMed: 33361521]

Meng D, Ragi SD, Tsang SH, 2022. Therapy in rhodopsin-mediated autosomal dominant retinitis pigmentosa. Mol. Ther 30, 2633. [PubMed: 35709761]

Mercurio AM, Holtzman E, 1982. Smooth endoplasmic reticulum and other agranular reticulum in frog retinal photoreceptors. J. Neurocytol 11, 263–293. [PubMed: 6978386]

Miranda S, Gonzalez-Rodriguez A, Garcia-Ramirez M, Revuelta-Cervantes J, Hernandez C, Simo R, Valverde AM, 2012. Beneficial effects of fenofibrate in retinal pigment epithelium by the modulation of stress and survival signaling under diabetic conditions. J. Cell. Physiol 227, 2352–2362. [PubMed: 21826649]

Missiroli S, Patergnani S, Caroccia N, Pedriali G, Perrone M, Previati M, Wieckowski MR, Giorgi C, 2018. Mitochondria-associated membranes (MAMs) and inflammation. Cell Death Dis. 9, 329. [PubMed: 29491386]

Mitchell P, Liew G, Gopinath B, Wong TY, 2018. Age-related macular degeneration. Lancet 392, 1147–1159. [PubMed: 30303083]

Mitter SK, Song C, Qi X, Mao H, Rao H, Akin D, Lewin A, Grant M, Dunn W Jr., Ding J, Bowes Rickman C, Boulton M, 2014. Dysregulated autophagy in the RPE is associated with increased susceptibility to oxidative stress and AMD. Autophagy 10, 1989–2005. [PubMed: 25484094]

Moreno JA, Halliday M, Molloy C, Radford H, Verity N, Axten JM, Ortori CA, Willis AE, Fischer PM, Barrett DA, Mallucci GR, 2013. Oral treatment targeting the unfolded protein response prevents neurodegeneration and clinical disease in prion-infected mice. Sci. Transl. Med 5, 206ra138.

Murase H, Tsuruma K, Shimazawa M, Hara H, 2015. TUDCA promotes phagocytosis by retinal pigment epithelium via MerTK activation. Invest. Ophthalmol. Vis. Sci 56, 2511–2518. [PubMed: 25804419]

Murray AR, Vuong L, Brobst D, Fliesler SJ, Peachey NS, Gorbatyuk MS, Naash MI, Al-Ubaidi MR, 2015. Glycosylation of rhodopsin is necessary for its stability and incorporation into photoreceptor outer segment discs. Hum. Mol. Genet 24, 2709–2723. [PubMed: 25637522]

Nadanaka S, Okada T, Yoshida H, Mori K, 2007. Role of disulfide bridges formed in the luminal domain of ATF6 in sensing endoplasmic reticulum stress. Mol. Cell Biol 27, 1027–1043. [PubMed: 17101776]

Nadanaka S, Yoshida H, Kano F, Murata M, Mori K, 2004. Activation of mammalian unfolded protein response is compatible with the quality control system operating in the endoplasmic reticulum. Mol. Biol. Cell 15, 2537–2548. [PubMed: 15020717]

Nadanaka S, Yoshida H, Mori K, 2006. Reduction of disulfide bridges in the lumenal domain of ATF6 in response to glucose starvation. Cell Struct. Funct 31, 127–134. [PubMed: 17130669]

Nashine S, Bhootada Y, Lewin AS, Gorbatyuk M, 2013. Ablation of C/EBP homologous protein does not protect T17M RHO mice from retinal degeneration. PLoS One 8, e63205. [PubMed: 23646198]

National Eye Institute, 2019. Age-Related Macular Degeneration (AMD) Data and Statistics.

Ning J, Glausier J, Hsieh C, Schmelzer T, Buck S, Franks J, Hampton C, Lewis D, Marko M, Freyberg Z, 2023. Cryo-FIB Workflow for Imaging Brain Tissue via in Situ Cryo-Electron Microscopy. bioRxiv.

Nunes P, Cornut D, Bochet V, Hasler U, Oh-Hora M, Waldburger JM, Demaurex N, 2012. STIM1 juxtaposes ER to phagosomes, generating Ca(2)(+) hotspots that boost phagocytosis. Curr. Biol 22, 1990–1997. [PubMed: 23041196]

Oh WJ, Jacinto E, 2011. mTOR complex 2 signaling and functions. Cell Cycle 10, 2305–2316. [PubMed: 21670596]

Ohoka N, Yoshii S, Hattori T, Onozaki K, Hayashi H, 2005. TRB3, a novel ER stress-inducible gene, is induced via ATF4-CHOP pathway and is involved in cell death. EMBO J. 24, 1243–1255. [PubMed: 15775988]

Okada T, Yoshida H, Akazawa R, Negishi M, Mori K, 2002. Distinct roles of activating transcription factor 6 (ATF6) and double-stranded RNA-activated protein kinase-like endoplasmic reticulum kinase (PERK) in transcription during the mammalian unfolded protein response. Biochem. J 366, 585–594. [PubMed: 12014989]

Orci L, Ravazzola M, Le Coadic M, Shen WW, Demaurex N, Cosson P, 2009. From the Cover: STIM1-induced precortical and cortical subdomains of the endoplasmic reticulum. Proc. Natl. Acad. Sci. U. S. A 106, 19358–19362. [PubMed: 19906989]

Ord D, Meerits K, Ord T, 2007. TRB3 protects cells against the growth inhibitory and cytotoxic effect of ATF4. Exp. Cell Res 313, 3556–3567. [PubMed: 17707795]

Ord D, Ord T, 2003. Mouse NIPK interacts with ATF4 and affects its transcriptional activity. Exp. Cell Res 286, 308–320. [PubMed: 12749859]

Ord D, Ord T, 2005. Characterization of human NIPK (TRB3, SKIP3) gene activation in stressful conditions. Biochem. Biophys. Res. Commun 330, 210–218. [PubMed: 15781252]

Ord D, Ord T, Biene T, Ord T, 2016. TRIB3 increases cell resistance to arsenite toxicity by limiting the expression of the glutathione-degrading enzyme CHAC1. Biochim. Biophys. Acta 1863, 2668–2680. [PubMed: 27526673]

Ord T, Ord D, Adler P, Vilo J, Ord T, 2015. TRIB3 enhances cell viability during glucose deprivation in HEK293-derived cells by upregulating IGFBP2, a novel nutrient deficiency survival factor. Biochim. Biophys. Acta 1853, 2492–2505. [PubMed: 26094770]

Ord T, Ord D, Koivomagi M, Juhkam K, Ord T, 2009. Human TRB3 is upregulated in stressed cells by the induction of translationally efficient mRNA containing a truncated 5'-UTR. Gene 444, 24–32. [PubMed: 19505541]

Ord T, Ord T, 2017. Mammalian pseudokinase TRIB3 in normal physiology and disease: charting the progress in old and new avenues. Curr. Protein Pept. Sci 18, 819–842. [PubMed: 28393700]

Oshitari T, Yoshida-Hata N, Yamamoto S, 2011. Effect of neurotrophin-4 on endoplasmic reticulum stress-related neuronal apoptosis in diabetic and high glucose exposed rat retinas. Neurosci. Lett 501, 102–106. [PubMed: 21767604]

Oskolkova OV, Afonyushkin T, Leitner A, von Schlieffen E, Gargalovic PS, Lusis AJ, Binder BR, Bochkov VN, 2008. ATF4-dependent transcription is a key mechanism in VEGF up-regulation by oxidized phospholipids: critical role of oxidized sn-2 residues in activation of unfolded protein response. Blood 112, 330–339. [PubMed: 18451308]

Ouyang S, Ji D, He S, Xia X, 2022. Endoplasmic reticulum stress as a novel target to inhibit transdifferentiation of human retinal pigment epithelial cells. Front. Biosci 27, 38.

Öztürk Z, O'Kane CJ, Pérez-Moreno JJ, 2020. Axonal Endoplasmic Reticulum Dynamics and its Roles in Neurodegeneration, vol. 14.

Pakos-Zebrucka K, Koryga I, Mnich K, Ljujic M, Samali A, Gorman AM, 2016. The integrated stress response. EMBO Rep. 17, 1374–1395. [PubMed: 27629041]

Palay SL, Palade GE, 1955. The fine structure of neurons. J. Biophys. Biochem. Cytol 1, 69–88. [PubMed: 14381429]

Pariente A, Pérez-Sala Á, Ochoa R, Bobadilla M, Villanueva-Martínez Á, Peláez R, Larráyoz IM, 2023. Identification of 7-ketocholesterol-modulated pathways and sterculic acid protective effect in retinal pigmented epithelium cells by using genome-wide transcriptomic analysis. Int. J. Mol. Sci 24.

Park G, Xu K, Chea L, Kim K, Safarta L, Song KH, Wu J, Park S, Min H, Hiramatsu N, Han J, Lin JH, 2023. Neurodegeneration risk factor, EIF2AK3 (PERK), influences tau protein aggregation. J. Biol. Chem 299, 102821. [PubMed: 36563857]

Park J, Choi H, Min JS, Park SJ, Kim JH, Park HJ, Kim B, Chae JI, Yim M, Lee DS, 2013. Mitochondrial dynamics modulate the expression of pro-inflammatory mediators in microglial cells. J. Neurochem 127, 221–232. [PubMed: 23815397]

Pavitt GD, Ron D, 2012. New insights into translational regulation in the endoplasmic reticulum unfolded protein response. Cold Spring Harbor Perspect. Biol 4.

Paxman R, Plate L, Blackwood EA, Glembotski C, Powers ET, Wiseman RL, Kelly JW, 2018. Pharmacologic ATF6 activating compounds are metabolically activated to selectively modify endoplasmic reticulum proteins. Elife 7.

Pearring JN, Salinas RY, Baker SA, Arshavsky VY, 2013. Protein sorting, targeting and trafficking in photoreceptor cells. Prog. Retin. Eye Res 36, 24–51. [PubMed: 23562855]

Peng J, Qin C, Ramatchandirin B, Pearah A, Guo S, Hussain M, Yu L, Wondisford FE, He L, 2022a. Activation of the canonical ER stress IRE1-XBP1 pathway by insulin regulates glucose and lipid metabolism. J. Biol. Chem 298, 102283. [PubMed: 35863429]

Peng W, Wu Y, Peng Z, Qi W, Liu T, Yang B, He D, Liu Y, Wang Y, 2022b. Cyanidin-3-glucoside improves the barrier function of retinal pigment epithelium cells by attenuating endoplasmic reticulum stress-induced apoptosis. Food Res. Int 157, 111313. [PubMed: 35761606]

Perea V, Cole C, Lebeau J, Dolina V, Baron KR, Madhavan A, Kelly JW, Grotjahn DA, Wiseman RL, 2023. PERK signaling promotes mitochondrial elongation by remodeling membrane phosphatidic acid. EMBO J., e113908 [PubMed: 37306086]

Pfeiffer RL, Marc RE, Jones BW, 2020. Persistent remodeling and neurodegeneration in late-stage retinal degeneration. Prog. Retin. Eye Res 74, 100771. [PubMed: 31356876]

Pitale PM, Saltykova IV, Adu-Agyeiwaah Y, Calzi SL, Satoh T, Akira S, Gorbatyuk O, Boulton ME, Pardue MT, Garvey WT, Athar M, Grant MB, Gorbatyuk MS, 2021. Tribbles homolog 3 mediates the development and progression of diabetic retinopathy. Diabetes.

Planas-Serra L, Launay N, Goicoechea L, Heron B, Jou C, Julia-Palacios N, Ruiz M, Fourcade S, Casasnovas C, De La Torre C, Gelot A, Marsal M, Loza-Alvarez P, Garcia-Cazorla A, Fatemi A, Ferrer I, Portero-Otin M, Area-Gomez E, Pujol A, 2023. Sphingolipid desaturase DEGS1 is essential for mitochondria-associated membrane integrity. J. Clin. Invest 133.

Plate L, Cooley CB, Chen JJ, Paxman RJ, Gallagher CM, Madoux F, Genereux JC, Dobbs W, Garza D, Spicer TP, Scampavia L, Brown SJ, Rosen H, Powers ET, Walter P, Hodder P, Wiseman RL, Kelly JW, 2016. Small molecule proteostasis regulators that reprogram the ER to reduce extracellular protein aggregation. Elife 5.

Podust LM, Krezel AM, Kim Y, 2001. Crystal structure of the CCAAT box/enhancer-binding protein beta activating transcription factor-4 basic leucine zipper heterodimer in the absence of DNA. J. Biol. Chem 276, 505–513. [PubMed: 11018027]

Porter KR, Yamada E, 1960. Studies on the endoplasmic reticulum. V. Its form and differentiation in pigment epithelial cells of the frog retina. J. Biophys. Biochem. Cytol 8, 181–205. [PubMed: 13737277]

Porter LF, Saptarshi N, Fang Y, Rathi S, den Hollander AI, de Jong EK, Clark SJ, Bishop PN, Olsen TW, Liloglou T, Chavali VRM, Paraoan L, 2019. Whole-genome methylation profiling of the retinal pigment epithelium of individuals with age-related macular degeneration reveals differential methylation of the SKI, GTF2H4, and TNXB genes. Clin. Epigenet 11, 6.

Prestes EB, Bruno JCP, Travassos LH, Carneiro LAM, 2021. The unfolded protein response and autophagy on the crossroads of coronaviruses infections. Front. Cell. Infect. Microbiol 11, 668034. [PubMed: 33996638]

Prischi F, Nowak PR, Carrara M, Ali MMU, 2014. Phosphoregulation of Ire1 RNase splicing activity. Nat. Commun 5, 3554. [PubMed: 24704861]

Prudente S, Sesti G, Pandolfi A, Andreozzi F, Consoli A, Trischitta V, 2012. The mammalian tribbles homolog TRIB3, glucose homeostasis, and cardiovascular diseases. Endocr. Rev 33, 526–546. [PubMed: 22577090]

Puthalakath H, O'Reilly LA, Gunn P, Lee L, Kelly PN, Huntington ND, Hughes PD, Michalak EM, McKimm-Breschkin J, Motoyama N, Gotoh T, Akira S, Bouillet P, Strasser A, 2007. ER stress triggers apoptosis by activating BH3-only protein Bim. Cell 129, 1337–1349. [PubMed: 17604722]

Qi L, Heredia JE, Altarejos JY, Screaton R, Goebel N, Niessen S, Macleod IX, Liew CW, Kulkarni RN, Bain J, Newgard C, Nelson M, Evans RM, Yates J, Montminy M, 2006. TRB3 links the E3 ubiquitin ligase COP1 to lipid metabolism. Science (New York, N.Y.) 312, 1763–1766. [PubMed: 16794074]

Qiao X, Jia S, Ye J, Fang X, Zhang C, Cao Y, Xu C, Zhao L, Zhu Y, Wang L, Zheng M, 2017. PTPIP51 regulates mouse cardiac ischemia/reperfusion through mediating the mitochondria-SR junction. Sci. Rep 7, 45379. [PubMed: 28345618]

Qiu Y, Yao J, Jia L, Thompson DA, Zacks DN, 2019. Shifting the balance of autophagy and proteasome activation reduces proteotoxic cell death: a novel therapeutic approach for restoring photoreceptor homeostasis. Cell Death Dis. 10, 547. [PubMed: 31320609]

Quwaider D, Corchete LA, Martín-Izquierdo M, Hernández-Sánchez JM, Rojas EA, Cardona-Benavides IJ, García-Sanz R, Herrero AB, Gutiérrez NC, 2022. RNA sequencing identifies novel regulated IRE1-dependent decay targets that affect multiple myeloma survival and proliferation. Exp. Hematol. Oncol 11, 18. [PubMed: 35361260]

Raeisossadati R, Ferrari MFR, 2022. Mitochondria-ER tethering in neurodegenerative diseases. Cell. Mol. Neurobiol 42, 917–930. [PubMed: 33196974]

Rainbolt TK, Saunders JM, Wiseman RL, 2014. Stress-responsive regulation of mitochondria through the ER unfolded protein response. Trends Endocrinol. Metabol 25, 528–537.

Rana T, Shinde VM, Starr CR, Kruglov AA, Boitet ER, Kotla P, Zolotukhin S, Gross AK, Gorbatyuk MS, 2014. An activated unfolded protein response promotes retinal degeneration and triggers an inflammatory response in the mouse retina. Cell Death Dis. 5, e1578. [PubMed: 25522272]

Rangasamy S, Monickaraj F, Legendre C, Cabrera AP, Llaci L, Bilagody C, McGuire P, Das A, 2020. Transcriptomics analysis of pericytes from retinas of diabetic animals reveals novel genes and molecular pathways relevant to blood-retinal barrier alterations in diabetic retinopathy. Exp. Eye Res 195, 108043. [PubMed: 32376470]

Reggiori F, Molinari M, 2022. ER-phagy: mechanisms, regulation, and diseases connected to the lysosomal clearance of the endoplasmic reticulum. Physiol. Rev 102, 1393–1448. [PubMed: 35188422]

Rieusset J, Fauconnier J, Paillard M, Belaidi E, Tubbs E, Chauvin MA, Durand A, Bravard A, Teixeira G, Bartosch B, Michelet M, Theurey P, Vial G, Demion M, Blond E, Zoulim F, Gomez L, Vidal H, Lacampagne A, Ovize M, 2016. Disruption of calcium transfer from ER to mitochondria links alterations of mitochondria-associated ER membrane integrity to hepatic insulin resistance. Diabetologia 59, 614–623. [PubMed: 26660890]

Rizzuto R, Brini M, Murgia M, Pozzan T, 1993. Microdomains with high Ca2+ close to IP3-sensitive channels that are sensed by neighboring mitochondria. Science (New York, N.Y.) 262, 744–747. [PubMed: 8235595]

Rizzuto R, Pinton P, Carrington W, Fay FS, Fogarty KE, Lifshitz LM, Tuft RA, Pozzan T, 1998. Close contacts with the endoplasmic reticulum as determinants of mitochondrial Ca2+ responses. Science (New York, N.Y.) 280, 1763–1766. [PubMed: 9624056]

Rojas-Rivera D, Delvaeye T, Roelandt R, Nerinckx W, Augustyns K, Vandenabeele P, Bertrand MJM, 2017. When PERK inhibitors turn out to be new potent RIPK1 inhibitors: critical issues on the specificity and use of GSK2606414 and GSK2656157. Cell Death Differ. 24, 1100–1110. [PubMed: 28452996]

Rorth P, Szabo K, Texido G, 2000. The level of C/EBP protein is critical for cell migration during Drosophila oogenesis and is tightly controlled by regulated degradation. Mol. Cell 6, 23–30. [PubMed: 10949024]

Rosarda JD, Giles S, Harkins-Perry S, Mills EA, Friedlander M, Wiseman RL, Eade KT, 2023. Imbalanced unfolded protein response signaling contributes to 1-deoxysphingolipid retinal toxicity. Nat. Commun 14, 4119. [PubMed: 37433773]

Roybal CN, Yang S, Sun CW, Hurtado D, Vander Jagt DL, Townes TM, Abcouwer SF, 2004. Homocysteine increases the expression of vascular endothelial growth factor by a mechanism involving endoplasmic reticulum stress and transcription factor ATF4. J. Biol. Chem 279, 14844–14852. [PubMed: 14747470]

Saint-Geniez M, Kurihara T, Sekiyama E, Maldonado AE, D'Amore PA, 2009. An Essential Role for RPE-Derived Soluble VEGF in the Maintenance of the Choriocapillaris, vol. 106, pp. 18751–18756.

Salazar M, Lorente M, Garcia-Taboada E, Gomez EP, Davila D, Zuniga-Garcia P, Flores JM, Rodriguez A, Hegedus Z, Mosen-Ansorena D, Aransay AM, Hernandez-Tiedra S, Lopez-Valero I, Quintanilla M, Sanchez C, Iovanna JL, Dusetti N, Guzman M, Francis SE, Carracedo A, Kiss-Toth E, Velasco G, 2015. TRIB3 suppresses tumorigenesis by controlling mTORC2/AKT/FOXO signaling. Mol Cell Oncol 2, e980134. [PubMed: 27308456]

Salazar M, Lorente M, Garcia-Taboada E, Hernandez-Tiedra S, Davila D, Francis SE, Guzman M, Kiss-Toth E, Velasco G, 2013. The pseudokinase tribbles homologue-3 plays a crucial role in cannabinoid anticancer action. Biochim. Biophys. Acta 1831, 1573–1578. [PubMed: 23567453]

Saltykova IV, Elahi A, Pitale PM, Gorbatyuk OS, Athar M, Gorbatyuk MS, 2021. Tribbles homolog 3-mediated targeting the AKT/mTOR axis in mice with retinal degeneration. Cell Death Dis. 12, 664. [PubMed: 34215725]

Saltykova IV, Zhylkibayev A, Gorbatyuk OS, Gorbatyuk MS, 2022. GADD34 ablation exacerbates retinal degeneration in P23H RHO mice. Int. J. Mol. Sci 23.

Sanchez-Contreras MY, Kouri N, Cook CN, Serie DJ, Heckman MG, Finch NA, Caselli RJ, Uitti RJ, Wszolek ZK, Graff-Radford N, Petrucelli L, Wang LS, Schellenberg GD, Dickson DW, Rademakers R, Ross OA, 2018. Replication of progressive supranuclear palsy genome-wide association study identifies SLCO1A2 and DUSP10 as new susceptibility loci. Mol. Neurodegener 13, 37. [PubMed: 29986742]

Sano R, Reed JC, 2013. ER stress-induced cell death mechanisms. Biochim. Biophys. Acta 1833, 3460–3470. [PubMed: 23850759]

Saptarshi N, Porter LF, Paraoan L, 2022. PERK/EIF2AK3 integrates endoplasmic reticulum stress-induced apoptosis, oxidative stress and autophagy responses in immortalised retinal pigment epithelial cells. Sci. Rep 12, 13324. [PubMed: 35922637]

Sarkar H, Toms M, Moosajee M, 2021. Involvement of oxidative and endoplasmic reticulum stress in RDH12-related retinopathies. Int. J. Mol. Sci 22.

Sato Y, Nadanaka S, Okada T, Okawa K, Mori K, 2011. Luminal domain of ATF6 alone is sufficient for sensing endoplasmic reticulum stress and subsequent transport to the Golgi apparatus. Cell Struct. Funct 36, 35–47. [PubMed: 21150130]

Schwarz DS, Blower MD, 2016. The endoplasmic reticulum: structure, function and response to cellular signaling. Cell. Mol. Life Sci. : CM 73, 79–94.

Schwarzer R, Dames S, Tondera D, Klippel A, Kaufmann J, 2006. TRB3 is a PI 3-kinase dependent indicator for nutrient starvation. Cell. Signal 18, 899–909. [PubMed: 16129579]

Sears AE, Palczewski K, 2016. Lecithin:Retinol acyltransferase: a key enzyme involved in the retinoid (visual) cycle. Biochemistry 55, 3082–3091. [PubMed: 27183166]

Sharma BR, Kanneganti TD, 2021. NLRP3 inflammasome in cancer and metabolic diseases. Nat. Immunol 22, 550–559. [PubMed: 33707781]

Shen J, Chen X, Hendershot L, Prywes R, 2002. ER stress regulation of ATF6 localization by dissociation of BiP/GRP78 binding and unmasking of Golgi localization signals. Dev. Cell 3, 99–111. [PubMed: 12110171]

Shi W, Sun C, He B, Xiong W, Shi X, Yao D, Cao X, 2004. GADD34-PP1c recruited by Smad7 dephosphorylates TGFbeta type I receptor. J. Cell Biol 164, 291–300. [PubMed: 14718519]

Shoulders MD, Ryno LM, Genereux JC, Moresco JJ, Tu PG, Wu C, Yates JR, Su AI, Kelly JW, Wiseman RL, 2013. Stress-independent activation of XBP1s and/or ATF6 reveals three functionally diverse ER proteostasis environments. Cell Rep. 3, 1279–1292. [PubMed: 23583182]

Simo R, Simo-Servat O, Bogdanov P, Hernandez C, 2022. Diabetic retinopathy: role of neurodegeneration and therapeutic perspectives. Asia Pac J Ophthalmol (Phila) 11, 160–167. [PubMed: 35533335]

Simo R, Stitt AW, Gardner TW, 2018. Neurodegeneration in diabetic retinopathy: does it really matter? Diabetologia 61, 1902–1912. [PubMed: 30030554]

Simó R, Villarroel M, Corraliza L, Hernández C, Garcia-Ramírez M, 2010. The retinal pigment epithelium: something more than a constituent of the blood-retinal barrier–implications for the pathogenesis of diabetic retinopathy. J. Biomed. Biotechnol 2010, 190724. [PubMed: 20182540]

Siwecka N, Rozpędek-Kamińska W, Wawrzynkiewicz A, Pytel D, Diehl JA, Majsterek I, 2021. The structure, activation and signaling of IRE1 and its role in determining cell fate. Biomedicines 9.

Skorczyk-Werner A, Chiang WC, Wawrocka A, Wicher K, Jarmuż-Szymczak M, Kostrzewska-Poczekaj M, Jamsheer A, Płoski R, Rydzanicz M, Pojda-Wilczek D, Weisschuh N, Wissinger B, Kohl S, Lin JH, Krawczyński MR, 2017. Autosomal recessive cone-rod dystrophy can be caused by mutations in the ATF6 gene. Eur. J. Hum. Genet. : EJHG (Eur. J. Hum. Genet.) 25, 1210–1216. [PubMed: 28812650]

Sonenberg N, Hinnebusch AG, 2009. Regulation of translation initiation in eukaryotes: mechanisms and biological targets. Cell 136, 731–745. [PubMed: 19239892]

Song J-Y, Fan B, Che L, Pan Y-R, Zhang S-M, Wang Y, Bunik V, Li G-Y, 2020. Suppressing endoplasmic reticulum stress-related autophagy attenuates retinal light injury. Aging 12, 16579. [PubMed: 32858529]

Song M, Mihara K, Chen Y, Scorrano L, Dorn GW 2nd, 2015. Mitochondrial fission and fusion factors reciprocally orchestrate mitophagic culling in mouse hearts and cultured fibroblasts. Cell Metabol. 21, 273–286.

Sonn SK, Seo S, Yang J, Oh KS, Chen H, Chan DC, Rhee K, Lee KS, Yang Y, Oh GT, 2021. ER-associated CTRP1 regulates mitochondrial fission via interaction with DRP1. Exp. Mol. Med 53, 1769–1780. [PubMed: 34837016]

Sonoda S, Sreekumar PG, Kase S, Spee C, Ryan SJ, Kannan R, Hinton DR, 2009. Attainment of polarity promotes growth factor secretion by retinal pigment epithelial cells: relevance to age-related macular degeneration. Aging 2, 28–42. [PubMed: 20228934]

Sood R, Porter AC, Ma K, Quilliam LA, Wek RC, 2000. Pancreatic eukaryotic initiation factor-2alpha kinase (PEK) homologues in humans, Drosophila melanogaster and Caenorhabditis elegans that mediate translational control in response to endoplasmic reticulum stress. Biochem. J 346 Pt 2, 281–293. [PubMed: 10677345]

Spaide RF, Jaffe GJ, Sarraf D, Freund KB, Sadda SR, Staurenghi G, Waheed NK, Chakravarthy U, Rosenfeld PJ, Holz FG, Souied EH, Cohen SY, Querques G, Ohno-Matsui K, Boyer D, Gaudric A, Blodi B, Baumal CR, Li X, Coscas GJ, Brucker A, Singerman L, Luthert P, Schmitz-Valckenberg S, Schmidt-Erfurth U, Grossniklaus HE, Wilson DJ, Guymer R, Yannuzzi LA, Chew EY, Csaky K, Monés JM, Pauleikhoff D, Tadayoni R, Fujimoto J, 2020. Consensus nomenclature for reporting neovascular age-related macular degeneration data: consensus on

neovascular age-related macular degeneration nomenclature study group. Ophthalmology 127, 616–636. [PubMed: 31864668]

Sree S, Parkkinen I, Their A, Airavaara M, Jokitalo E, 2021. Morphological heterogeneity of the endoplasmic reticulum within neurons and its implications in neurodegeneration. Cells 10.

Sreekumar PG, Ishikawa K, Spee C, Mehta HH, Wan J, Yen K, Cohen P, Kannan R, Hinton DR, 2016. The mitochondrial-derived peptide humanin protects RPE cells from oxidative stress, senescence, and mitochondrial dysfunction. Invest. Ophthalmol. Vis. Sci 57, 1238–1253. [PubMed: 26990160]

Sriburi R, Jackowski S, Mori K, Brewer JW, 2004. XBP1: a link between the unfolded protein response, lipid biosynthesis, and biogenesis of the endoplasmic reticulum. J. Cell Biol 167, 35–41. [PubMed: 15466483]

Starr CR, Gorbatyuk MS, 2019. Delineating the role of eIF2alpha in retinal degeneration. Cell Death Dis. 10, 409. [PubMed: 31138784]

Starr CR, Nyankerh CNA, Qi X, Hu Y, Gorbatyuk OS, Sonenberg N, Boulton ME, Gorbatyuk MS, 2019. Role of translational attenuation in inherited retinal degeneration. Invest. Ophthalmol. Vis. Sci 60, 4849–4857. [PubMed: 31747684]

Starr CR, Pitale PM, Gorbatyuk M, 2018. Translational attenuation and retinal degeneration in mice with an active integrated stress response. Cell Death Dis. 9, 484. [PubMed: 29706649]

Stefanovska B, Andre F, Fromigue O, 2021. Tribbles pseudokinase 3 regulation and contribution to cancer. Cancers 13.

Stendahl O, Krause KH, Krischer J, Jerstrom P, Theler JM, Clark RA, Carpentier JL, Lew DP, 1994. Redistribution of intracellular Ca2+ stores during phagocytosis in human neutrophils. Science 265, 1439–1441. [PubMed: 8073285]

Stoica R, De Vos KJ, Paillusson S, Mueller S, Sancho RM, Lau KF, Vizcay-Barrena G, Lin WL, Xu YF, Lewis J, Dickson DW, Petrucelli L, Mitchell JC, Shaw CE, Miller CC, 2014. ER-mitochondria associations are regulated by the VAPB-PTPIP51 interaction and are disrupted by ALS/FTD-associated TDP-43. Nat. Commun 5, 3996. [PubMed: 24893131]

Strauss O, 1995. The retinal pigment epithelium. In: Kolb H, Fernandez E, Nelson R (Eds.), Webvision: the Organization of the Retina and Visual System, Salt Lake City (UT).

Suárez Y, Sessa WC, 2009. MicroRNAs as novel regulators of angiogenesis. Circ. Res 104, 442–454. [PubMed: 19246688]

Sudhakar A, Krishnamoorthy T, Jain A, Chatterjee U, Hasnain SE, Kaufman RJ, Ramaiah KV, 1999. Serine 48 in initiation factor 2 alpha (eIF2 alpha) is required for high-affinity interaction between eIF2 alpha(P) and eIF2B. Biochemistry 38, 15398–15405. [PubMed: 10563826]

Sudhakar A, Ramachandran A, Ghosh S, Hasnain SE, Kaufman RJ, Ramaiah KV, 2000. Phosphorylation of serine 51 in initiation factor 2 alpha (eIF2 alpha) promotes complex formation between eIF2 alpha(P) and eIF2B and causes inhibition in the guanine nucleotide exchange activity of eIF2B. Biochemistry 39, 12929–12938. [PubMed: 11041858]

Suryanarayanan A, Slaughter MM, 2006. Synaptic transmission mediated by internal calcium stores in rod photoreceptors. J. Neurosci. : the official journal of the Society for Neuroscience 26, 1759–1766.

Swarup A, Samuels IS, Bell BA, Han JYS, Du J, Massenzio E, Abel ED, Boesze-Battaglia K, Peachey NS, Philp NJ, 2019. Modulating GLUT1 expression in retinal pigment epithelium decreases glucose levels in the retina: impact on photoreceptors and Müller glial cells. Am. J. Physiol. Cell Physiol 316, C121–c133. [PubMed: 30462537]

Talukder AH, Wang RA, Kumar R, 2002. Expression and transactivating functions of the bZIP transcription factor GADD153 in mammary epithelial cells. Oncogene 21, 4289–4300. [PubMed: 12082616]

Tang L, Zhang Y, Jiang Y, Willard L, Ortiz E, Wark L, Medeiros D, Lin D, 2011. Dietary wolfberry ameliorates retinal structure abnormalities in db/db mice at the early stage of diabetes. Exp. Biol. Med 236, 1051–1063.

Taniuchi S, Miyake M, Tsugawa K, Oyadomari M, Oyadomari S, 2016. Integrated stress response of vertebrates is regulated by four eIF2alpha kinases. Sci. Rep 6, 32886. [PubMed: 27633668]

Tao J, Chen H, Li X, Wang J, 2021. The role of activating transcription factor 6 in hydroxycamptothecin-induced fibroblast autophagy and apoptosis. J. Orthop. Surg. Res 16, 1. [PubMed: 33397415]

Tenbrock L, Wolf J, Boneva S, Schlecht A, Agostini H, Wieghofer P, Schlunck G, Lange C, 2022. Subretinal fibrosis in neovascular age-related macular degeneration: current concepts, therapeutic avenues, and future perspectives. Cell Tissue Res. 387, 361–375. [PubMed: 34477966]

Thameem F, Farook VS, Bogardus C, Prochazka M, 2006. Association of amino acid variants in the activating transcription factor 6 gene (ATF6) on 1q21-q23 with type 2 diabetes in Pima Indians. Diabetes 55, 839–842. [PubMed: 16505252]

Thiagalingam S, McGee TL, Weleber RG, Sandberg MA, Trzupek KM, Berson EL, Dryja TP, 2007. Novel mutations in the KCNV2 gene in patients with cone dystrophy and a supernormal rod electroretinogram. Ophthalmic Genet. 28, 135–142. [PubMed: 17896311]

Thoudam T, Jeon JH, Ha CM, Lee IK, 2016. Role of mitochondria-associated endoplasmic reticulum membrane in inflammation-mediated metabolic diseases. Mediat. Inflamm 2016, 1851420.

Torres SE, Gallagher CM, Plate L, Gupta M, Liem CR, Guo X, Tian R, Stroud RM, Kampmann M, Weissman JS, Walter P, 2019. Ceapins block the unfolded protein response sensor ATF6α by inducing a neomorphic inter-organelle tether. Elife 8.

Tsaytler P, Harding HP, Ron D, Bertolotti A, 2011. Selective inhibition of a regulatory subunit of protein phosphatase 1 restores proteostasis. Science (New York, N.Y.) 332, 91–94. [PubMed: 21385720]

Tsuru A, Imai Y, Saito M, Kohno K, 2016. Novel mechanism of enhancing IRE1alpha-XBP1 signalling via the PERK-ATF4 pathway. Sci. Rep 6, 24217. [PubMed: 27052593]

Tubbs E, Theurey P, Vial G, Bendridi N, Bravard A, Chauvin MA, Ji-Cao J, Zoulim F, Bartosch B, Ovize M, Vidal H, Rieusset J, 2014. Mitochondria-associated endoplasmic reticulum membrane (MAM) integrity is required for insulin signaling and is implicated in hepatic insulin resistance. Diabetes 63, 3279–3294. [PubMed: 24947355]

Uemura A, Oku M, Mori K, Yoshida H, 2009. Unconventional splicing of XBP1 mRNA occurs in the cytoplasm during the mammalian unfolded protein response. J. Cell Sci 122, 2877–2886. [PubMed: 19622636]

Usui M, Yamaguchi S, Tanji Y, Tominaga R, Ishigaki Y, Fukumoto M, Katagiri H, Mori K, Oka Y, Ishihara H, 2012. Atf6α-null mice are glucose intolerant due to pancreatic β-cell failure on a high-fat diet but partially resistant to diet-induced insulin resistance. Metabolism 61, 1118–1128. [PubMed: 22386934]

van Vliet AR, Giordano F, Gerlo S, Segura I, Van Eygen S, Molenberghs G, Rocha S, Houcine A, Derua R, Verfaillie T, Vangindertael J, De Keersmaecker H, Waelkens E, Tavernier J, Hofkens J, Annaert W, Carmeliet P, Samali A, Mizuno H, Agostinis P, 2017. The ER stress sensor PERK coordinates ER-plasma membrane contact site formation through interaction with filamin-A and F-actin remodeling. Mol. Cell 65, 885–899.e886. [PubMed: 28238652]

Vance JE, 1990. Phospholipid synthesis in a membrane fraction associated with mitochondria. J. Biol. Chem 265, 7248–7256. [PubMed: 2332429]

Vannuvel K, Renard P, Raes M, Arnould T, 2013. Functional and morphological impact of ER stress on mitochondria. J. Cell. Physiol 228, 1802–1818. [PubMed: 23629871]

Vats A, Xi Y, Feng B, Clinger OD, St Leger AJ, Liu X, Ghosh A, Dermond CD, Lathrop KL, Tochtrop GP, Picaud S, Chen Y, 2022. Nonretinoid chaperones improve rhodopsin homeostasis in a mouse model of retinitis pigmentosa. JCI insight 7.

Vattem KM, Wek RC, 2004. Reinitiation involving upstream ORFs regulates ATF4 mRNA translation in mammalian cells. Proc. Natl. Acad. Sci. USA 101, 11269–11274. [PubMed: 15277680]

Verbakel SK, van Huet RAC, Boon CJF, den Hollander AI, Collin RWJ, Klaver CCW, Hoyng CB, Roepman R, Klevering BJ, 2018. Non-syndromic retinitis pigmentosa. Prog. Retin. Eye Res 66, 157–186. [PubMed: 29597005]

Verfaillie T, Rubio N, Garg AD, Bultynck G, Rizzuto R, Decuypere JP, Piette J, Linehan C, Gupta S, Samali A, Agostinis P, 2012. PERK is required at the ER-mitochondrial contact sites to convey apoptosis after ROS-based ER stress. Cell Death Differ. 19, 1880–1891. [PubMed: 22705852]

Vicencio JM, Galluzzi L, Tajeddine N, Ortiz C, Criollo A, Tasdemir E, Morselli E, Ben Younes A, Maiuri MC, Lavandero S, Kroemer G, 2008. Senescence, apoptosis or autophagy? When a damaged cell must decide its path–a mini-review. Gerontology 54, 92–99. [PubMed: 18451641]

Vidal RL, Sepulveda D, Troncoso-Escudero P, Garcia-Huerta P, Gonzalez C, Plate L, Jerez C, Canovas J, Rivera CA, Castillo V, Cisternas M, Leal S, Martinez A, Grandjean J, Sonia D, Lashuel HA, Martin AJM, Latapiat V, Matus S, Sardi SP, Wiseman RL, Hetz C, 2021. Enforced dimerization between XBP1s and ATF6f enhances the protective effects of the UPR in models of neurodegeneration. Mol. Ther 29, 1862–1882. [PubMed: 33545358]

Viegas FO, Neuhauss SCF, 2021. A metabolic landscape for maintaining retina integrity and function. Front. Mol. Neurosci 14, 656000. [PubMed: 33935647]

Voeltz GK, Rolls MM, Rapoport TA, 2002. Structural organization of the endoplasmic reticulum. EMBO Rep. 3, 944–950. [PubMed: 12370207]

Walter P, Ron D, 2011. The unfolded protein response: from stress pathway to homeostatic regulation. Science (New York, N.Y.) 334, 1081–1086. [PubMed: 22116877]

Walton GM, Gill GN, 1975. Nucleotide regulation of a eukaryotic protein synthesis initiation complex. Biochim. Biophys. Acta 390, 231–245. [PubMed: 167829]

Wang CH, Wang CH, Hung PJ, Wei YH, 2022a. Disruption of mitochondria-associated ER membranes impairs insulin sensitivity and thermogenic function of adipocytes. Front. Cell Dev. Biol 10, 965523. [PubMed: 36158195]

Wang JJ, Park KS, Dhimal N, Shen S, Tang X, Qu J, Zhang SX, 2022b. Proteomic analysis of retinal mitochondria-associated ER membranes identified novel proteins of retinal degeneration in long-term diabetes. Cells 11.

Wang M, Cotter E, Wang YJ, Fu X, Whittsette AL, Lynch JW, Wiseman RL, Kelly JW, Keramidas A, Mu TW, 2022c. Pharmacological activation of ATF6 remodels the proteostasis network to rescue pathogenic GABA. Cell Biosci. 12, 48. [PubMed: 35477478]

Wang N, Wang C, Zhao H, He Y, Lan B, Sun L, Gao Y, 2021a. The MAMs structure and its role in cell death. Cells 10.

Wang P, Li J, Tao J, Sha B, 2018. The luminal domain of the ER stress sensor protein PERK binds misfolded proteins and thereby triggers PERK oligomerization. J. Biol. Chem 293, 4110–4121. [PubMed: 29386355]

Wang QC, Sheng W, Yi CJ, Lv H, Cheng B, 2020. Retrobulbarly injecting nerve growth factor attenuates visual impairment in streptozotocin-induced diabetes rats. Int. Ophthalmol 40, 3501–3511. [PubMed: 32776300]

Wang X, Luo D, Wu S, 2021b. Molecular dysfunctions of mitochondria-associated endoplasmic reticulum contacts in atherosclerosis. Oxid. Med. Cell. Longev 2021, 2424509. [PubMed: 34336087]

Wang X, Wang G, Kunte M, Shinde V, Gorbatyuk M, 2013. Modulation of angiogenesis by genetic manipulation of ATF4 in mouse model of oxygen-induced retinopathy [corrected]. Invest. Ophthalmol. Vis. Sci 54, 5995–6002. [PubMed: 23942974]

Wei Q, Hu W, Lou Q, Yu J, 2019. NAD+ inhibits the metabolic reprogramming of RPE cells in early AMD by upregulating mitophagy. Discov. Med 27, 189–196. [PubMed: 31361981]

West ER, Lapan SW, Lee C, Kajderowicz KM, Li X, Cepko CL, 2022. Spatiotemporal patterns of neuronal subtype genesis suggest hierarchical development of retinal diversity. Cell Rep. 38, 110191. [PubMed: 34986354]

Wilson SP, Cassel SL, 2010. Inflammasome-mediated autoinflammatory disorders. Postgrad. Med 122, 125–133.

Wong TH, van der Lee SJ, van Rooij JGJ, Meeter LHH, Frick P, Melhem S, Seelaar H, Ikram MA, Rozemuller AJ, Holstege H, Hulsman M, Uitterlinden A, Neumann M, Hoozemans JJM, van Duijn CM, Rademakers R, van Swieten JC, 2019. EIF2AK3 variants in Dutch patients with Alzheimer's disease. Neurobiol. Aging 73, 229.e211–229.e218.

Wong YL, LeBon L, Edalji R, Lim HB, Sun C, Sidrauski C, 2018. The small molecule ISRIB rescues the stability and activity of Vanishing White Matter Disease eIF2B mutant complexes. Elife 7.

Wu DM, Ji X, Ivanchenko MV, Chung M, Piper M, Rana P, Wang SK, Xue Y, West E, Zhao SR, Xu H, Cicconet M, Xiong W, Cepko CL, 2021. Nrf2 overexpression rescues the RPE in mouse models of retinitis pigmentosa. JCI insight 6.

Wu J, Rutkowski DT, Dubois M, Swathirajan J, Saunders T, Wang J, Song B, Yau GD, Kaufman RJ, 2007. ATF6alpha optimizes long-term endoplasmic reticulum function to protect cells from chronic stress. Dev. Cell 13, 351–364. [PubMed: 17765679]

Wu M, Xu LG, Zhai Z, Shu HB, 2003. SINK is a p65-interacting negative regulator of NF-kappaB-dependent transcription. J. Biol. Chem 278, 27072–27079. [PubMed: 12736262]

Wu M, Yang S, Elliott MH, Fu D, Wilson K, Zhang J, Du M, Chen J, Lyons T, 2012. Oxidative and endoplasmic reticulum stresses mediate apoptosis induced by modified LDL in human retinal Muller cells. Invest. Ophthalmol. Vis. Sci 53, 4595–4604. [PubMed: 22678501]

Wu W, Lin C, Wu K, Jiang L, Wang X, Li W, Zhuang H, Zhang X, Chen H, Li S, Yang Y, Lu Y, Wang J, Zhu R, Zhang L, Sui S, Tan N, Zhao B, Zhang J, Li L, Feng D, 2016. FUNDC1 regulates mitochondrial dynamics at the ER-mitochondrial contact site under hypoxic conditions. EMBO J. 35, 1368–1384. [PubMed: 27145933]

Wu Z, Mei F, Gan Y, Liu A, Hu J, Jin Y, Yin Y, 2023. FAM69C functions as a kinase for eIF2α and promotes stress granule assembly. EMBO Rep. 24, e55641. [PubMed: 36929224]

Xu M, Gelowani V, Eblimit A, Wang F, Young MP, Sawyer BL, Zhao L, Jenkins G, Creel DJ, Wang K, Ge Z, Wang H, Li Y, Hartnett ME, Chen R, 2015a. ATF6 is mutated in early onset photoreceptor degeneration with macular involvement. Invest. Ophthalmol. Vis. Sci 56, 3889–3895. [PubMed: 26070061]

Xu N, Xiao Z, Zou T, Huang Z, 2015b. Induction of GADD34 regulates the neurotoxicity of amyloid β. Am. J. Alzheimer's Dis. Other Dementias 30, 313–319.

Xu Z, Chikka MR, Xia H, Ready DF, 2016. Ire1 supports normal ER differentiation in developing Drosophila photoreceptors. J. Cell Sci 129, 921–929. [PubMed: 26787744]

Xu Z, Liao X, Li N, Zhou H, Li H, Zhang Q, Hu K, Yang P, Hou S, 2021. A Single-Cell Transcriptome Atlas of the Human Retinal Pigment Epithelium, vol. 9.

Yamaguchi H, Wang HG, 2004. CHOP is involved in endoplasmic reticulum stress-induced apoptosis by enhancing DR5 expression in human carcinoma cells. J. Biol. Chem 279, 45495–45502. [PubMed: 15322075]

Yamamoto K, Sato T, Matsui T, Sato M, Okada T, Yoshida H, Harada A, Mori K, 2007. Transcriptional induction of mammalian ER quality control proteins is mediated by single or combined action of ATF6alpha and XBP1. Dev. Cell 13, 365–376. [PubMed: 17765680]

Yamamoto K, Takahara K, Oyadomari S, Okada T, Sato T, Harada A, Mori K, 2010. Induction of liver steatosis and lipid droplet formation in ATF6alpha-knockout mice burdened with pharmacological endoplasmic reticulum stress. Mol. Biol. Cell 21, 2975–2986. [PubMed: 20631254]

Yamamoto K, Yoshida H, Kokame K, Kaufman RJ, Mori K, 2004. Differential contributions of ATF6 and XBP1 to the activation of endoplasmic reticulum stress-responsive cis-acting elements ERSE, UPRE and ERSE-II. J. Biochem 136, 343–350. [PubMed: 15598891]

Yamoah A, Tripathi P, Guo H, Scheve L, Walter P, Johnen S, Muller F, Weis J, Goswami A, 2023. Early alterations of RNA binding protein (RBP) homeostasis and ER stress-mediated autophagy contributes to progressive retinal degeneration in the rd10 mouse model of retinitis pigmentosa (RP). Cells 12.

Yan Q, Zhu H, Wang FH, Feng JY, Wang WQ, Shi X, Zhou YP, Zhang X, Sun XD, 2016. Inhibition of TRB3 protects photoreceptors against endoplasmic reticulum stress-induced apoptosis after experimental retinal detachment. Curr. Eye Res 41, 240–248. [PubMed: 25860695]

Yang J, Chen C, McLaughlin T, Wang Y, Le YZ, Wang JJ, Zhang SX, 2019. Loss of X-box binding protein 1 in Muller cells augments retinal inflammation in a mouse model of diabetes. Diabetologia 62, 531–543. [PubMed: 30612139]

Yang L, Dai R, Wu H, Cai Z, Xie N, Zhang X, Shen Y, Gong Z, Jia Y, Yu F, Zhao Y, Lin P, Ye C, Hu Y, Fu Y, Xu Q, Li Z, Kong W, 2022. Unspliced XBP1 counteracts β-catenin to inhibit vascular calcification. Circ. Res 130, 213–229. [PubMed: 34870453]

Yang L, Wu L, Wang D, Li Y, Dou H, Tso MO, Ma Z, 2013. Role of endoplasmic reticulum stress in the loss of retinal ganglion cells in diabetic retinopathy. Neural Regen Res 8, 3148–3158. [PubMed: 25206636]

Yang LP, Wu LM, Guo XJ, Tso MO, 2007. Activation of endoplasmic reticulum stress in degenerating photoreceptors of the rd1 mouse. Invest. Ophthalmol. Vis. Sci 48, 5191–5198. [PubMed: 17962473]

Yang M, Luo S, Wang X, Li C, Yang J, Zhu X, Xiao L, Sun L, 2021. ER-phagy: a new regulator of ER homeostasis. Front. Cell Dev. Biol 9, 684526. [PubMed: 34307364]

Yang X, Zhuang J, Song W, Shen W, Wu W, Shen H, Han S, 2023a. Mitochondria-associated endoplasmic reticulum membrane: overview and inextricable link with cancer. J. Cell Mol. Med 27, 906–919. [PubMed: 36852470]

Yang Y, Wu J, Lu W, Dai Y, Zhang Y, Sun X, 2023b. Mitochondria-associated endoplasmic reticulum membranes dysfunction contributes to PARP-1-dependent cell death under oxidative stress in retinal precursor cells. J. Biochem. Mol. Toxicol 37, e23303. [PubMed: 36639873]

Yasuda H, Tanaka M, Nishinaka A, Nakamura S, Shimazawa M, Hara H, 2021. Role of activating transcription factor 4 in murine choroidal neovascularization model. Int. J. Mol. Sci 22.

Yau JWY, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen S-J, Dekker JM, Fletcher A, Grauslund J, Haffner S, Hamman RF, Ikram MK, Kayama T, Klein BEK, Klein R, Krishnaiah S, Mayurasakorn K, O'Hare JP, Orchard TJ, Porta M, Rema M, Roy MS, Sharma T, Shaw J, Taylor H, Tielsch JM, Varma R, Wang JJ, Wang N, West S, Xu L, Yasuda M, Zhang X, Mitchell P, Wong TY, for the Meta-Analysis for Eye Disease Study, G, 2012. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 35, 556–564. [PubMed: 22301125]

Ye J, Rawson RB, Komuro R, Chen X, Davé UP, Prywes R, Brown MS, Goldstein JL, 2000. ER stress induces cleavage of membrane-bound ATF6 by the same proteases that process SREBPs. Mol. Cell 6, 1355–1364. [PubMed: 11163209]

Yoshida H, Matsui T, Yamamoto A, Okada T, Mori K, 2001a. XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. Cell 107, 881–891. [PubMed: 11779464]

Yoshida H, Okada T, Haze K, Yanagi H, Yura T, Negishi M, Mori K, 2000. ATF6 activated by proteolysis binds in the presence of NF-Y (CBF) directly to the cis-acting element responsible for the mammalian unfolded protein response. Mol. Cell Biol 20, 6755–6767. [PubMed: 10958673]

Yoshida H, Okada T, Haze K, Yanagi H, Yura T, Negishi M, Mori K, 2001b. Endoplasmic reticulum stress-induced formation of transcription factor complex ERSF including NF-Y (CBF) and activating transcription factors 6alpha and 6beta that activates the mammalian unfolded protein response. Mol. Cell Biol 21, 1239–1248. [PubMed: 11158310]

Yoshida H, Uemura A, Mori K, 2009. pXBP1(U), a negative regulator of the unfolded protein response activator pXBP1(S), targets ATF6 but not ATF4 in proteasome-mediated degradation. Cell Struct. Funct 34, 1–10. [PubMed: 19122331]

Yuan SH, Hiramatsu N, Liu Q, Sun XV, Lenh D, Chan P, Chiang K, Koo EH, Kao AW, Litvan I, Lin JH, 2018. Tauopathy-associated PERK alleles are functional hypomorphs that increase neuronal vulnerability to ER stress. Hum. Mol. Genet 27, 3951–3963. [PubMed: 30137327]

Zadorozhnii PV, Pokotylo IO, Kiselev VV, Okhtina OV, Kharchenko AV, 2019. Molecular docking studies of salubrinal and its analogs as inhibitors of the GADD34: PP1 enzyme. Admet dmpk 7, 140–150. [PubMed: 35350543]

Zhan J, He J, Zhou Y, Wu M, Liu Y, Shang F, Zhang X, 2016. Crosstalk between the autophagy-lysosome pathway and the ubiquitin-proteasome pathway in retinal pigment epithelial cells. Curr. Mol. Med 16, 487–495. [PubMed: 27132793]

Zhang C, Xu Y, Tan HY, Li S, Wang N, Zhang Y, Feng Y, 2018. Neuroprotective effect of He-Ying-Qing-Re formula on retinal ganglion cell in diabetic retinopathy. J. Ethnopharmacol 214, 179–189. [PubMed: 29253613]

Zhang K, Kaufman RJ, 2008. From endoplasmic-reticulum stress to the inflammatory response. Nature 454, 455–462. [PubMed: 18650916]

Zhang K, Shen X, Wu J, Sakaki K, Saunders T, Rutkowski DT, Back SH, Kaufman RJ, 2006. Endoplasmic reticulum stress activates cleavage of CREBH to induce a systemic inflammatory response. Cell 124, 587–599. [PubMed: 16469704]

Zhang L, Zhou Y, Xia Q, Chen Y, Li J, 2020. All-trans-retinal induces autophagic cell death via oxidative stress and the endoplasmic reticulum stress pathway in human retinal pigment epithelial cells. Toxicol. Lett 322, 77–86. [PubMed: 31931077]

Zhang P, McGrath B, Li S, Frank A, Zambito F, Reinert J, Gannon M, Ma K, McNaughton K, Cavener DR, 2002. The PERK eukaryotic initiation factor 2 alpha kinase is required for the development of the skeletal system, postnatal growth, and the function and viability of the pancreas. Mol. Cell Biol 22, 3864–3874. [PubMed: 11997520]

Zhang SX, Ma JH, Bhatta M, Fliesler SJ, Wang JJ, 2014. The unfolded protein response in retinal vascular diseases: implications and therapeutic potential beyond protein folding. Prog. Retin. Eye Res

Zhang Y, Cross SD, Stanton JB, Marmorstein AD, Le YZ, Marmorstein LY, 2017. Early AMD-like defects in the RPE and retinal degeneration in aged mice with RPE-specific deletion of Atg5 or Atg7. Mol. Vis 23, 228–241. [PubMed: 28465655]

Zhao G, Fu Y, Cai Z, Yu F, Gong Z, Dai R, Hu Y, Zeng L, Xu Q, Kong W, 2017. Unspliced XBP1 confers VSMC homeostasis and prevents aortic aneurysm formation via FoxO4 interaction. Circ. Res 121, 1331–1345. [PubMed: 29089350]

Zhao N, Li N, Wang T, 2023. PERK prevents rhodopsin degradation during retinitis pigmentosa by inhibiting IRE1-induced autophagy. J. Cell Biol 222.

Zheng S, Jian D, Gan H, Wang L, Zhao J, Zhai X, 2021. FUNDC1 inhibits NLRP3-mediated inflammation after intracerebral hemorrhage by promoting mitophagy in mice. Neurosci. Lett 756, 135967. [PubMed: 34022268]

Zheng W, Xie W, Yin D, Luo R, Liu M, Guo F, 2019. ATG5 and ATG7 induced autophagy interplays with UPR via PERK signaling. Cell Commun. Signal 17, 42. [PubMed: 31060556]

Zhivotovsky B, Orrenius S, 2011. Calcium and cell death mechanisms: a perspective from the cell death community. Cell Calcium 50, 211–221. [PubMed: 21459443]

Zhong Y, Li J, Chen Y, Wang JJ, Ratan R, Zhang SX, 2012a. Activation of endoplasmic reticulum stress by hyperglycemia is essential for muller cell-derived inflammatory cytokine production in diabetes. Diabetes 61, 492–504. [PubMed: 22228718]

Zhong Y, Li J, Wang JJ, Chen C, Tran J-TA, Saadi A, Yu Q, Le Y.-z., Mandal MNA, Anderson RE, Zhang SX, 2012b. X-box binding protein 1 is essential for the anti-oxidant defense and cell survival in the retinal pigment epithelium. PLoS One 7, e38616. [PubMed: 22715395]

Zhang Y, Wang JJ, Zhang SX, 2012c. Intermittent but not constant high glucose induces ER stress and inflammation in human retinal pericytes. Adv. Exp. Med. Biol 723, 285–292. [PubMed: 22183344]

Zhou R, Yazdi AS, Menu P, Tschopp J, 2011. A role for mitochondria in NLRP3 inflammasome activation. Nature 469, 221–225. [PubMed: 21124315]

Zhou S, Yang J, Wang M, Zheng D, Liu Y, 2020. Endoplasmic reticulum stress regulates epithelial-mesenchymal transition in human lens epithelial cells. Mol. Med. Rep 21, 173–180. [PubMed: 31746423]

Zhou Y, Zhang S, Dai C, Tang S, Yang X, Li D, Zhao K, Xiao X, 2016. Quinocetone triggered ER stress-induced autophagy via ATF6/DAPK1-modulated mAtg9a trafficking. Cell Biol. Toxicol 32, 141–152. [PubMed: 27085326]

Zhu S, Liu H, Sha H, Qi L, Gao DS, Zhang W, 2017. PERK and XBP1 differentially regulate CXCL10 and CCL2 production. Exp. Eye Res 155, 1–14. [PubMed: 28065589]

Zhu X, Wang K, Zhang K, Zhou F, Zhu L, 2016. Induction of oxidative and nitrosative stresses in human retinal pigment epithelial cells by all-trans-retinal. Exp. Cell Res 348, 87–94. [PubMed: 27616142]

Zobor D, Zobor G, Kohl S, 2015. Achromatopsia: on the doorstep of a possible therapy. Ophthalmic Res. 54, 103–108. [PubMed: 26304472]

Zou CG, Cao XZ, Zhao YS, Gao SY, Li SD, Liu XY, Zhang Y, Zhang KQ, 2009. The molecular mechanism of endoplasmic reticulum stress-induced apoptosis in PC-12 neuronal cells: the

protective effect of insulin-like growth factor I. Endocrinology 150, 277–285. [PubMed: 18801901]

Zyryanova AF, Kashiwagi K, Rato C, Harding HP, Crespillo-Casado A, Perera LA, Sakamoto A, Nishimoto M, Yonemochi M, Shirouzu M, Ito T, Ron D, 2021. ISRIB blunts the integrated stress response by allosterically antagonising the inhibitory effect of phosphorylated eIF2 on eIF2B. Mol. Cell 81, 88–103.e106. [PubMed: 33220178]

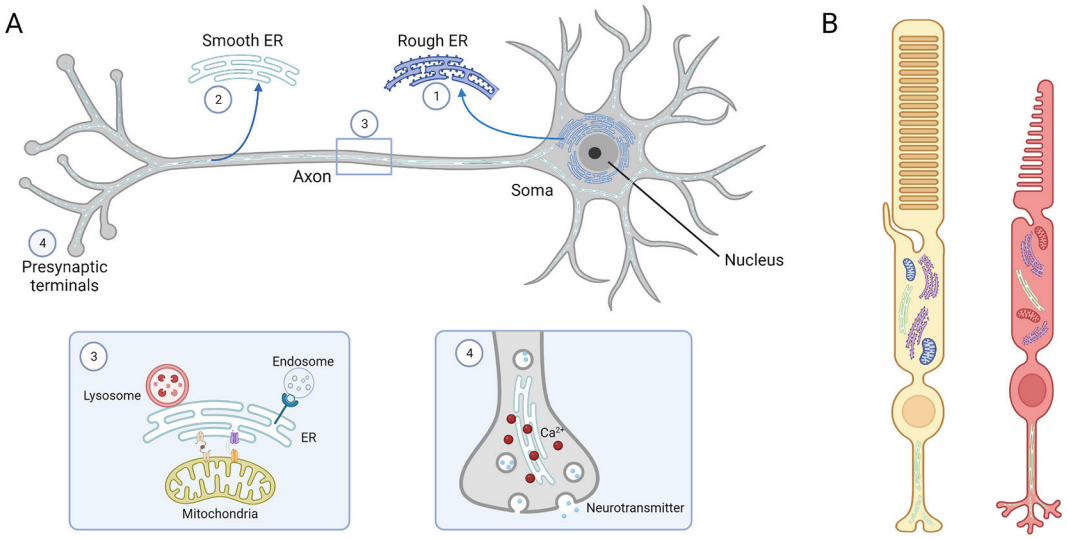

Fig. 1.

ER localization in retinal neurons. **A)** Morphology and distribution of ER in the soma, axon, presynaptic terminals of a neuron. 1) Rough ER is distributed around the nuclear envelope in the soma and in somato-dendritic regions. 2) Smooth ER is localized predominantly to distal dendritic regions and axons. 3) The ER forms physical contacts with mitochondria, microtubules, endosomes, and lysosomes to support axon growth and organelle transportation. 4) In presynaptic terminals, the ER contributes to neurotransmitter production and regulation of calcium signaling. **B)** Distribution of ER in rod and cone photoreceptors.

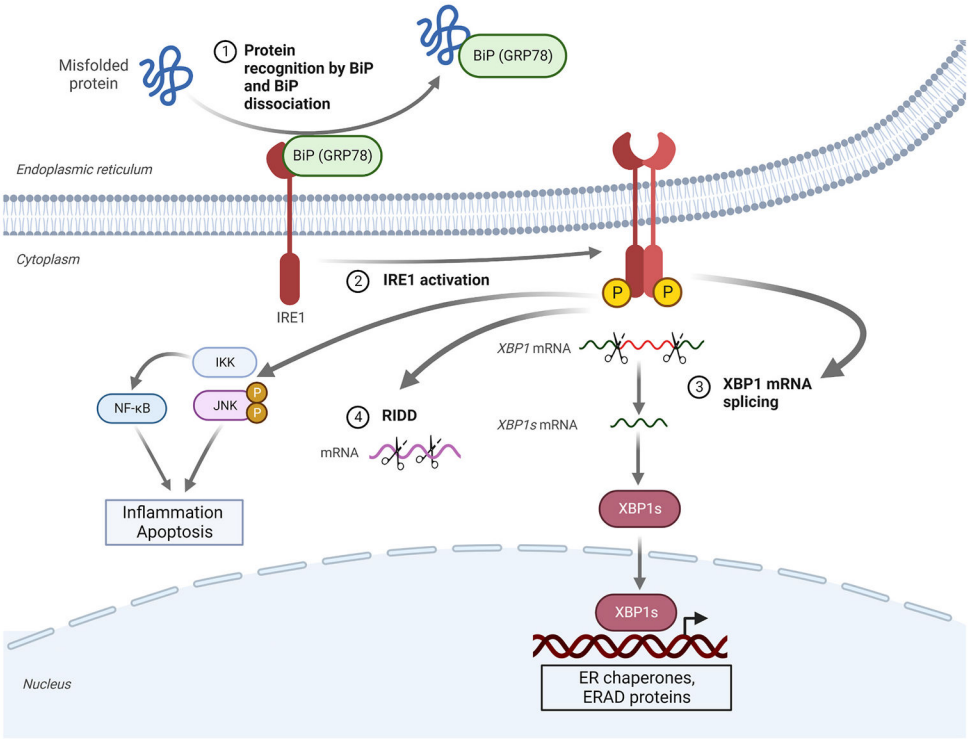

Fig. 2.

The IRE1/XBP1 signaling pathway. In resting cells, ER stress sensors including IRE1 bind to Bip/GRP78, which keeps them in inactive state. 1) Upon ER stress, Bip dissociates from IRE1 and binds to accumulated unfolded or misfolded proteins. 2) IRE1 is activated by dimerization and autophosphorylation. Increased kinase activity of IRE1 promotes JNK and IKK activation resulting in inflammation and apoptosis. 3–4) The endoribonucease domain of IRE1 is activated resulting in an unconventional splicing of XBP1 mRNA (3) and regulated IRE1-dependent decay of mRNA (RIDD) (4). The resulting spliced XBP1 (XBP1s) encodes an active transcription factor that upregulates ER chaperones and genes encoding ER-associated degradation (ERAD) proteins.

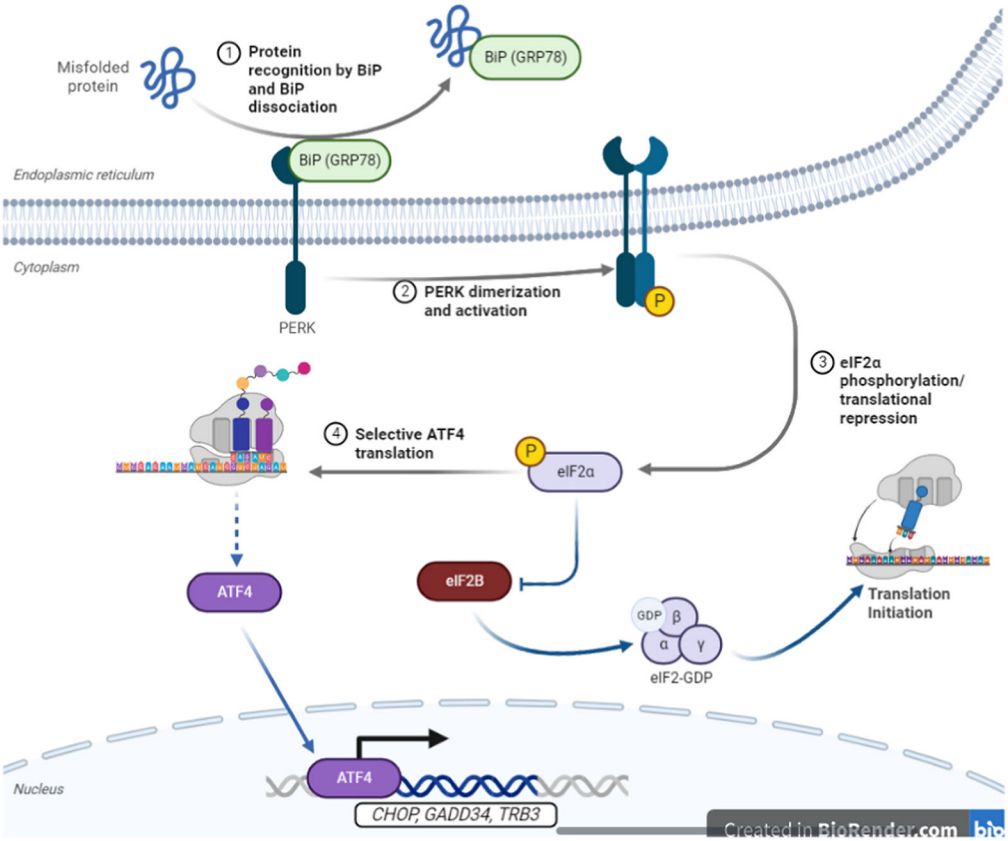

Fig. 3.

The PERK signaling pathway. 1) PERK is held inactive by the binding of its luminal domain by Grp78/BiP. BiP dissociates from PERK's luminal domain upon misfolded protein accumulation, leaving PERK unbound. 2) PERK dimerizes and becomes activated by autophosphorylation. 3) PERK phosphorylates eIF2α at S51, resulting in the eIF2 complex's inhibition of eIF2B's guanine nucleotide exchange function, halting general protein synthesis. 4) Inhibition of general protein synthesis allows key stress related mRNAs (such as ATF4) to be selectively translated. ATF4 is a transcription factor that travels to the nucleus to promote transcription of pro-apoptotic genes such as CHOP, GADD34 and TRB3.

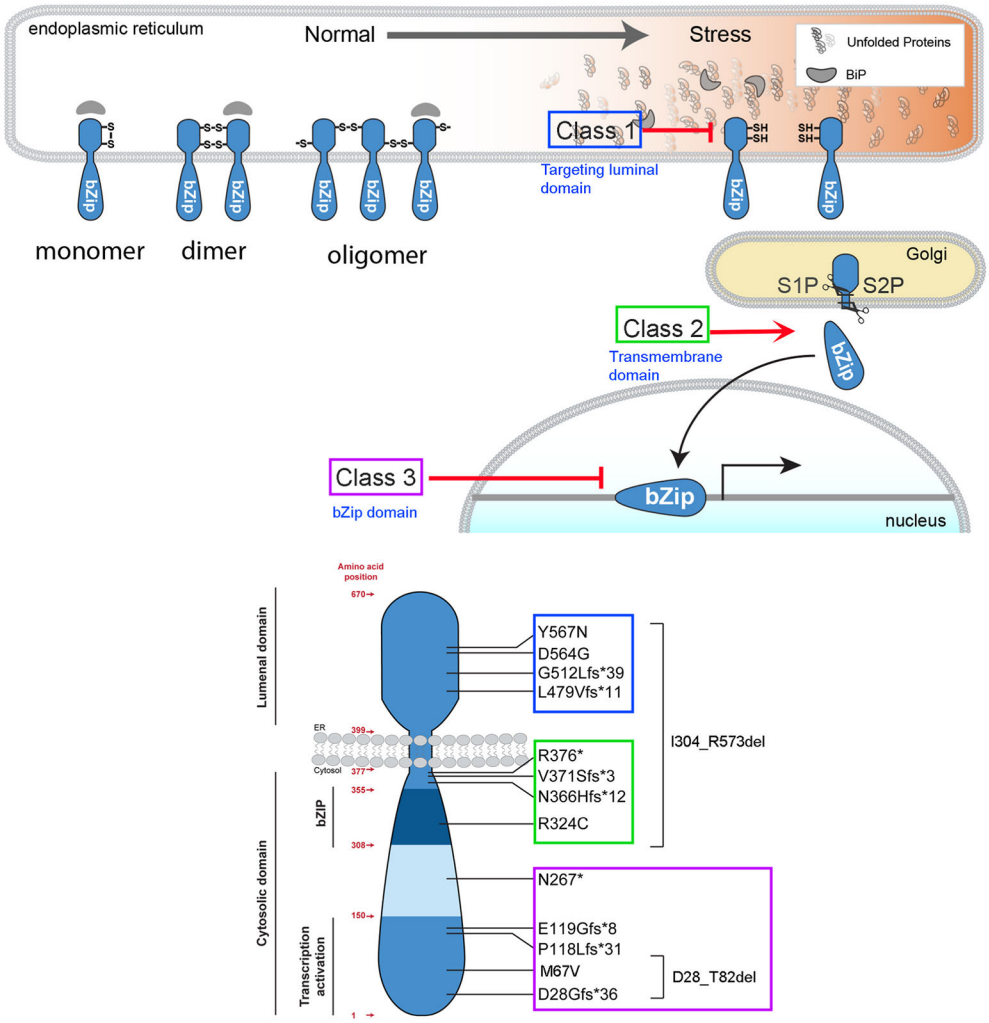

Fig. 4.

The ATF6 signaling pathway. Full length ATF6 can be present as a monomer, dimer, or oligomer via disulfide bond. Under ER stress, reduced ATF6 monomers traffics from the ER to the Golgi compartment. S1P and S2P proteases cleave ATF6 in the Golgi apparatus to release the cytosolic bZIP transcriptional activator ATF6 domain. Liberated ATF6 moves to nucleus to transcribe target genes. Class 1 ATF6 mutants Y567N, D564G, G512Lfs*39, and L479Vfs*11 show impaired ER-to-Golgi trafficking (blue box). Class 2 ATF6 mutants R376*, V371Sfs*3, N366Hfs*12, and R324C have fully intact ATF6 cytosolic domain and show constitutive transcriptional activator function (green box). The ATF6 mutant I304_R573del has defect in the in-frame bZip, transmembrane, and luminal domains of ATF6. Class 3 ATF6 mutants N267*, E119Gfs*8, P118Lfs*31, M67V, D28Gfs*36, and D28_T82del do not have a functional bZIP domain (purple box) and fail to up-regulate ATF6 target genes. Activation of the ATF6 pathway of the UPR.

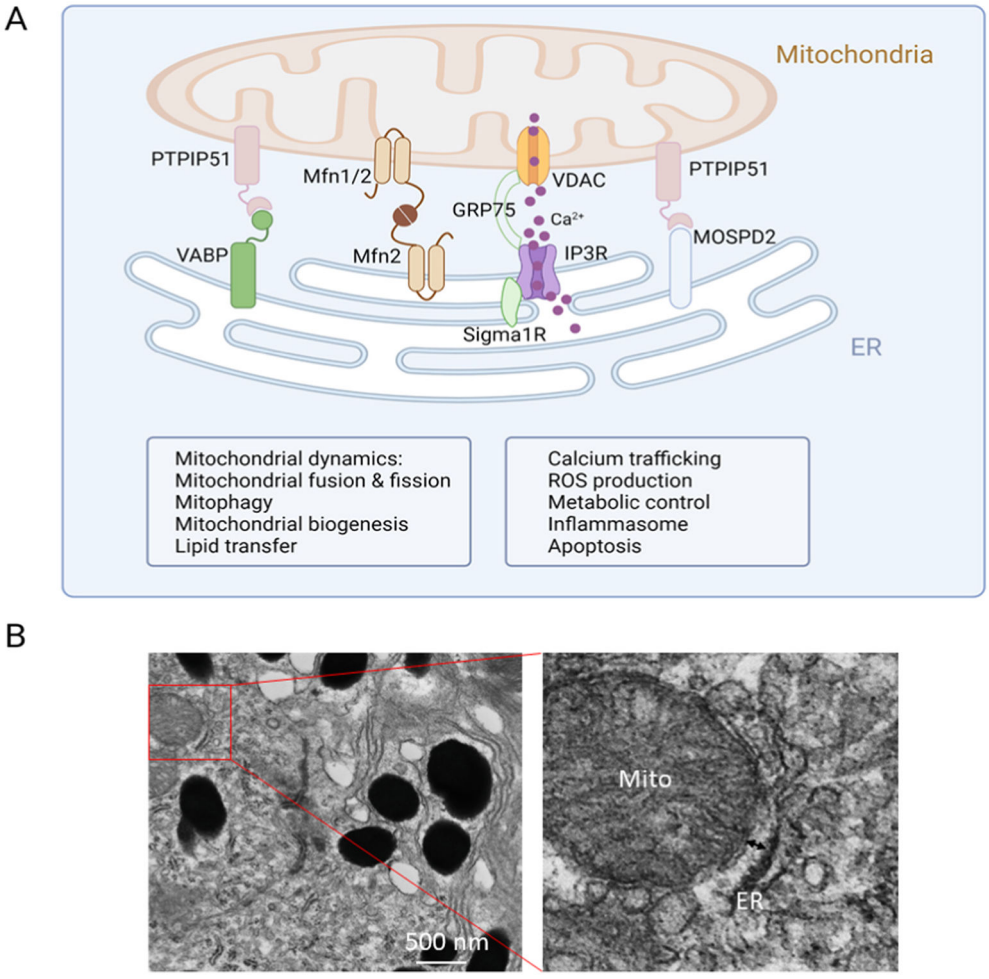

Fig. 5.

The mitochondria-associated ER membrane (MAM). **A).** Schematic diagram of MAM structure and function. MAM is formed through several pairs of tethering proteins localized to the outer mitochondrial membrane and ER membrane, including Mfn1/2-Mfn2, FPTPIP51-VABP, VDAC-GRP75-IP3R, PTPIP51-MOSPD2, and others. The VDAC-GRP75-IP3R is responsible for Ca2+ trafficking from the ER to the mitochondria. Sigma-1R can bind to IP3R and regulate calcium transfer to the mitochondria. **B).** Electron microscopic image shows a close contact of mitochondria with the ER in the RPE of a wild-type mouse. Double-headed arrow denotes the distance between the ER and the mitochondria.

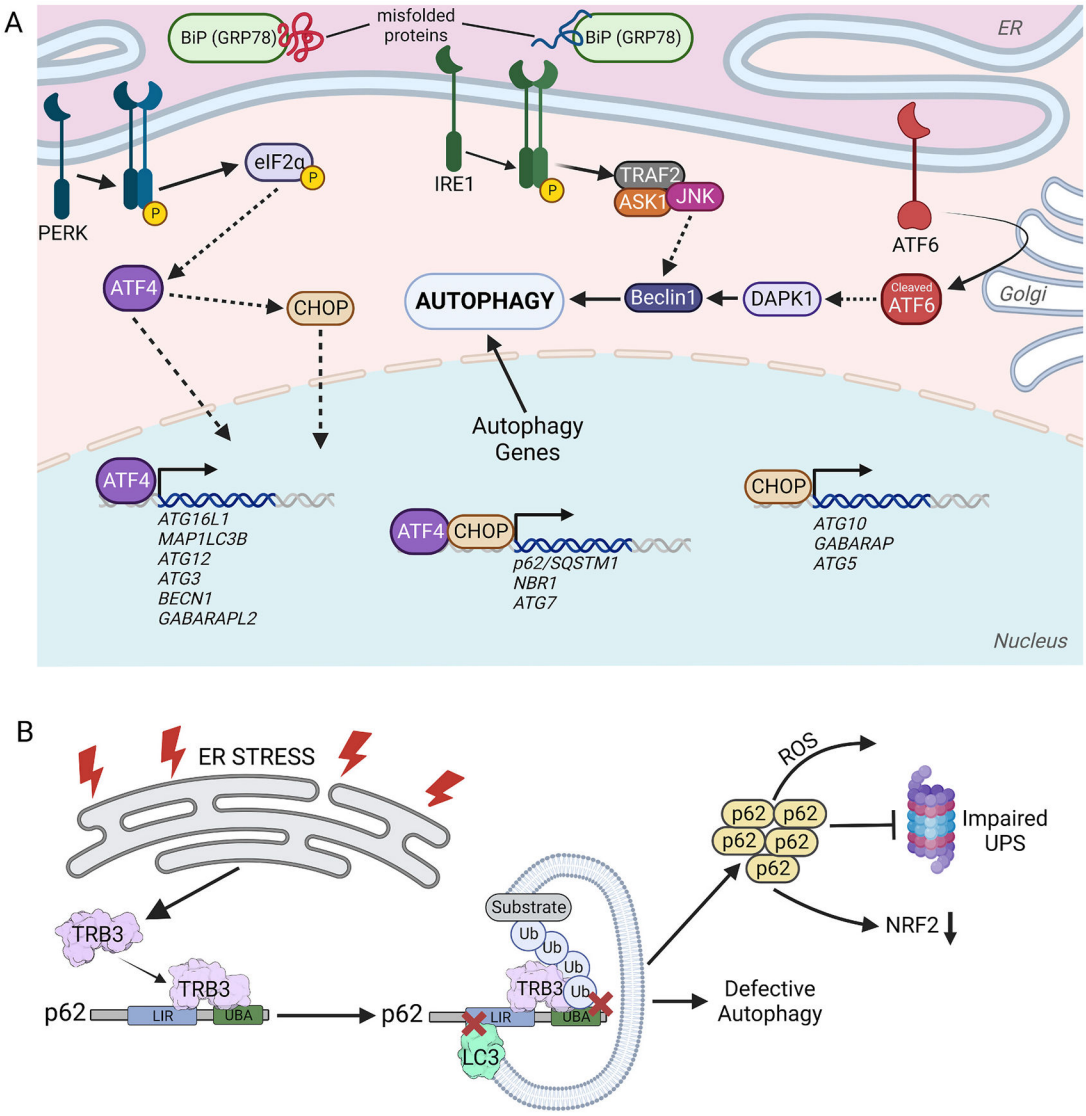

Fig. 6.

The UPR and autophagy. A) All three UPR pathways alter autophagy. IRE1 and ATF6 can regulate autophagy by acting on regulators of Beclin1 while the PERK pathway results in the upregulation of transcription of autophagy related genes. These pathways alter the transcriptional landscape to promote autophagy. B) The UPR alters autophagy through TRB3's interaction with P62 resulting in its subsequent impairment of autophagy.

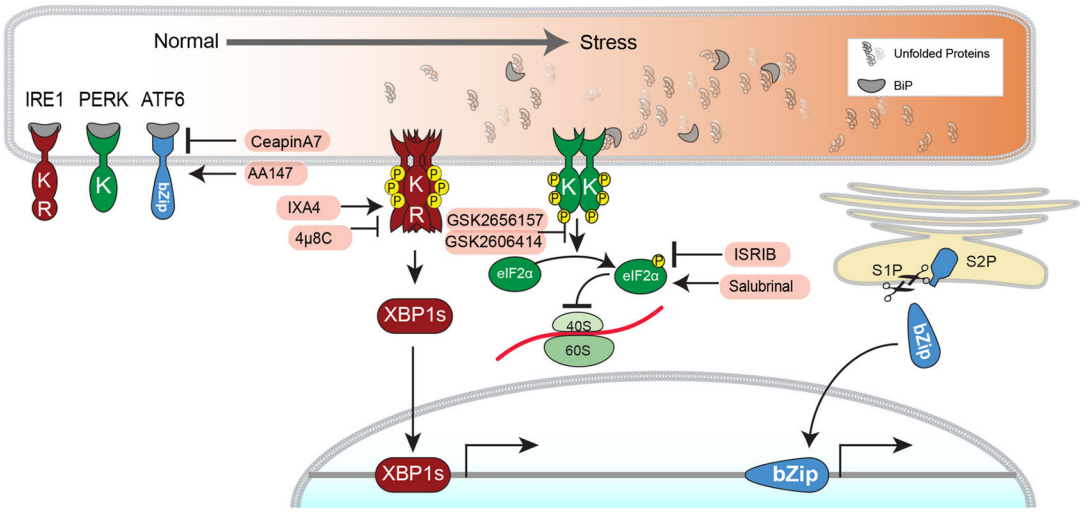

Fig. 7.

Small molecules targeting ATF6, PERK, and IRE1 pathways. Ceapin-A7 inhibits ATF6 signaling by trapping the ATF6 molecule in the ER, thereby preventing the generation of ATF6 transcriptional activator. AA147 selectively activate the ATF6 signaling by inhibiting the activity of protein disulfide isomerases to increase reduced ATF6 monomers in the ER. IXA4 selectively upregulates IRE1/XBP1s target genes. 4u8c, covalently modifies and inactivates that RNase domain of IRE1. The PERK inhibitor, GSK2606414 and GSK2656157 bind to the PERK kinase and thereby inhibit the PERK pathway. The ISRIB binds and stabilizes the active form of eIF2B which is normally rendered inactive by PERK signaling. Salubrinal inhibits p-eIF2α dephosphorylation.

Table 1

UPR and ER stress gene variants linked to human diseases.

Gene	Molecular Function	Human Disease (Phenotype)	Reference
WFS1	ER membrane ion channel	Wolfram Syndrome (juvenile diabetes, optic nerve atrophy)	Inoue et al. (1998)
EIF2AK3 (PERK)	Unfolded Protein Response kinase	Wolcott-Rallison Syndrome (juvenile diabetes, failure to thrive, early death)	Delépine et al. (2000)
EIF2B	Integrated Stress Response translation initiation factor	Vanishing White Matter disease	Leegwater et al. (2001)
XBP1	Unfolded Protein Response transcription factor	Bipolar Disorder risk factor	Kakiuchi et al. (2003)
SIL1	ER Co-chaperone for BiP/GRP78 chaperone	Marinesco-Sjogren Syndrome	Anttonen et al. (2005)
EIF2AK3 (PERK)	Unfolded Protein Response kinase	Progressive Supranuclear Palsy (tauopathy neurodegeneration) risk factor	Höglinger et al. (2011a)
EIF2AK4 (GCN2)	Integrated Stress Response kinase	Pulmonary hypertension	Eyries et al. (2014)
ATF6	Unfolded Protein Response transcription factor	Achromatopsia	Kohl et al. (2015)
ATF6	Unfolded Protein Response transcription factor	Cone-Rod Dystrophy	Skorczyk-Werner et al. (2017)
EIF2AK1(HRI)	Integrated Stress Response kinase	Leukoencephalopathy	Mao et al. (2020)
EIF2AK2(PKR)	Integrated Stress Response kinase	Leukoencephalopathy	Calame et al. (2021)