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Endoplasmic Reticulum Stress: New Insights into the Pathogenesis and Treatment of Retinal Degenerative Diseases

Marina Gorbatyuk[1,*], **Christopher R. Starr**[1], **Oleg Gorbatyuk**[1]

[1]The University of Alabama at Birmingham, Department of Optometry and Vision Science, School of Optometry, USA.

Abstract

Physiological equilibrium in the retina depends on coordinated work between rod and cone photoreceptors and can be compromised by the expression of mutant proteins leading to inherited retinal degeneration (IRD). IRD is a diverse group of retinal dystrophies with multifaceted molecular mechanisms that are not fully understood. In this review, we focus on the contribution of chronically activated unfolded protein response (UPR) to inherited retinal pathogenesis, placing special emphasis on studies employing genetically modified animal models. As constitutively active UPR in degenerating retinas may activate pro-apoptotic programs associated with oxidative stress, pro-inflammatory signaling, dysfunctional autophagy, free cytosolic Ca^{2+} overload, and altered protein synthesis rate in the retina, we focus on the regulatory mechanisms of translational attenuation and approaches to overcoming translational attenuation in degenerating retinas. We also discuss current research on the role of the UPR mediator PERK and its downstream targets in degenerating retinas and highlight the therapeutic benefits of reprogramming PERK signaling in preclinical animal models of IRD. Finally, we describe pharmacological approaches targeting UPR in ocular diseases and consider their potential applications to IRD.

Keywords

Unfolded Protein Response; Retinal Degeneration; Translation; Translational Repressor; Neuroprotection

1. Retinal structure: Rod and cone photoreceptors

The retina is stratified neurological tissue lining the back of the eye that relays visual information to the brain (Bloomfield and Dacheux, 2001; Wassle, 2004; Yarfitz and Hurley, 1994). Vision begins when light enters the eye through the cornea and traverses the entirety of the eye until it strikes visual pigments located in the outer segments (OSs) of

[*]To whom correspondence should be addressed: Dr. Marina Gorbatyuk. Department of Optometry and Vision Science, School of Optometry, University of Alabama at Birmingham. 1670 University Blvd., Birmingham, Alabama 35233. Tel: 205- 934-6762. Fax: 205-934-3425. mgortk@uab.edu.

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photoreceptor cells at the back of the retina (Bloomfield and Dacheux, 2001). There are two types of classical photoreceptors in the retina of vertebrates: rods and cones (Curcio et al., 1987; Wassle, 2004). These two types of cells differ in their morphology, function, retinal structure integrative properties, and biochemical and metabolic characteristics.

Rods are more common than cones; there are approximately 120 million rods but only 5 million cones in the human retina. Rods are active in dim light and account for nighttime (i.e., scotopic) vision, whereas cones are more active at higher lighting intensities and are responsible for daytime (i.e., photopic) and color vision (Schnapf et al., 1988). Rods are more cylindrical, whereas cones are more cone-shaped. Until recently, the entire OS membrane of cones was believed to be continuous with the plasma membrane of the inner segment and enfolded to form a lamellar structure, generating stacks of disk membranes, whereas the rod plasma membrane was believed to surround disk membranes, generating space between disk and plasma membranes. However, studies now show that like cones, rod disks are formed via plasma membrane evagination (Burgoyne et al., 2015; Ding et al., 2015; Volland et al., 2015).

When photoreceptors receive photons, they send signals through other neurons that eventually exit the eye and route to the brain. Rods and cones exhibit different connectivity with other retinal neurons, resulting in differences in their transmission of electrical signals. For example, cone signals exit the retina fairly directly. The transmission process begins as visual pigment molecules in the OS of photoreceptors interact with photons and initiate phototransduction, a complex signaling cascade that converts a light signal into a chemical response (Yarfitz and Hurley, 1994). During phototransduction, cone photoreceptors hyperpolarize, reducing glutamate release at the synapse and thereby depolarizing ON-center and hyperpolarizing OFF-center cone bipolar cells (Bloomfield and Dacheux, 2001; Wassle, 2004; Werblin and Dowling, 1969), likely due to the expression of different types of glutamate receptors (DeVries, 2000; Nomura et al., 1994). Depolarization of ON-center bipolar cells prompts their release of glutamate at the inner plexiform layer, where they synapse with amacrine and ganglion cells.

For rod signals to reach ganglion cells, rod-originating impulses piggyback on cone bipolar signaling; rod bipolar cells send signals to cone bipolar cells through All amacrine cells (Bloomfield and Dacheux, 2001; Masland, 2012; Wassle, 2004). Cone bipolar cells then project this signal to ganglion cells (Bloomfield and Dacheux, 2001; Masland, 2012; Wassle, 2004), which in turn projects to the lateral granular nucleus and higher visual areas in the cortex (Ghodrati et al., 2017). In both the retina and higher brain regions, visual processing depends on the ability of photoreceptors to detect changes in lighting parameters and their capacity to relay information to downstream neural circuitry.

Rods and cones also show differences in cell physiology. Rods have the ability to respond to a single photon in the dark-adapted state (Baylor et al., 1979; Rieke and Baylor, 1998), largely because phototransduction results in much higher gain in rods than in cones. The light sensitivity of rods is proposed to be at least 25–100 times greater than that in cones (Fain and Dowling, 1973; Kefalov, 2012). However, the kinetic response of rods is believed to be five times slower than that in cones (Rushton, 1965), perhaps because rods have slower

transduction machinery. For example, reaction product lifetimes are 10–20 times longer in rods than in cones (Morshedian and Fain, 2015). Rods also have about 10 times faster recovery of visual molecules following bleaching than cones, perhaps because the higher rate of pigment thermal activation in cones could lower their sensitivity (Kefalov, 2012). These differences could explain why cones have the remarkable ability to adjust their sensitivity in extremely bright light and remain photosensitive, whereas rods saturate in even moderately bright light and remain nonfunctional during most of the day (Kefalov, 2012).

Rods and cones also have different compositions of visual pigment molecules. The visual pigment in rods is rhodopsin, whereas cones contain three different types of opsins—blue, green, and red—which differ in their absorption maximum efficiency: a wavelength of 420 nm for blue cones, 530 nm for green cones, and 560 nm for red cones. The rhodopsin molecule is composed of a chromophore, 11-cis retinal, and a protein moiety called opsin. The chromophore is covalently linked to the ε-amino group of the lysine residue of opsin and is embedded in the protein moiety (Palczewski et al., 2000). In a mammalian rod, there are about 10^8 rhodopsin molecules present in the OS, with an overall concentration reaching up to 3 mM (Harosi, 1975).

In addition to biochemical differences in the enzymatic activity, lifespan, and recovery time of major phototransduction molecules between rods and cones, the two photoreceptors are also distinguished by specific expression profiles of genes involved in the phototransduction cascade. For example, in humans, rods and cones have different G-protein receptor kinases (GRKs)—GRK1 in rods and GRK1 and/or GRK7 in cones—whereas mice have only GRK1 in both types of photoreceptors (Chen et al., 2001; Ingram et al., 2016). Mice also have arrestin-1 in rods but arrestin-1 and arrestin-4 in cones (Ingram et al., 2016). Although GTPase-accelerating protein complex proteins are the same in rods and cones, their expression is significantly higher in cones (Zhang et al., 2003b). Rod photoreceptors express α1, β1, and γ1 isoforms of the G protein transducin, whereas cones express α2, β3, and γ8 isoforms. Furthermore, rods and cones have different catalytic subunits of the photoreceptor effector enzyme phosphodiesterase 6 (PDE6), which bind a subunit of activated transducin (in GTP form); rods have PDE6A and PDE6B, whereas cones have two identical PDE6C subunits. Additionally, the inhibitory subunits of PDE6 differ between rods and cones; rods express PDE6G, whereas cones express PDE6H (Ingram et al., 2016).

Rods and cones also show metabolic differences in regard to their sensitivity and demand, partially because the two photoreceptors contain different numbers of mitochondria per cell. For example, in mice, cones have twice the number of mitochondria than rods, whereas in primates, cones contain ~10 times more mitochondria than rods (Perkins et al., 2003). This may explain why cones produce more ATP and are more resistant to metabolic stress and apoptosis than rods (Scarpelli and Craig, 1963). Interestingly, there are also difference in the expression of major metabolic kinases; cones co-express cytosolic creatine kinase isozyme and mitochondrial creatine kinase, which maintain ATP homeostasis, whereas rods do not produce these proteins (Leveillard, 2015).

The retina exhibits the Warburg effect similar to some cancer cells (Leveillard, 2015; Noell, 1952a; Winkler, 1981), suggesting that aerobic glycolysis is a main mode of glucose

metabolism and that only a small fraction of glucose-derived pyruvate enters mitochondria (Grenell et al., 2019). Indeed, photoreceptors and their synapses exhibit high capacity for glycolysis, aerobic glycolysis, and oxidative phosphorylation and regulate glucose metabolism through compartment-selective expression of hexokinase-1 and −2 and pyruvate kinase-M1 and -M2 (Rueda et al., 2016). Glycolysis and oxidative phosphorylation are major metabolic pathways that synthesize ATP, and impairments in their signaling not only affect photoreceptor function but can also cause cell death. Previous studies of relationships between energy metabolism and retinal function demonstrate that the two process have interdependent effects (Rueda et al., 2016). For example, studies using an iodoacetate that "kills" the retinal pigment epithelium (RPE), resulting in retinal degeneration, show that inhibition of glycolysis induces the death of rods before cones (Noell, 1951; Wang et al., 2011) and that rods and cones have different sensitivities as measured by electroretinogram (ERG) responses to variations in experimentally-induced cellular glucose concentrations (Dawson et al., 2000). In a monkey model of retinal degeneration, blocking glycolysis with iodoacetate does not induce rapid cell death in cones as it does in rods, suggesting that cones depend on glycolysis to a lesser extent than rods (Noell, 1952b). Consistently, another study showing that diabetic patients have difficulty seeing in the dark suggests that rod function is affected early in the course of diabetes (Bailey and Sparrow, 2001). By contrast, the amplitude of the S cone ERG b-wave is significantly reduced in both non-retinopathic and retinopathic diabetic patients under poor hyperglycemia control (Yamamoto et al., 1996).

Both rods and cones produce reactive oxygen species (ROS) and are sensitive to compromised cellular homeostasis. Increased oxidative stress is associated with varied ocular pathogeneses, including retinitis pigmentosa (RP) (Campochiaro and Mir, 2018; Campochiaro et al., 2015). Under pathological conditions involving rod death leading to high oxygen tissue levels, progressive oxidative damage first affects cones and then other retinal cells. Thus, remaining cones experience an extra burden of production of superoxide radicals, which are powerful damaging agents. The accumulation of these free superoxide radicals overwhelms the cellular antioxidant system and triggers oxidative stress-induced cone cell death. This cell death fate decision occurs through production of peroxynitrites, which results from a reaction of superoxide with nitric oxide (Beckman et al., 1990). Another mode of cone cell death occurs via lack of glucose. Cone glucose uptake depends on rod-derived cone viability factor and insulin signaling (Leveillard, 2015), which may contribute to cone survival during rod photoreceptor degeneration. Altogether, the biochemical, structural, functional, and metabolic differences between rods and cones generate equilibrium in the coordinated work of photoreceptors in the retina. However, no biological system is flawless, and varying factors can result in dying photoreceptors and retinal diseases. Given the differences in light sensitivity and metabolic activity between rods and cones and the activation of cell death pathways as a result of light damage (Wang and Chen, 2014) or metabolic dysfunction (Punzo et al., 2009), it would be interesting to compare activation of the endoplasmic reticulum (ER) stress response of these two photoreceptors in animals expressing different mutant photoreceptor-specific proteins.

2. Retinal degenerative disorders

Many factors can affect vision loss, including inheritance, the environment, aging, and mechanical trauma. Inherited retinal degeneration (IRD) can affect rods (e.g., RP and rod-cone dystrophy) and cones (e.g., cone-rod dystrophy (CORD)), primarily due to mutations in rod- or cone-specific genes. In addition, mutations in genes particularly expressed in RPE cells, such as RPE65, can affect photoreceptors and lead to IRD (e.g., Leber's congenital amaurosis (LCA)). Environmental factors and aging contribute to age-related macular degeneration (AMD). Physical trauma can cause retinal detachment, which can lead to retinal degeneration. However, cases of retinal detachment as a complication of retinoschisis, uveitis, degenerative myopia, or diabetic retinopathy are also known.

Genetics is a key factor leading to IRD (Birtel et al., 2018; Maeder et al., 2019; Mizobuchi et al., 2019; Tayebi et al., 2019; Tsang and Sharma, 2018; Wu et al., 2018), which is associated with irreversible vision loss and affects an estimated 1 in 2500 individuals (Abisambra et al., 2013). Different classes of genetic retinal dystrophies differ greatly in their etiology and age of onset. About 50% of all inherited human retinal diseases belong to a class of pigmentary retinopathies called RP (Daiger et al., 2013), which is broad heterogenic group of rare genetic disorders characterized by a progressive loss of vision leading to blindness due to degeneration of photoreceptors, primarily rods, in the retina. The prevalence of RP is approximately 1 in 4000 individuals worldwide. The name RP was selected because ophthalmoscopic observation shows an ischemic appearance of the neural retina, with a waxy, pale optic nerve head and brown or black pigmented 'bone spicules' in the periphery (Jones and Marc, 2005).

The most common form of RP is rod-cone dystrophy, in which initial night blindness is followed by progressive loss of the peripheral visual field. Cones are maintained for some time and die following rod cell death. Varying modes of RP inheritance include 50–60% autosomal recessive, 30–40% autosomal dominant, and 5–15% X-linked (Bunel et al., 2019). In addition to its mode of inheritance, RP is classified as syndromic or non-syndromic. Examples of syndromic RP are Usher syndrome, which is also associated with deafness, and Bardet Biedl syndrome, which is also associated with obesity and intellectual disability. Non-syndromic RP is more common, accounting for 70–80% of all RP cases (Pfeiffer et al., 2019).

In the clinic, RP patients are usually examined by ERG recordings. In the early stage of the disease, ERG amplitudes are affected more in rods than in cones. However, with RP progression, both rod and cone amplitudes become diminished. Photoreceptor degeneration continues until the retina completely lacks photoreceptors, leaving patients deficient in perceiving light for years to decades of life (Pfeiffer et al., 2019). In addition, RP patients can experience epiretinal membrane formation, atrophy of the RPE, posterior subcapsular cataracts, and cystoid macular edema (Musarella and Macdonald, 2011).

RP patients often become legally blind by their mid-40s. However, the onset and mechanism of photoreceptor deterioration varies widely across RP diseases. Thus, some patients experience vision loss early in life, whereas others may not show signs of retinal

degeneration until adulthood (Hartong et al., 2006). As of today, over 60 genes are known to cause non-syndromic RP, and over 20 genes are associated with autosomal dominant RP. Mutations in rhodopsin genes are the most common cause of autosomal dominant RP and are present in 20–30% of cases. For example, the substitution of proline-to-histidine at position 23 (P23H) is the most common mutation found in the United States. Autosomal recessive RP is associated with mutations of at least 35 genes. Although mutations in six genes cause the X-linked form of RP, mutations in the RP GTPase regulator gene account for most cases.

Different from RP, CORD is characterized by deterioration of cones followed by a decline in rod function. Thus, daylight and color vision is affected before night vision in RP patients, whereas CORD often occurs in childhood and manifests as decreased sharpness of vision and increased light sensitivity followed by impaired color vision (i.e., dyschromatopsia), blind spots (i.e., scotomas) in the center of the visual field, and partial side (i.e., peripheral) vision loss (https://ghr.nlm.nih.gov/condition/cone-rod-dystrophy). CORD patients soon develop night blindness and experience a worsening of their peripheral vision, which can limit their independent mobility. A decrease in visual acuity makes reading incredibly difficult, and most affected individuals are legally blind by mid-adulthood. Mutations in at least 10 genes are associated with CORD, which are inherited in an autosomal dominant pattern. Mutations in guanylate cyclase 2D and cone-rod homeobox genes account for about half of these cases. Mutations in the ATP binding cassette subfamily A member 4 protein account for 30–60% of cases.

LCA was first described by Theodore Leber in 1869 (Perrault et al., 1999) and is the most common type of IRD resulting in neonatal blindness (Maeder et al., 2019; Miraldi Utz et al., 2018; Tsang and Sharma, 2018). Currently, there are 18 forms of LCA based on the affected gene (https://omim.org/entry/204000). One is the RPE-specific 65 kDa protein (RPE65), a key player in the visual cycle. RPE65 is responsible for the conversion of all-trans-retinal to 11-cis-retinol during phototransduction. Mutations in this gene affect photoreceptors and result in LCA2. However, mutations in photoreceptor-specific proteins also cause other forms of LCA. Currently, U.S. Food and Drug Administration (FDA)-approved Luxturna is an treatment option for patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy, which can lead to vision loss (https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss). LCA is typically inherited in an autosomal recessive pattern (Kumaran et al., 2017; Perrault et al., 1999), meaning that both copies of a gene must be mutant for a patient to present a significant phenotype. In the United States, LCA affects 1–3 per 100,000 newborns, representing ~2% of all cases of inherited retinal dystrophy (Kumaran et al., 2017).

LCA is typically diagnosed within the first few months of life when a parent or doctor notices a lack of visual responsiveness and aberrant eye movements, termed nystagmus (Kumaran et al., 2017). It is common for a fundus image, or clinical image of the retina, to appear normal in an infant with LCA (Weisschuh et al., 2018). However, ERG recordings assessing retinal response to light stimuli reveal that retinal neurons show little or no activity in response to flashes of light (Brecelj and Stirn-Kranjc, 1999; Koenekoop et al., 2002;

Kumaran et al., 2017; Perrault et al., 1999; Weisschuh et al., 2018). LCA patients in early adolescence to adulthood typically show several signs and/or symptoms including nystagmus and deep-set eyes (Kumaran et al., 2017; Perrault et al., 1999; Weisschuh et al., 2018). Some LCA patients experience sensitivity to bright light, known as photophobia (Weisschuh et al., 2018). In addition, numerous changes to the retina become apparent in adolescence. In many cases, retinal blood vessels become attenuated, or more constricted, as occurs in RP patients(Ma et al., 2012). It is also common for the retinas of LCA patients to exhibit changes in pigmentation due to alterations in the RPE, which is just superficial to the retina (Kumaran et al., 2017; Weisschuh et al., 2018). Although various physical changes occur in the retinas of LCA patients, vision often remains stable into young adulthood for most patients (Kumaran et al., 2017; Perrault et al., 1999). Patients with LCA typically have visual acuity ranging from 20/200 to complete blindness (Kumaran et al., 2017; Weisschuh et al., 2018). Mutations in as many as 25 genes are known to cause LCA (Kumaran et al., 2017). LCA etiology depends on the mutated gene, as mutations in certain genes can result in differences in the severity of the phenotype. In North America and Europe, mutations in the gene encoding the centrosomal protein of 290 kDa (CEP290) account for 15–20% of cases, which is more than any other gene (Kumaran et al., 2017).

AMD predominantly affects elderly individuals over the age of 50 years. Today, the disease is a leading cause of vision loss worldwide, and its prevalence dramatically increases with aging. Additional risk factors for AMD are the environment, smoking, and nutrition. AMD exists in two forms: dry and wet. The dry form (80–85% of all cases) is associated with accumulation of drusen deposits, creating a distance between the RPE and photoreceptors and a shortening and loss of the photoreceptor OS. The mechanism of retinal pathogenesis is the loss of functional RPE cells, which results in photoreceptor cell death at late stages. Due to the metabolic and phagocytotic dependency of photoreceptors on RPE cells, the loss of retinal integrity results in AMD development. The wet form (15–20% of all cases) originates from neovascularization in the choroid, neural retina, and vitreous, during which leakage of the blood and serum damages ocular tissues. Both wet and dry forms eventually lead to blurriness of vision in the central retinal area if not treated. These symptoms often progress to vision loss that spreads to the periphery of the retina.

Retinal detachment can also induce photoreceptor degeneration. Clinically, patients with retinal detachment often experience photopsias and progressive loss of vision due to damaged photoreceptors and other serious impacts to the retina. Following detachment, OSs degenerate, which is accompanied by the death of retina ganglion cells and glial involvement (Sorensen et al., 2019). For example, Muller cells experience hypertrophy (Liu et al., 2018b) and changes in gene expression (Matsumoto et al., 2018). Together, these events can trigger rewiring and remodeling in degenerating retinas.

Recently, retinal remodeling was proposed to be a consequence of photoreceptor degeneration, with three common phases across different forms of retinal degeneration (Pfeiffer et al., 2019). In phase 1, degeneration triggered by stress begins to launch neural reprogramming and glial responses. In phase 2, the progressive loss of remaining photoreceptors, particularly cones, induces remodeling. This stage persists as long as remnant cones are viable. Phase 3 starts upon the complete loss of photoreceptors. At this

point in degeneration, retinal disintegration is complete, leading to neurite outgrowth and widespread cell death (Pfeiffer et al., 2019). Despite progress toward understanding variations in retinal pathogenesis, the question of whether the molecular mechanisms contributing to photoreceptor cell death at the same phase of retinal degeneration are similar regardless of the etiology of retinal degeneration remains to be addressed.

3. Animal models of retinal degeneration

Transgenic, knock-out (KO), and knock-in animal models enable scientific investigation of the pathogenesis of photoreceptor degeneration in RP, CORD, LCA, AMD, and retinal detachment. Due to the focus of this review, we have highlighted animal models with retinal dystrophies mimicking RP and LCA in humans that have been used by our laboratory to unravel the molecular mechanisms of retinal degeneration; however, many more models of RP and LCA exist.

Rhodopsin is an essential 39 kDa protein for phototransduction. It belongs to a class of G protein-coupled receptors consisting of scotopsin and the covalently bound cofactor retinal. Embedded in the lipid bilayer of the disk's membranes, rhodopsin forms three general domains: intracellular, transmembrane, and extracellular. Its structure consists of an extracellular N-terminal segment, seven transmembrane segments (TM1–7), and an intracellular C-terminus tail. Three segments link TM regions on the extracellular surface (E1–3), and another three segments link TM regions on the cytoplasmic surface (C1–3) in addition to a final cytoplasmic segment (C4). The rhodopsin protein (RHO) efficiently absorbs green-blue light and appears reddish-purple, giving it the name "visual pigment".

Rhodopsin undergoes a few conformational changes, including Meta II state, which involves isomerization of retinol into its active all-trans-retinal conformation. Meta II activates the transducin protein, the α subunit of which activates cGMP PDE. In the "dark" state, cGMP directly activates cation channels, resulting in a net depolarization of rods. This depolarization leads to the release of glutamate, which hyperpolarizes some surrounding cells and depolarizes others. In the "light" state, the transducin α subunit activates PDE, which hydrolyses cGMP into GMP, decreasing cation channel activity and causing hyperpolarization of rods. This reduces the release of glutamate by rods, which results in the sensation of light. Notably, rods exhibit a significant extent of signal amplification. *In vitro* electrophysiological experiments with intact rod photoreceptors indicate that a single photon activates 16 G protein molecules in the mouse and ~60 in the frog (Arshavsky and Burns, 2014). This further results in hydrolysis of ~2000 and ~72 000 molecules of cGMP, respectively, representing the total degree of biochemical amplification of the phototransduction cascade in these species. The return of rods to a resting state occurs through RHO deactivation, closure of cGMP channels, inactivation of transduction, and a decrease in intracellular Ca^{2+}, triggering intracellular proteins to activate guanylate cyclase and restore the level of cGMP. Given the pivotal role of RHO in vision signaling, it is worth mentioning that varied mutations in the rhodopsin gene correlate with congenital retinopathies like RP and congenital stationary night blindness (Toledo et al., 2011).

P23H RHO mutation exhibits characteristics of both types of dominant mutation: toxic gain-of-function and dominant negative (Mendes and Cheetham, 2008; Wilson and Wensel, 2003). Currently, a few animal models express aberrant P23H RHO, including transgenic mice, rats, and frogs as well as knock-in mice. P23H transgenic rats express a mouse *RHO* transgene with a defective N-terminal domain. These rats were developed to manifest different rates of retinal degeneration, from relatively slow-progressing (line 3) to moderate (line 1) retinal degeneration (Bryda and LaVail, 2019). We previously investigated the molecular mechanism of photoreceptor deterioration in P23H line 3 rats (Gorbatyuk et al., 2012a; Gorbatyuk et al., 2010; Sizova et al., 2014). At postnatal day (P)30, these rats show only a 20% reduction in outer nuclear layer thickness as compared with wild-type (i.e., albino background) rats, whereas P23H line 1 rats show a 50% reduction. In these rats, scotopic ERG responses generally follow degeneration curves that closely mimic those of outer nuclear layer thickness degeneration (https://view.officeapps.live.com/op/view.aspx?src=http%3A%2F%2Fophthalmology.ucsf.edu%2Fwp-content%2Fuploads%2FLaVail-RD-Rat-Model-Resource-063011.docx).

Another model is P23H transgenic mice, which express a human P23H *RHO* transgene that leads to relatively slow retinal degeneration. At P30, these mice already show a marked reduction in scotopic ERG amplitudes and thinning of the outer nuclear layer, which further proceeds with age (Mao et al., 2012). At P90, these mice show a 30% loss of photoreceptors accompanied by diminishing scotopic ERG responses (Chiang et al., 2016).

P23H *RHO* knock-in mice are proposed to more closely mimic the genetic background and pathological progression of human autosomal dominant RP with P23H opsin mutation (Sakami et al., 2014), as they have photoreceptors that undergo rapid degeneration after P14. In this model, P23H RHO is improperly glycosylated and expressed at a level 1–10% of that of wild-type opsin (Sakami et al., 2011). Moreover, expression of P23H RHO disrupts rod disk formation, resulting in greater functional deficits in rods than in cones. At P40, these mice show a ~50% decline in rod photoreceptor function measured by scotopic ERG responses as compared with wild-type mice. In addition, these mice exhibit a strong intraretinal gradient of degeneration, with a greater degree of degeneration in the inferior retina, similar to that observed in humans (Olsson et al., 1992; Sakami et al., 2011). By contrast, P23H *RHO* transgenic rats show greater involvement of the superior retina (LaVail et al., 2000).

Another animal model expressing aberrant rhodopsin is T17M *RHO* mice. The T17M (tyrosine-to-methionine at position 17) mutation is located close to the rhodopsin glycosylation site (N2–15) on the N-terminal and likely affects protein folding due to lack of glycosylation (Murray et al., 2015). These mice develop severe retinopathy (Choudhury et al., 2013; Choudhury et al., 2014; Kunte et al., 2012; Nashine et al., 2013). At P30, scotopic ERG amplitudes are diminished by over 60%, and this decline in retinal function is tightly associated with photoreceptor loss (Nashine et al., 2013). Interestingly, photopic ERG amplitudes are also reduced at P30, resulting in massive cone loss at P90 (Rana et al., 2017). These findings indicate that these mice exhibit rapid retinal degeneration, which makes rescue of deficits challenging. Moreover, T17M *RHO* mouse retinal function and morphology change dramatically after light exposure (Krebs et al., 2009); 3 hours of

illumination results in 50% recovery of scotopic ERG amplitudes, whereas up to 6 hours of illumination results in normal photopic responses. Interestingly, extensive light exposure can damage photoreceptor cells via activation of the ER stress response (Nakanishi et al., 2013). Therefore, it not surprising that cell death in these mice peaks 1 day after exposure, and outer nuclear layer thickness declines between 1 and 5 days (Krebs et al., 2009).

rd1 and rd10 mice harbor different mutations in PDEβ subunits and transmit retinal degeneration through an autosomal recessive mode. In rd1 mice, the affected allele in the *Pde6b* gene carries a nonsense mutation resulting from viral insertion in intron 1 or nonsense mutation in exon 7 C→A transversion in codon 347 (Dong et al., 2017). These mice show early onset of retinal degeneration; the outer retina starts deteriorating at P8, which rapidly proceeds to the complete loss of rods by P36 (Carter-Dawson et al., 1978). However, cones degenerate at a slower pace in these mice. At P17, ~75% of cones exist in the retina, whereas at 18 months of age, 1.5% of cones are still present. Photoreceptor cell death occurs through via activation of apoptosis-inducing factor, calpains, and caspases and elevation of Ca^{2+} concentration (Johnson et al., 2005; Sanges et al., 2006). In rd10 mice, spontaneous mutation in the PDE gene also leads to development of autosomal recessive RP. Retinal degeneration in these mice starts at P18 and peaks around P25 with significant rod degeneration, although cones also eventually deteriorate. At P30, these mice still show light responses as assessed by ERG mimicking the typical progression of RP in humans. The overall changes observed in these mice are similar to those found in rd1 mice except that decay in retinal integrity and function occurs at a slower pace.

An animal model of rapid retinal degeneration is BXD24/TyJ-CEP290$^{rd16/J}$ (rd16) mice, which have a spontaneous mutation in *Cep290* that was discovered in the BXD24 inbred strain at Jackson Laboratories (Chang et al., 2006). Since their discovery, rd16 mice have been well characterized (Chang et al., 2006; Craige et al., 2010; Drivas et al., 2013; Mookherjee et al., 2018; Rachel et al., 2015; Starr et al., 2018; Subramanian et al., 2014; Wu et al., 2017; Zhang et al., 2018). Chang et al. discovered that 897 base pairs corresponding to exons 35–39 of the *Cep290* gene are deleted in rd16 mice (Chang et al., 2006). This deletion corresponds to amino acids 1599–1897 that contain region M, the microtubule binding region or myosin tail homology domain (Chang et al., 2006; Mookherjee et al., 2018; Rachel et al., 2015). rd16 mice display rapid degeneration of the retina from as early as P18, but the gross morphology of kidneys and the brain, which are known to be susceptible to CEP290-associated ciliopathies, surprisingly remain unaffected (Chang et al., 2006; Subramanian et al., 2014). This suggests that the region deleted in *Cep290* encodes a domain that plays a specific role in retinal photoreceptors (Chang et al., 2006). Although rods degenerate rapidly in rd16 mice as demonstrated by a low but detectable scotopic ERG response (Chang et al., 2006; Mookherjee et al., 2018; Murga-Zamalloa et al., 2011; Subramanian et al., 2014; Zhang et al., 2018), cones are still present in the retina until at least P60 despite a near complete loss of photopic response at P18 (Chang et al., 2006). The remainder of the retina appears to be mainly unaffected, with no loss of rows in the inner nuclear layer or ganglion cell layer until at least P60 (Chang et al., 2006). Photoreceptors in rd16 mice display uncharacteristic ciliogenesis and form a shorter than normal OS (Chang et al., 2006; Rachel et al., 2015), different from CEP290 KO mice that do not form an OS (Rachel et al., 2015). In these mice, the 9+0 microtubule doublet of the axoneme of cilia appears relatively

normal, but the microtubule ring has an irregular shape (Rachel et al., 2015). As expected, multiple proteins, including those that typically reside in the transition zone or OS, are mislocalized to the photoreceptor inner segment (Chang et al., 2006; Mookherjee et al., 2018; Murga-Zamalloa et al., 2011; Subramanian et al., 2014). For example, RHO and arrestin are mislocalized to the inner segment of rd16 mouse photoreceptors (Chang et al., 2006). Thus, we found that the level of RHO protein is significantly diminished (Starr et al., 2019) and mislocalized in rd16 mice, consistent with a lower level of total protein synthesis in photoreceptors (Starr et al., 2018). A few ciliary proteins that interact with CEP290 show aberrant interactions in rd16 mice, indicating that CEP290 is at least partially responsible for the localization of proteins to the connecting cilium (Chang et al., 2006; Murga-Zamalloa et al., 2011; Subramanian et al., 2014). However, the exact role of CEP290 in trafficking is not clear, and whether OS proteins are mislocalized in rd16 mouse photoreceptors due to improper transport or the lack of a proper OS remains elusive.

4. Molecular mechanisms of retinal degeneration

IRD has varied etiologies due to causative mutations in genes. Despite this fact, the molecular mechanisms promoting advanced-stage RP and photoreceptor cell death could be similar. In this regard, apoptosis has been proposed as a general pathway of photoreceptor cell death in retinal degeneration involving rod defects (Chang et al., 1993; Gregory and Bird, 1995; Reme et al., 1998). However, the causative role of apoptosis as a mechanism underlying all rod degenerative diseases has been questioned. For example, cells that normally die by apoptosis execute cell death by necrosis if the normal pathway is blocked (Kunchithapautham and Rohrer, 2007a) and that multiple rescue paradigms targeting all active cellular pathways should be considered until a common upstream initiator of a given photoreceptor dystrophy cannot be found (Kunchithapautham and Rohrer, 2007b). To demonstrate the connection between apoptosis and photoreceptor cell death in T17M *RHO* transgenic mice, our laboratory conducted an experiment in which we ablated the UPR mediator, C/EBP homologous protein (CHOP), also known for its pro-apoptotic properties in the mouse retina (Nashine et al., 2013). The results were surprising, as CHOP ablation did not rescue degenerating retinas. However, later two independent groups also came to the same conclusion; ablation of pro-apoptotic CHOP does not prevent loss of visual function or photoreceptor cell death in another IRD model, P23H *RHO* mice (Adekeye et al., 2014; Chiang et al., 2016). Altogether, these results suggest that photoreceptor cell death occurs through either the activation of multiple upstream pro-apoptotic pathways or another pro-death signaling pathway.

Alternatively, programmed necrosis (i.e., necroptosis) was proposed as mode of photoreceptor cell death when investigators observed that photoreceptors can execute necrosis in a programmed manner and that the immunogenic nature of this process favors suicide through a caspase-independent approach (Arango-Gonzalez et al., 2014; Murakami et al., 2012; Sato et al., 2013; Viringipurampeer et al., 2019). Since its discovery, necroptosis has become an attractive therapeutic target for retinal degenerative diseases. However, the study of necroptotic cell death has primarily focused on cones. Deficiency in receptor-interacting protein kinase 3 (RIP3), which contributes to inflammation by regulating programmed necrosis, preserves cones in rd10 mice despite their sustained rod degeneration

(Murakami et al., 2012). This study also reports that necrotic mechanisms engaging RIP3 may be crucial to cone cell death in IRD, implicating this molecule as a potential target for treating central and peripheral vision loss in patients with RP. Another study in a pde6c^{w59} mutant zebrafish model of RP reveals that the underlying mechanism of cone cell death occurs through necroptosis, whereas rods degenerate via a caspase-dependent mechanism (Viringipurampeer et al., 2014). Thus, knocking down RIP3 in pde6c^{w59} mutant zebrafish rescues dying cones by preventing ROS generation, leading to improved cone adaptation and upregulation of PDE6A and PDE6B expression. In this study, degenerating rods were not responsive to inhibition of RIP1/3 activity and showed positive immunostaining for caspase 3.

In further investigations of the RIP kinase pathway, mice lacking interphotoreceptor retinoid-binding protein were found to show a 3-fold elevation of RIP1 and RIP3 kinases and 10-fold elevation of TNFα receptor 1, a membrane death receptor that triggers both programmed apoptosis and necrosis (Sato et al., 2013). In this study, investigators found that overall TNF-RIP-mediated necrosis strongly contributes to photoreceptor cell death (Sato et al., 2013) and that pharmacological inhibition of RIP1 kinase significantly prevents both cone and rod cell death. Although the results of this study are generally consistent with previous findings, the proposed mode of rod cell death is inconsistent with the role of RIP kinases in rod deterioration and should be further investigated. Interestingly, our study with T17M *RHO* mice also shows a 2-fold elevation in TNF receptor-associated factor 2, which is a part of the RIP1 kinase complex that promotes apoptosis in the retina (Choudhury et al., 2013).

As cone degeneration usually follows mutation-induced rod cell death in RP, a few hypotheses concerning the specific pathways triggering cone cell death were recently proposed. One hypothesis is that dying rods secrete toxic substances transmitted through gap junctions, which serve as intercellular communication pathways between rods and cones (Smith et al., 1986), and thereby affects cone viability (Ripps, 2002). Migration of activated microglia and inflammation during retinal degeneration is another potential mechanism of the demise of cones in affected retinas (Peng et al., 2014). In one study, degenerating retinas in rd10 mice were treated with minocycline, a pharmacological inhibitor of microglia activation, showing that both rods and cones are responsive to microglia activation and survive via anti-inflammatory and anti-apoptotic mechanisms. However, given the nature of pharmacological treatment, it would be difficult to draw a firm conclusion about the major factor contributing to cone viability. Therefore, it remains to be determined whether cone survival is a result of rod survival or a direct benefit of treatment. Interestingly, in rd1 mice, microglia-regulated photoreceptor survival also occurs by necroptosis as well as activation of RIP1 and RIP3 kinase and the toll-like receptor 4 (TLR4) pathway. A study conducted in our laboratory with T17M *RHO* mice shows that deficits in TNFα, an activator of the TNF receptor-RIP kinase pathway, dramatically increases photopic ERG amplitudes and the number of surviving cones, suggesting a role of this signaling pathway in cone survival (Rana et al., 2017). However, as in the above-mentioned study in which microglia were pharmacologically inhibited (Peng et al., 2014), we could not conclude that cone viability was a direct result of TNFα deficiency. Therefore, future investigations should identify

whether autocrine versus paracrine regulation of TNFα expression affects cone survival in TNFα-deficient T17M *RHO* mice.

Another factor affecting cone survival is rod-derived cone viability factor, the level of which dramatically reduces upon the loss of rods (Rana et al., 2017). Cone survival is also affected by oxidative stress, which leads to modifications in DNA, proteins, and lipids, as well as exposure to high oxygen content due to a loss of rods (Campochiaro and Mir, 2018). Together, however, the existing literature reveals a gap in our knowledge of how rods and cones die during retinal degeneration and whether the major mode of cell death can switch based on the duration of the disease and its causative factors. Many studies with various animal models of retinal degeneration propose multiple signaling pathways triggering apoptosis. The list includes, but is not limited to, oxidative stress, aberrant autophagy, Ca^{2+} dysfunction, the inflammatory response, and the ER stress response. Although these processes could be involved in degenerating retinas by themselves, results from our laboratory suggest that activation of these processes could result from sustained activation of the ER stress response or unfolded protein response (UPR), which is the focus of the current review.

5. ER and UPR

5.1. ER

The ER is a eukaryotic organelle composed of a complex membranous network of branching tubules and flattened sacs. The ER has multiple functions including protein maturation, sorting and degradation, and lipid biosynthesis (Aviram and Schuldiner, 2017; Schwarz and Blower, 2016). The ER is also involved in carbohydrate metabolism due to the fact that glucose-6 phosphatase is an ER membrane protein (Burchell et al., 1994). Furthermore, the ER controls Ca^{2+} homeostasis in cells by buffering free Ca^{2+} (Wakai and Fissore, 2013).

In eukaryotic cells, the largest targeting destinations for nascent proteins include the ER, mitochondria, nucleus, lysosomes, and peroxisomes. Nearly all proteins destined for the ER, Golgi apparatus, cell membrane, or lysosomes are synthesized on the ER membrane and transported inside the ER through a process known as co-translational ER translocation (Aviram and Schuldiner, 2017). Inside the ER, proteins undergo various post-translational modifications that aid their folding into three-dimensional, or tertiary, structures (Shrimal et al., 2015). Through their catalytic activity, glycosylating enzymes (Bause and Lehle, 1979) and oxidoreductases (Noiva et al., 1991) help immature proteins achieve proper folding. Also, inside the ER are protein chaperones that stabilize proteins while they correctly fold (Garcia-Huerta et al., 2016; Sun et al., 2019). The ionic environment in the ER is optimally suited for chaperones and enzymes participating in protein folding (Garcia-Huerta et al., 2016). In fact, the ER is the primary site of Ca^{2+} storage in cells, with a Ca^{2+} concentration 1,000–10,000 times higher than that in cytosol (Bollimuntha et al., 2017; Bygrave and Benedetti, 1996; Glaser et al., 2018; Samtleben et al., 2013) depending on the measurement method and cell type (Bygrave and Benedetti, 1996). After proteins correctly fold, they are trafficked to their destination (Liu et al., 2018a). The ER has a complex surveillance system known as the UPR that detects misfolded proteins, and any terminally misfolded proteins are

trafficked out of the ER to be degraded through a process called ER-associated degradation (ERAD) (McCracken and Brodsky, 1996; Wu and Rapoport, 2018).

5.2. UPR

The UPR is a series of signaling cascades originating in the ER that are initiated in response to ER stress (Kohno et al., 1993; Partaledis and Berlin, 1993; Robinson et al., 1993). The UPR can become active following insults to the ER, many of which result in the misfolding and retention of proteins in the ER. For example, stresses such as glucose deprivation (Doerrler and Lehrman, 1999) and Ca^{2+} irregularities (Hojmann Larsen et al., 2001; Li et al., 1997) are well-described triggers of ER stress signaling (Wang and Kaufman, 2016). Glucose deprivation or fluctuating Ca^{2+} concentrations can result in the accumulation of misfolded proteins in the ER due to the vital role of these components in protein folding. Glucose is essential for protein glycosylation; without it, proteins cannot properly fold or exit the ER (Doerrler and Lehrman, 1999). Ca^{2+} is found in the catalytic site of many ER enzymes that assist in protein folding (Appenzeller-Herzog and Simmen, 2016). A reduction in the protein folding capacity of the ER results in the accumulation of misfolded proteins and activation of the ER stress response. In addition, genetic predispositions, such as those involved in IRD, can also result in activation of the UPR (Athanasiou et al., 2017b; Bhootada et al., 2015; Bhootada et al., 2016; DeLuca et al., 2016; Rana et al., 2014).

Following an insult to the ER, the UPR initiates the activation of three ER transmembrane enzymes: inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6), and protein kinase R-like endoplasmic reticulum kinase (PERK) (Figure 1). The widely accepted model for UPR signaling initiation involves a dynamic interaction between glucose-regulated protein 78 (GRP78), an ER-resident protein chaperone, and the three ER enzymes (Oikawa et al., 2009; Pobre et al., 2019; Walter and Ron, 2011; Wang and Kaufman, 2016). In unstressed conditions, GRP78, also known as binding immunoglobulin protein, physically interacts with the luminal domains of the three UPR enzymes, keeping them in an inactive state (Bertolotti et al., 2000; Oikawa et al., 2009). Upon ER stress, misfolded proteins accumulate in the ER lumen, and as GRP78 has a higher affinity for misfolded proteins than for enzymes, it dissociates from PERK, ATF6, and IRE1 and associates with the misfolded proteins. Now unbound, the three UPR enzymes are free to activate the ER stress response by triggering PERK, ATF4, and the IRE1 UPR arms (Bertolotti et al., 2000) (Figure 1).

5.2.1. ATF6—When GRP78 dissociates from ATF6, the ~90-kDa ATF6 travels to the Golgi body, where it is cleaved by site 1 and 2 proteases (Haze et al., 1999; Shen et al., 2002; Shen et al., 2005). This leaves a soluble ~50-kDa transcription factor that migrates to the nucleus (Haze et al., 1999) and promotes the transcription of dozens of genes (Walter and Ron, 2011; Wang and Kaufman, 2016). Most proteins whose genes are targeted following ATF6 cleavage are protein chaperones that assist in protein folding, proteins involved in Ca^{2+} homeostasis, or proteins involved in ERAD (Wang and Kaufman, 2016; Yoshida et al., 2000). A recent study shows that ATF6 plays a key role in homeostatic adaptation to ER stress, whereas IRE1α and PERK are expendable in this process (Vitale et al., 2019). Another study reports that mutations in ATF6 lead to achromatopsia, an

autosomal recessive disorder characterized by cone photoreceptor dysfunction (Chiang et al., 2017).

5.2.2. IRE1—Following the departure of GRP78 from the luminal domain of IRE1 unbound, IRE1 enzymes dimerize, forming a catalytically active homodimer that becomes active by autophosphorylation (Ali et al., 2011; Credle et al., 2005). The cytosolic portion of IRE1 has two catalytic domains: a kinase and an endoribonuclease (Ali et al., 2011; Tirasophon et al., 2000; Yoshida et al., 2001). Following ER stress, an activated IRE1 dimer alternatively splices RNAs via its endoribonuclease activity (Walter and Ron, 2011), such as that encoding XBP1 (Yoshida et al., 2001). Interestingly, transcription of *XBP1* is promoted by cleaved ATF6 (Walter and Ron, 2011), demonstrating crosstalk between these two arms of the UPR. When translated, spliced XBP1 is a highly active transcription factor for genes encoding chaperones and proteins involved in ERAD (Walter and Ron, 2011; Yoshida et al., 2001). IRE1 also has the ability to phosphorylate targets such as JNK, which can activate MAPK signaling (Urano et al., 2000). A recent study shows that IRE1α activity is repressed by the binding of endogenous BiP to the lumen domain of IRE1α and promotes IRE1α monomerization (Amin-Wetzel et al., 2019). Furthermore, enforced loading of BiP on IRE1 results in repression of the UPR in CHO cells.

5.2.3. PERK—Similar to IRE1 activation, PERK is activated in response to dissociation of GRP78 and dimerizes to form an active homodimer (Cui et al., 2011; Liu et al., 2000). PERK is a ~125 kDa kinase with multiple domains (Carrara et al., 2015; Cui et al., 2011; Walter and Ron, 2011; Wang et al., 2018) and a structure similar to that of other two-lobed membrane kinases. The luminal domain of PERK consists of its smaller N-terminal lobe (Carrara et al., 2015; Wang et al., 2018), whereas a larger C-terminal lobe constitutes its cytosolic domain (Cui et al., 2011) and contains its catalytic site (Cui et al., 2011). Together with IRE1, PERK switches BiP from its chaperone cycle into an ER stress sensor cycle by inhibiting ATPase stimulation upon the binding of BiP to the luminal domains of UPR mediators (Kopp et al., 2019).

Recent research has focused on understanding the role of PERK in the induction of ER stress. One study shows that mammalian PERK interacts with misfolded proteins at a region of its luminal domain, meaning that upon induction of ER stress, PERK itself may act as a chaperone that binds exposed hydrophobic regions of misfolded polypeptides and initiates its dimerization and subsequent activation (Wang et al., 2018), which directly argues against canonical UPR activation. Furthermore, this study provides evidence that PERK activation is independent of its interaction with GRP78, as cells expressing PERK lacking a luminal domain do not exhibit higher than normal PERK signaling but are still susceptible to induction of ER stress following treatment with UPR-inducing compounds.

Following dimerization, PERK becomes activated by phosphorylation at Thr982 through a process known as trans-autophosphorylation, meaning each PERK monomer phosphorylates the other (Su et al., 2008; Walter and Ron, 2011). PERK is also known as eukaryotic translation initiation factor 2-alpha kinase 3 (EIF2AK3), named after its first described and primary role of interacting with and phosphorylating the α subunit of the eukaryotic translation initiation factor 2 (eIF2α) complex (Shi et al., 1998; Taniuchi et al., 2016). PERK

is also required for the formation of ER-plasma membrane associations, which is important for regulating Ca^{2+} stores in the ER (van Vliet et al., 2017). As the name EIF2AK3 suggests, PERK is a kinase that phosphorylates eIF2α (Taniuchi et al., 2016). To fully appreciate the impact of eIF2α phosphorylation on cells, we must first understand the role of the protein under normal conditions. The following section discusses the role of eIF2 in normal and stressed conditions.

5.2.4. eIF2 and the integrated stress response—eIF2 is a heterotrimeric translation factor important for the initiation of protein synthesis in eukaryotes. The eIF2 complex consists of three subunits—α, β, and γ—each of which has distinct roles (Alone and Dever, 2006; Barrieux and Rosenfeld, 1977, 1978). The role of eIF2 in translation initiation involves the ternary complex (TC), which consists of eIF2, Met-tRNA, and guanosine tri-phosphate (GTP). In forming the TC, the initiator Met-tRNA is brought to a start codon on an mRNA in a process that depends on GTP being bound to the eIF2γ subunit (Barrieux and Rosenfeld, 1977, 1978; Hinnebusch, 2017; Hinnebusch and Lorsch, 2012; Sonenberg and Hinnebusch, 2009) (Figure 2). The TC joins the 40S ribosomal subunit with other initiation factors, and the pre-initiation complex (PIC) scans the mRNA until a start codon is located. When the start codon binds the anti-codon on Met-tRNA, GTP is hydrolyzed by eIF2, and the TC, which now contains guanosine diphosphate (GDP), exits the PIC and must be reactivated to begin another round of initiation (Hinnebusch, 2017; Hinnebusch and Lorsch, 2012). GDP must be exchanged by a nucleotide exchange factor for eIF2, with EIF2B being a guanine exchange factor that binds eIF2β to exchange GTP for GDP on eIF2γ (Konieczny and Safer, 1983). When this exchange occurs, eIF2 is free to participate in translation initiation (Hinnebusch, 2017).

Numerous cellular stresses can increase eIF2α phosphorylation (Taniuchi et al., 2016). In addition to PERK, three kinases (i.e., heme-regulated kinase, protein kinase R, and general control nonderepressible 2) in vertebrates phosphorylate eIF2α at serine 51 in response to stress (Taniuchi et al., 2016). eIF2α phosphorylation prevents canonical translation initiation resulting from failed guanine nucleotide exchange between eIF2 and EIF2B (Bogorad et al., 2018). This is because EIF2B has a higher affinity for phosphorylated eIF2α than it does for eIF2β; therefore, what is typically a transient complex between EIF2B and eIF2β becomes a stable complex of EIF2B and phosphorylated eIF2α. This is thought to result in the entrapment of EIF2B, the rate-limiting component of TC formation, which prevents canonical translation initiation (Bogorad et al., 2017). When general translation comes to a halt, synthesis of most proteins is inhibited; however, translation of some stress-related mRNAs are upregulated under these conditions. One of these mRNAs encodes ATF4. Interestingly, translation of *ATF4* mRNA occurs in the presence of an active TC (Ross et al., 2018), arguing against central model ATF4 activation.

5.2.5. ATF4—Exactly how *ATF4* mRNA escapes canonical regulation is unknown but involves the existence of upstream open-reading frames (uORFs) in *ATF4*. The general structure of mRNAs with uORFs consists of one or more regions upstream from the primary ORF region of the mRNA that is converted to a stable protein (Kearse and Wilusz, 2017). Although a type of mRNA modification, N^6-methyladenosine, regulates *ATF4* mRNA (Zhou

et al., 2018), how this modification modulates translation has not been determined, leaving the exact mechanism of stress-induced upregulation of ATF4 unknown.

ATF4 promotes transcription of several genes involved in various cellular processes ranging from development to apoptosis (Bhootada et al., 2016; Fusakio et al., 2016; Pitale et al., 2017; Zhao et al., 2015b). The most studied targets of ATF4 are those that are promoted after cellular stressors that result in elevated phosphorylated eIF2α levels (Pitale et al., 2017; Taniuchi et al., 2016). Together with the phosphorylation of eIF2α and the subsequent halt in translation, this alternative translational program is known as the integrative stress response (ISR) (Taniuchi et al., 2016). Growth arrest and DNA damage-inducible 34 (GADD34), CHOP, and tribbles homolog 3 (TRB3) are a few examples of proteins whose genes are targeted by ATF4 during stress (Fusakio et al., 2016; Gorbatyuk and Gorbatyuk, 2013). Interestingly, ATF4 regulates the transcription of 254 downstream genes, one of which is another molecule involved in 5' cap dependent translation—eukaryotic translation initiation factor 4E-binding protein 1, a translational repressor (Han et al., 2013). Studies in our laboratory with T17M *RHO* (Bhootada et al., 2016) and rd16 mice deficient in ATF4 show that reductions in ATF4 significantly retard retinal degeneration (Figure 3). For example, ATF4 deficiency in rd16 retinas delays photoreceptor cell death.

5.2.6. GADD34—GADD34, first identified as a pro-apoptotic member of the GADD family of proteins that suppress cell growth and division (Zhan et al., 1994), is best known for its role as a phosphatase regulatory subunit responsible for initiating the dephosphorylation of eIF2α by bringing protein phosphatase 1 (PP1) to eIF2α and thereby promoting translational recovery (Harding et al., 2009; Kojima et al., 2003; Novoa et al., 2001). To this end, GADD34 provides the ISR with a feedback mechanism that restores translational homeostasis. Although ATF4 acts on the *GADD34* promoter to restore protein synthesis rates (Ma and Hendershot, 2003), c-Jun can also upregulate transcription of *GADD34* under DNA damage (Haneda et al., 2004) and proteotoxic stress associated with Alzheimer's disease (AD) (Xu et al., 2015). It is well known that GADD34 levels correlate with apoptosis in multiple cell types (Farook et al., 2013; Gu et al., 2014; Honjo et al., 2015; Kang et al., 2019; Zhan et al., 1994). For example, Farook et al. show that the pro-apoptotic role of GADD34 could stem from its inhibition of AKT phosphorylation (Farook et al., 2013). Recently, our laboratory demonstrated that *Gadd34* ablation in rd16 mouse retinas reduces apoptosis and elevates phosphorylated AKT, suggesting that GADD34 has a powerful impact on cell fate decision (Starr and Gorbatyuk, 2019). We proposed that *Gadd34* ablation could selectively regulate translation of anti-apoptotic proteins in degenerating retinas, which could be due to a 5′-cap independent or internal ribosome entry site (IRES) mechanism (Starr and Gorbatyuk, 2019).

In addition, GADD34 interacts with TRAF6 and inhibits TRAF6-mediated polyubiquitination of AKT, a process that primes AKT for subsequent phosphorylation. Also, GADD34 interacts with and initiates PP1-mediated dephosphorylation of SMAD7 (Shi et al., 2004). However, GADD34 is proposed to play a pro-survival role apart from its contribution to restoring protein synthesis. For example, GADD34 is important for the integrity of the Golgi apparatus, as its deficiency causes Golgi bodies to become fractionated in hyperosmotic corneal cells (Krokowski et al., 2017). Golgi fractionation also lessens the

membrane translocation of receptors in these cells, suggesting that the role of GADD34 may be more complicated than previously thought. In fact, GADD34/PP1 alters the metabolic states of cells by acting on hundreds of proteins (Dedigama-Arachchige et al., 2018). Therefore, recent research is allowing us to grasp the full breadth of roles played by GADD34. For example, studies from our laboratory indicate that the role of GADD34 in the retinal degeneration of rd16 mice is multifaceted and that in addition to regulating gliosis and apoptosis in degenerating retinas, GADD34 controls apoptotic photoreceptor cell death (Starr and Gorbatyuk, 2019).

5.2.7. CHOP and TRB3—CHOP (also known as GADD153) is a pro-apoptotic molecule that promotes the transcription of several stress-related genes in response to stress (Bartlett et al., 1992; Ron and Habener, 1992; Wang et al., 1996). By forming heterodimers with ATF4, some transcription factors whose genes are ATF4 targets can alter the activity of ATF4. For example, CHOP forms heterodimers with ATF4 (Talukder et al., 2002) and thus could mediate the transcription of tribbles homolog 3 protein (*TRB3*) (Ohoka et al., 2005). In turn, the activity of ATF4 can be regulated by TRB3 (Jousse et al., 2007). In addition, the migration of CEP290 to the nucleus elevates ATF4 activity (Sayer et al., 2006). The role of TRB3 in the progression of RP is currently under investigation in our laboratory.

5.3. ERAD

Approximately 30% of newly synthesized proteins in eukaryotes undergo degradation within minutes of formation, likely due to unsuccessful folding or failure in multimer assembly (Greene and McElvaney, 2010). After multiple unsuccessful attempts to assist proteins in folding, they are redirected for degradation. Thus, ERAD regulates protein levels in response to cellular demands. This quality control process generally consists of four distinct steps: substrate recognition, retro-translocation across the ER membrane, substrate polyubiquitination, and proteasomal degradation (Dupzyk and Tsai, 2016). ER-resident chaperones recognize misfolded proteins and target them to re-translocation machinery. These misfolded proteins are identified by improper glycosylation patterns or inaccurate disulfide bonds that can result in aberrant folding due to exposure of hydrophobic spots or oligomer formation. Recently, we demonstrated that expression of non-glycosylated rhodopsin in the retina leads to a retinal degenerative disorder involving OS malformation, similar to that observed in mice with the human T17M *RHO* transgene (Murray et al., 2015).

A few ER-resident enzymes, such as protein disulfide isomerase, BiP/GRP78/HSPA5, ER class I mannosidase, ER degradation-enhancing mannosidase-like 1/3, and osteosarcoma amplified 9/XTP3, carry out the initial step of the ERAD pathway. In subsequent steps, identified proteins translocate from the ER into the cytosol. The ER transmembrane proteins Hrd1, sel-1 homolog 1, and Derlins assist in this process. For example, sel-1 homolog 1 binds a misfolded protein and passes it to Hrd1, which prepares the targeted protein for transport across the ER membrane. Hrd1, a self-regulating protein, is capable of translocating targeted proteins through both its structural properties and autoubiquitination function. Hrd1 contains a catalytic really interesting new gene (RING)-finger domain facing the cytosol. In the presence of the ubiquitin-conjugating enzyme UBC7, this domain exhibits *in vitro* ubiquitination activity for Lys^{48}-specific polyubiquitin linkage (Kikkert et al., 2004).

Polyubiquitination of Hrd1 prevents sliding a client protein back to the ER lumen, thereby providing release into the cytosol. Thus, in the next step, this process is catalyzed by cytosolic chaperones, and polyubiquitinated substrates are directed to the proteasome for degradation. Delivery to the proteasome is provided by a recently discovered holdase complex that consists of Bcl2-associated athanogene 6, ubiquitin-like protein 4A, transmembrane domain recognition complex 35, and small glutamine-rich tetratricopeptide repeat-containing protein alpha, which prevents the aggregation of misfolded proteins in the cytosol.

Recent studies have examined the role of ERAD in general and Hrd1 in particular in retinal degeneration, including the role of members of the ER membrane complex that physically interact with ERAD components (e.g., UbAC2, Derlin1/2) and thus influence ERAD (Christianson et al., 2011). A point mutation in the ER membrane complex *EMC1* gene has been proposed to cause retinal dystrophy in humans (Abu-Safieh et al., 2013). However, it is worth mentioning that, apart from its hypothetical role in human retinal dystrophy, the role of *EMC1* has not been validated by *in vivo* studies. Another study shows that EMC3, EMC5, and EMC6 regulate the biogenesis and trafficking of rhodopsin protein in Drosophila and mice, implying a link between ERAD and the accumulation of misfolded rhodopsin (Xiong et al., 2019). ERAD induction leads to ubiquitination and induces rapid degradation of P23H rhodopsin *in vivo* (Chiang et al., 2015). In addition, Hrd1 overexpression suppresses the late onset of retinal degeneration in a Drosophila model of autosomal dominant RP (Kang and Ryoo, 2009). Together, these findings suggest that the proper function of ERAD is critical for photoreceptor homeostasis and that enhancing ERAD could have beneficial effects in degenerating retinas.

5.4. Interplay between UPR and other signaling pathways

A broad spectrum of signaling pathways are regulated by the UPR, include autophagy, oxidative stress, Ca^{2+}-mediated cell death, and inflammation.

5.4.1. UPR and autophagy—Autophagy is a catabolic process that removes unnecessary or dysfunctional cellular components. It exists in three forms: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) (Boya et al., 2016). Each pathway degrades substances by lysosomal enzymes. Macroautophagy affords a substantial portion of cellular protection under normal conditions. This process destroys targeted dysfunctional cytoplasmic components within the autophagosome. After incorporation of a substance, an autophagosome fuses with a lysosome to form an autolysosome that degrades incorporated content. Unlike macroautophagy, microautophagy is mediated by direct lysosomal engulfment of cytoplasmic dysfunctional content after it becomes trapped in lysosomes through membrane invagination (Sahu et al., 2011). This process plays an important role in membrane protein turnover and glycogen delivery into the lysosome. CMA usually refers to the chaperone-dependent targeting of soluble cytosolic proteins that are destined for further degradation in lysosomes (Kaushik and Cuervo, 2012). The most distinguishing feature of this pathway is the high specificity of the process. Heat shock protein 70 recognizes cytosolic proteins and targets them for CMA based on a specific amino acid sequence. Also, CMA contributes to several other cellular functions, including

recycling the amino acids of degraded proteins and cellular metabolism (Kaushik and Cuervo, 2012).

Under certain conditions, such as a low nutrition supply for an extended period of time, the UPR can use cellular autophagy to generate energy through lysosomal degradation (Dash et al., 2019). Specifically, activation of the UPR PERK-peIF2α and IRE1 arms trigger autophagy (Senft and Ronai, 2015). The PERK-eIF2α pathway is essential for autophagy induction after stress initiated by tunicamycin (TM) treatment (B'Chir et al., 2013). Indeed, ATF4 and CHOP transcriptionally regulate multiple ATG genes. However, despite the overall role of PERK arm mediators in autophagy signaling, their specific contributions to regulating autophagy genes may not be the same. For example, one study reports that ATF4 and PERK play distinct roles in autophagy (Luhr et al., 2019); ATF4 controls transcription and is essential for autophagosome formation, whereas PERK is involved in the post-sequestration step of autophagy. Interestingly, the over-expression of ATF4 in T17M *RHO* mouse retinas is associated with defective autophagy as evidenced by p62 and LC3-II levels (Bhootada et al., 2016).

The other UPR mediator, IRE1, is also implicated in the activation of autophagy (Senft and Ronai, 2015). TNF receptor-associated factor 2-dependent activation of IRE1 and c-Jun N-terminal kinase (JNK) cause Bcl-2 phosphorylation, leading to dissociation of Beclin-1 and activation of the phosphoinositide-3-kinase (PI3K) complex, thereby activating autophagy (Deegan et al., 2013). By contrast, another study concludes that under TM-induced UPR activation, IRE1 acts as a negative regulator of autophagy (Luhr et al., 2019), indicating that the role of IRE1 remains to be clarified. Although current literature suggests a link between UPR activation and regulation of autophagy, additional studies investigating the transcriptional or post-translational regulation of autophagy-associated genes via UPR mediators are necessary to unravel the precise mechanisms.

5.4.2. UPR and oxidative stress—Under normal conditions, the ER carries out oxidative protein folding and has limited antioxidant activity due to a balance between reduced and oxidized protein stages. Protein folding is associated with disulfide bond formation that is coupled with ROS formation in the ER (Malhotra and Kaufman, 2007). ER-resident oxidoreductase protein disulfide isomerases together with ER oxidoreductase 1 catalyze disulfide bond formation (Pollard et al., 1998), leading to the generation of hydrogen peroxide. Therefore, disulfide bond generation during folding requires a stable redox environment maintained by several buffering factors such as glutathione (GSH), ascorbic acid, and flavin nucleotides. For example, GSH reacts with non-native disulfide bonds formed as a result of oxidative stress or enzyme-catalyzed oxidation, allowing misfolded proteins to fold again. In addition, detoxification of ROS occurs with the help of reduced GSH, leading to a depletion of oxidized GSSG (Ushioda et al., 2008). The ratio of reduced-to-oxidized GSH/GSSG often serves as an indicator of oxidative stress within cells.

The adaptive stage of the UPR can not only reduce the folding demand but also trigger a compensative transcriptional program activating genes encoding antioxidant factors. Antioxidant control is associated with the PERK and IRE1 pathways (Harding et al., 2003). In particular, ATF4 is an essential factor for GSH synthesis (Dickhout et al., 2012; Huggins

et al., 2015). In addition to ATF4, the PERK arm controls the activation of a potent oxidative stress regulator and transcription factor involved in the antioxidant response: nuclear factor erythroid 2-related factor 2 (NRF2). By enhancing NRF2, PERK may be a critical survival factor in P23H *RHO* retinas (Comitato et al., 2019; Zhang et al., 2019).

In addition, activation of the UPR IRE1/XBP1 axis stimulates the hexosamine biosynthetic pathway and the production of UDP-N-acetylglucosamine, a crucial component for stress-induced O-GlcNAc modification and cellular defense against ROS (Vincenz and Hartl, 2014). The IRE1 arm regulates oxidative stress by activating apoptosis signal regulating kinase 1, which is associated with mitochondrial ROS production through its inhibition of the mitochondrial electron transport chain by downstream cJun (Urano et al., 2000; Win et al., 2014). Our study of T17M *RHO* retinas with chronic UPR activation also shows an increase in ROS production, confirming a link between the UPR and oxidative stress in degenerating retinas (Bhootada et al., 2016).

5.4.3. UPR and Ca^{2+} homeostasis—The ER is an essential organelle for Ca^{2+} storage. Photoreceptors show marked variations in Ca^{2+} concentrations depending on their cellular compartments and demands. These compartments are associated with varied functions: transduction, transcription, translation, metabolism, and synaptic transmission. This results in higher Ca^{2+} influx in the OS and lower Ca^{2+} influx in the cell body and synaptic terminal. Types of Ca^{2+} channels in photoreceptors include cyclic nucleotide-gated channels in the OS, which are regulated by the phototransduction cascade, and voltage-gated Ca^{2+} channels in the cell body and synaptic terminal, which are regulated by light-induced cell membrane hyperpolarization. Store-operated channels in the plasma membrane; sarco/ER Ca^{2+}-ATPase (SERCA) transporters, IP3 receptors, and ryanodine receptors in the ER; and voltage-dependent anion channels in IS mitochondria also contribute to the regulation of intracellular Ca^{2+} in photoreceptors (Butler et al., 2017; Shinde et al., 2016). For example, an important function of Grp78 is to keep Ca^{2+} within the ER lumen to control its free cytosolic form. Other ER-resident proteins include calreticulin and Bax inhibitor-1 protein. In addition, free Ca^{2+} is controlled by M calpain and calcineurin in the cytoplasm. Free intracellular Ca^{2+} can trigger several cellular pathways including mitochondria homeostasis, Ca^{2+} channels, and calmodulin signaling and eventually lead to apoptosis.

Aberrant intracellular Ca^{2+} signaling is found in a variety of neurodegenerative diseases including AD, Huntington disease, and Parkinson's disease (PD). Ca^{2+} homeostasis can be disturbed by leakage of Ca^{2+} from the ER, with inositol-1,4,5-trisphosphate receptors (IP3R1) and ryanodine receptors being two major intracellular Ca^{2+} channels releasing ER Ca^{2+} stores. Thus, mice lacking IP3R1 or carrying spontaneous mutations show severe ataxic behavior (Cheung et al., 2008; Joshi et al., 2016). By recording a single channel, researchers have demonstrated the stimulatory effect of IP3R1 in a mouse model of a familial form of AD, showing exaggerated cellular Ca^{2+} signaling in the presence of agonist stimulation or enhanced low-level Ca^{2+} signaling in untreated cells (Cheung et al., 2008). Another study suggests the importance of SERCA pumps, which are responsible for Ca^{2+} uptake from the cytoplasm, in neurodegeneration (Rahate et al., 2019). Our study shows that during autosomal dominant RP progression in P23H-3 and S334ter-*RHO* rat retinas, free cytosolic Ca^{2+} is elevated in photoreceptors and is accompanied by increased calpastatin,

VDAC, calreticulin, and BI-1 (Shinde et al., 2016). Interestingly, a study using rd1 mice reported a decrease in calpastatin (Paquet-Durand et al., 2006). In addition, we found increased expression of IP3R and SERCA2b mRNA and protein in degenerating photoreceptors and show that UPR activation is responsible for the increased calpain and JNK activity that, together with CDK5, result in cleavage of caspase 3 (Shinde et al., 2016).

5.4.4. UPR and inflammation—TNFα, interleukin (IL)-1b, and IL-6 are hallmarks of degenerating retinas. The UPR can promote pro-inflammatory cytokine production via activation of NF-kB, IRF-3, JNK, and JAK/STAT signaling (Beisel et al., 2017; Martinon et al., 2010; Meares et al., 2014). For example, TLR2 and TLR4 induce ER stress and activate IRE1a→spliced XBP1, resulting in production of IL-6 and TNF.

Neuroinflammation is also modulated through the NLR family pyrin domain-containing-3 (NLRP3) inflammasome. A multimeric protein complex composed of NLRP3, ASC adaptor, and activated caspase 1 mediates the proteolytic activation of IL-1b and IL-18 and promotes a type of inflammatory cell death referred to as pyroptosis (Labzin et al., 2018). The interplay between the UPR and inflammasome is carried out through the IRE1 UPR arm; the RNase domain of IRE1 regulates expression of thioredoxin-interacting protein (TXNIP), the activator of NLRP3, by degrading a miR-17 that destabilizes TXNIP (Lerner et al., 2012). Meantime, the PERK pathway is associated with production of IL-6 and the chemokines CCL2 and CCL20, which promote microglial activation (Guthrie et al., 2016; Meares et al., 2014). In spinal cord injury, ATF4 deficiency diminishes microglial activation and alters expression of IL-6, TNFα, and IL-1b (Hughes and Mallucci, 2019; Onate et al., 2016; Valenzuela et al., 2012).

Multiple studies show inflammation in the retina of animals with IRD. For example, rd10 mice exhibit strong upregulation of the microglia-specific genes *Cx3cr1*, *Aif1*, *Irf8*, and *C1qc* before the onset of neurodegeneration at P12 (Zhao et al., 2015a). Another study with rd1 mice demonstrates accumulation of Iba1, IL-4, and TGFβ cytokines in the retina at P14 (A et al., 2019). One study shows that NLRP3 inflammasome activation drives bystander cone cell death in a P23H rhodopsin model of retinal degeneration (Viringipurampeer et al., 2016). Another study with canine models of early-onset (*rcd1*, *xlpra2*, and *erd*) and late-onset (*xpra1*) RP shows that the inflammasome components *Nlrp3*, *Casp1*, *Asc*, *Il-1b*, and *Il-1ra* are present in the retina and participate in retinal degeneration (Appelbaum et al., 2017). Our group observed upregulation of pro-inflammatory cytokines in the retinas of T17M *RHO* and *Ter*349*Glu* mice, which show increased levels of TNFα, IL-1β, p65, monocyte chemoattractant protein-1, and IBA1 (Rana et al., 2014). Moreover, a variety of proinflammatory cytokines and chemokines, including monocyte chemotactic protein-1, are increased in the aqueous humor and vitreous fluid in RP patients as compared with control individuals (Yoshida et al., 2013). These findings lead to the conclusion that chronic inflammation may underlie the pathogenesis of RP, suggesting interventions for ocular inflammatory reactions as potential treatments for RP patients. We recently provided evidence that ATF4 and CHOP mediators of UPR PERK signaling could be responsible for elevated pro-inflammatory IL-1β cytokines in autosomal dominant RP retinas (Rana et al., 2017; Rana et al., 2014).

5.4.5 UPR and mitochondrial dysfunction—

The ER and outer mitochondrial membrane are in tight contact, with merged areas known as mitochondria-associated ER membranes (MAMs). In degenerating neurons, the association between the ER and mitochondria is stronger in the presence of accumulated Aβ and in APP Swe/Lon mice, confirming results obtained with human fibroblasts isolated from AD patients (Hedskog et al., 2013). Moreover, Aβ exposure significantly increases Ca^{2+} shuttling from the ER to mitochondria and expression of MAM-associated proteins in neurons. One common protein regulating communication between the two organelles is Sig-1R, which is highly enriched at MAMs (Hayashi, 2019). This protein interacts with BiP/GRP78/HSPA5, an UPR mediator in its dormant state. Upon dissociation from BiP, Sig-1R becomes activated and exerts innate chaperoning activity. It stabilizes IP3-R3 at MAMs and thereby regulates Ca^{2+} entry into mitochondria and ATP synthesis. In addition, Ser-1R controls expression of the transcription factors Xbp-1 and NF-KB.

In addition to physical contact and regulation of Ca^{2+} flux, the synthesis of lipids, including phosphatidylserine, steroids, and sphingolipids, also relies on communication between the ER and mitochondria (Hayashi, 2019). Despite that mitochondrial dysfunction may contribute to photoreceptor and other retinal cell degeneration in varied retinal degenerative diseases, the crosstalk between these two organelles is not understood in depth. Our laboratory and others reveal that activated apoptosis in photoreceptors arises from two apoptotic pathways—one related to the mitochondrial apoptosis-inducing factor (AIF) and other to ER-associated caspase-12 (Bhootada et al., 2015). Both AIF and caspase-12 translocate to the nucleus, which depends upon intracellular Ca^{2+} homeostasis and calpain activity (Sanges et al., 2006). However, more detailed studies characterizing ER-mitochondrial tethers in degenerating photoreceptors are necessary to determine whether all retinal degenerative diseases affect the ER-mitochondrial axis in a similar manner and how ER-mitochondrial crosstalk is regulated.

6. UPR and diseases

6.1. UPR and neurodegeneration

An activated UPR in general, and ISR in particular, are hallmarks of many neurodegenerative diseases including AD (Hoozemans et al., 2009; Lee et al., 2010), amyotrophic lateral sclerosis (ALS) (Atkin et al., 2008), and PD (Hoozemans et al., 2007), which belong to a group of diseases termed protein misfolding diseases (Chaudhuri and Paul, 2006). AD is estimated to affect as many 25 million people and is characterized by dysfunctional synapses and accumulation of phosphorylated Tau protein or β-amyloid plaque in the brain (Gerakis and Hetz, 2018). Upregulation of IRE1 and PERK signaling are detected in postmortem AD brain tissue (Hoozemans et al., 2009). In animal models, PERK signaling is activated in response to Tau accumulation (Ho et al., 2012; Hoozemans et al., 2009) but appears to precede the formation of tangles (Ho et al., 2012). In addition, PERK activation precedes localized expression of ATF4 (Baleriola et al., 2014), indicating the onset of ISR signaling.

ALS culminates in the death of motor neurons and is characterized by aggregation of ubiquitinated inclusions (Jaronen et al., 2014). ER stress is detected in brain tissue from

postmortem ALS patients and mouse models of ALS as evidenced by ER dilation, ER/Golgi fragmentation, and ribosomal detachment (Lautenschlaeger et al., 2012; Oyanagi et al., 2008). These changes to the rough ER and Golgi apparatus are involved in ALS pathogenesis in a mouse model, suggesting that ER stress could drive cell death (Stieber et al., 2000). Activation of all three arms of the UPR—PERK, IRE1, and ATF6—are reported in animal models of ALS (Jaronen et al., 2014). We also found UPR activation in animal models of PD involving α-synuclein-associated toxicity (Gorbatyuk et al., 2012b; Gully et al., 2016).

PD is characterized by the death of neurons in the substantia nigra pars compacta, which contains neurons responsible for producing dopamine, a neurotransmitter that plays a key role in regulating voluntary movement. In degenerating neurons in PD patients, misfolded α-synuclein forms inclusions known as Lewy bodies (Mercado et al., 2016). Neurons with Lewy bodies show elevated levels of phosphorylated PERK as well as ATF4 upregulation in nigral tissue from postmortem PD patients (Hoozemans et al., 2007). Activation of PERK signaling is also detected in rat (Gorbatyuk et al., 2012b) and mouse (Sun et al., 2013) models of PD. Intriguingly, induction of the pro-apoptotic protein CHOP appears to occur independently of ATF4 induction in PD (Sun et al., 2013), suggesting that ATF4 plays a pro-survival role in PD. Parkin, which is downstream of ATF4 activation, plays an important role in the survival of dopaminergic neurons. ATF4 is necessary for maintaining Parkin levels in cells after treatment with dopaminergic toxins (Sun et al., 2013). However, we show that sustained overexpression of ATF4 can also cause severe loss of dopaminergic nigral neurons (Gully et al., 2016). By contrast, IRE1-sXBP1 signaling was found to promote survival of dopaminergic neurons, as knocking out the gene encoding either of these proteins makes substantia nigra neurons more susceptible to ER stress-associated cell death (Valdes et al., 2014), indicating that the role of the IRE1-sXBP1 arm in regulating protein homeostasis is likely vital to substantia nigra neurons. This may be true of many neurons, as knocking out XBP1 in adult mice results in chronic ER stress and neurodegeneration (Valdes et al., 2014).

6.2. UPR and retinal degeneration

Interest in the UPR as a contributing factor to ocular disease progression is growing. In addition to IRD characterized by photoreceptor degeneration, other pathophysiological conditions such as glaucoma associated with deterioration of retinal ganglion cells (Marola et al., 2019); AMD driven by RPE damage (Periyasamy and Shinohara, 2017); diabetic retinopathy, a neuro-vascular diabetic complication (Zhang et al., 2015); and cataracts resulting from stressed lens epithelial cells (Berthoud et al., 2016; Ma et al., 2018; Zhou et al., 2016) have been associated with UPR activation. Activated UPR and ISR signaling is observed in several animal models of retinal degeneration including P23H RHO mice and rats (Athanasiou et al., 2018; Lin et al., 2007), T17M *RHO* mice (Choudhury et al., 2013), rd10 mice (Yu et al., 2018), Ter349Glu RHO mice (Rana et al., 2014), and Tubby mice expressing *TULP1* missense mutations (Cai et al., 2015; Lobo et al., 2016). Rhodopsin misfolding due to mutations in *RHO* is thought to play a role in photoreceptor cell death in human retinitis pigmentosa. P23H *RHO* mutation causes rhodopsin to misfold and accumulate in the ER, cell body, and nerve terminals (Gorbatyuk et al., 2010; Goto et al., 1995; Olsson et al., 1992). Lin et al. were the first to demonstrate that the retinas of P23H

RHO rats exhibit UPR activation as shown by an elevation in both *Chop* and *BiP* mRNA (Lin et al., 2007). One study describes three lines of P23H *RHO* transgenic rats expressing different copy numbers of the transgene (LaVail et al., 2018). Among these rats, the severity of retinal degeneration correlates with the ratio of transgene-to-endogenous opsin mRNA. Given that both P23H *RHO* lines 1 and 3 show activation of the UPR, it would be interesting to compare the degree of activated UPR markers in retinas with the extent of retinal degeneration and the ratio of transgene-to-wild-type opsin mRNA expression. Unfortunately, studies investigating the UPR in P23H Rho line 1 do not perform comparisons of UPR markers with wild-type retinas (Athanasiou et al., 2017a; Athanasiou et al., 2017c).

One study reported a broad list of RHO mutations trapped in the ER of COS-7-transfected cells (Behnen et al., 2018). However, additional experiments confirming their mislocalization in the retina should be conducted. Another study describes the definitive activation of PERK signaling in P23H *RHO* rats, as their treatment with a PERK inhibitor resulted in a decline in the level of phosphorylated eIF2α (Athanasiou et al., 2017b). In addition, we alleviated retinal degeneration in P23H *RHO* rats by overexpressing Grp78 via delivery of AAV vector to photoreceptors (Gorbatyuk et al., 2010), indicating that increasing the protein folding capacity of the ER is sufficient to promote survival of P23H RHO photoreceptors.

Several studies have sought to identify the role of PERK in degenerating retinas. One study reports that PERK inhibition exacerbates retinal degeneration in transgenic P23H *RHO* rats (Athanasiou et al., 2017b) and demonstrates that inhibiting the dephosphorylation of eIF2α via administration of salubrinal, a Gadd34/PP1 inhibitor, slightly ameliorates the disease. This signifies that in P23H-1 rats, PERK activation may promote photoreceptor survival. Another study confirmed these results, reporting that P23H RHO knock-in mice show UPR activation (Comitato et al., 2019) and that long-term stimulation of the PERK arm exerts a protective effect by phosphorylating NRF2 transcription, providing an antioxidant response. Our study indicates that PERK ablation in rd16 mouse photoreceptors does not change a- or b-wave scotopic ERG amplitudes (Starr and Gorbatyuk, 2019).

Moreover, photoreceptor-specific ablation of PERK in C57BL/6J mice does not affect ERG recordings at P60. As these studies utilize different animal models, the role of PERK during the course of IRD requires further clarity. In addition, the primary mode of PERK activation in these studies appears to engage different molecular players. Whereas sustained activation of phosphorylated eIF2α is proposed to be neuroprotective to P23H-1 rat retinas, the study with P23H RHO knock-in mice suggests that PERK exerts an anti-apoptotic effect by up-regulating NRF2. Therefore, we explored the role of phosphorylated eIF2α in retinal degeneration in rd16 mice (Starr and Gorbatyuk, 2019). Although the aim of our study was to delineate the role of phosphorylated eIF2α in protein synthesis, we demonstrate that specific and sustained up-regulation of phosphorylated eIF2α reduces apoptosis in rd16 mouse retinas.

Although the mechanisms of UPR activation in many neurodegenerative diseases have been characterized, they are likely much more complicated in models of retinal degeneration in which mutant proteins do not inherently misfold. One example is the Ter349Glu RHO

transgenic mouse line, which shows prominent activation of the ATF6 arm and ISR (Rana et al., 2014). These mice express transgenic rhodopsin in which the stop codon is replaced by a codon coding for glutamine, resulting in the addition of dozens of amino acids to the end of the protein (Bessant et al., 1999). In addition, Mockel et al. show that PERK signaling is at least partially responsible for the induction of apoptosis in retinal explants lacking the gene encoding Bardet-Biedl syndrome 12 (Mockel et al., 2012). We also found that rd16 mouse retinas expressing truncated CEP290 show activation of the UPR and ISR (Starr et al., 2018), resulting in sustained elevation of phosphorylated eIF2α, ATF4, and CHOP at P15 and P20.

It is completely unknown how the UPR become activated in these animal models. One similarity shared between models is that rhodopsin accumulates in the cell body due to mistrafficking (Hollingsworth and Gross, 2013; Mockel et al., 2012), but how this results in ER stress remains elusive. One possibility is the existence of a signaling network between the primary cilium and the ER. For example, Nakao et al. proposed that mislocalized phototransduction proteins such as rhodopsin could cause photoreceptor cell death by activating the adenylyl cyclase and cAMP pathway that leads to apoptosis (Nakao et al., 2012). cAMP is elevated in retinas expressing truncated rhodopsin (S334ter-4), which is known for its abnormal cellular distribution in photoreceptors due to mis-sorting problems (Green et al., 2000; Traverso et al., 2002). cAMP could further trigger the ER stress response through the cAMP/PKA pathway (Song et al., 2017).

The severity of rhodopsin mis-localization could also correlate with the rate of cell death in degenerating retinas. That is, a study shows that ERG responses in cyclic dark-reared S334ter-4 rats are 116% and 87% (a- and b-waves, respectively) greater than those in light/dark-reared rats (Green et al., 2000). The researchers proposed three scenarios by which apoptosis could occur in photoreceptors. In the first scenario, production of mutant proteins overwhelms the normal vesicular machinery of the plasma membrane and interferes with the routing of cargo. In the second scenario, the physical presence of high levels of mutant opsin in the plasma membrane interfere with normal neurotransmitter release in the synaptic zone. For example, mutations in genes encoding PDE6 subunits (i.e., *PDE6A*, *PDE6B*, *PDE6C*, *PDE6G*, *PDE6H*) prevent cGMP hydrolysis and thus lead to excessive accumulation in photoreceptors (Power et al., 2020). In the third scenario, the degradation of large amounts of mis-sorted proteins produces damage resulting from the metabolic load placed on photoreceptors.

Consistently, we found that rd16 mouse retinas with ongoing UPR exhibit both mis-localization of rhodopsin and up-regulation of adenylyl cyclase (Figure 3). Another possible explanation for UPR activation in these retinas is that the accumulation of rhodopsin in the cell body results in the back-up of proteins in the ER. However, neither of these two possibilities has been investigated. Finally, accumulation of proteins could affect cellular processes that signal for or result in UPR activation. For example, in a model of AD, β-amyloid oligomers or fibrils directly interact with N-methyl-D-aspartate receptors and perturb cytoplasmic Ca^{2+} balance, resulting in ER stress-dependent apoptosis (Alberdi et al., 2013).

Our research shows that targeting the UPR can retard retinal degeneration. One therapeutic strategy is to diminish ATF4 expression in T7M RHO retinas, which delays the onset of IRD by up to 3 months (Bhootada et al., 2016). Although this is also true in rd16 mice (Figure 3), the precise mechanism of ATF4-mediated cytoprotection is unknown, and this would be challenging to determine as ATF4, together with CHOP, controls the expression of 575 genes (Han et al., 2013). For example, the delay of photoreceptor cell death in rd16 mice is associated with enhanced synthesis of proteins in general and rhodopsin in particular (Figure 3). Among those proteins with altered expression levels could be those with anti-apoptotic activity. It is also worth noting that an increased translational rate is associated with accumulation of RHO in rd16 *ATF4*$^{+/-}$ retinas. Therefore, future studies are needed to understand modifications in translational profiles and verify whether expression and activation of the translational repressor 4e-BP1 is altered in rd16 *ATF4*$^{+/-}$ retinas. Our study of rd16 mice deficient in this unique ATF4 downstream target (Han et al., 2013) demonstrates not only an enhanced translational rate but also preservation of photoreceptors (Starr et al., 2019).

Therefore, similarities in stress signaling among animal models of neurodegeneration of the brain and retina can provide researchers with potential targets that could impact many diseases.

7. Animal models for studying the UPR in the retina

In this section, we describe mouse models available for studying the UPR in the retina to improve our understanding of IRD.

7.1. PERK KO mice

In a pioneering study, Zhang et al. examined the effect of systemically knocking out *Perk* in mice, providing the field with clues as to the importance of this protein (Zhang et al., 2002). Most PERK KO mice die before or shortly after birth (Zhang et al., 2002). As PERK is required for proper function of the pancreas (Gao et al., 2012; Zhang et al., 2002) and skeletal system development (Xiong et al., 2017; Zhang et al., 2002), pancreatic atrophy is likely the primary cause of lethality in these mice. The fact that PERK KO mice are not viable makes studying the role of PERK in specific cells and tissues challenging. However, the invention of the CRE-lox system helped overcome this issue and enables further investigation of the role of PERK (Gao et al., 2012; Nguyen et al., 2018; Sidoli et al., 2016; Xiong et al., 2017; Yang et al., 2016b; Zhang et al., 2002). By crossing *Perk*-floxed mice with those expressing Cre recombinase, *Perk* can be knocked out at specific times or in specific tissues or cell types. Although compounds that inhibit PERK were discovered (Axten et al., 2012), it was quickly realized that these compounds are highly toxic and have targets other than PERK (Rojas-Rivera et al., 2017), again making research on the role of PERK in certain tissues difficult without introducing a Cre-flox system through breeding, which is time-consuming. Despite the complicated breeding needed to introduce Cre into an animal, this system is an extremely powerful tool for studying proteins of interest without affecting other tissues, making data analysis much more streamlined. A mouse model was developed to express Cre on the mouse opsin promoter, iCre75, which restricts Cre

expression to rods (Li et al., 2005). Like rhodopsin, these mice start to express Cre around P7, making them particularly useful for knocking out genes that could be involved in retinal development but problematic for studying the development of photoreceptors. Our recent work with the rd16 mouse model of IRD highlights the role of PERK in photoreceptor homeostasis using a conditional PERK KO to avoid the issue of pancreatic atrophy. We demonstrate that knocking down PERK does not affect the loss of retinal function (Starr and Gorbatyuk, 2019). However, given that recombination occurs around loxP sites at P7 and persists as late as P18 (Li et al., 2005), we could not assess whether PERK is important for photoreceptor development. Moreover, we found that PERK deficits in unstressed C57BL6 mouse retinas do not cause any retinal abnormalities at P60. Two recent studies examining the role of PERK in mouse and rat models of IRD using PERK inhibitors (Athanasiou et al., 2017a; Comitato et al., 2019) show that PERK plays a protective role in the survival of P23H rhodopsin photoreceptors. In one study, inhibiting PERK with GSK2606414A led to inhibited eIF2α phosphorylation, reduced ERG function, and decreased photoreceptor survival. In the other study, long-term stimulation of the PERK arm of the ER stress response exerted a protective effect by phosphorylating NRF2 and thus bestowing an antioxidant response. In our previous study of rd16 mice with chronically activated UPR compared with wild-type mice, we found that ablation of PERK had no deleterious effects in C57BL6 mice and did not exacerbate IRD (Starr and Gorbatyuk, 2019). However, we must mention that the aim of this study was not to assess whether PERK ablation affects cell viability but to examine the role of up- or down-regulated phosphorylated eIF2α in promoting retinal degeneration, and we proposed that the role of PERK must be validated in other animal models of retinal degeneration. Although we emphasized in this study that deficient PERK does not kill photoreceptors in C57BL6 mice, this deficit must be studied under stress conditions in C57BL6 mice to understand the physiological meaning of PERK knockdown in healthy and diseased retinas.

7.2. GADD34 KO mice

The primary function of GADD34—initiation of PP1-mediated dephosphorylation of eIF2α—was not adequately demonstrated until the gene encoding Gadd34 (*Ppp1r15a*) was knocked out in mice (Kojima et al., 2003). Systemically knocking out *Gadd34* results in viable mice (Kojima et al., 2003) that are generally healthy with a few exceptions. Mice lacking GADD34 eventually become obese and are more likely to develop nonalcoholic fatty liver disease (Nishio and Isobe, 2015). In addition, they are more susceptible to developing hepatic carcinoma (Nishio et al., 2017; Nishio and Isobe, 2015) and insulin resistance (Nishio and Isobe, 2015). Furthermore, mice lacking GADD34 develop a blood disease resembling thalassemia syndrome (Patterson et al., 2006). Additionally, female *Gadd34*$^{-/-}$ mice exhibit systemic inflammation (Nishio et al., 2017). These mice likely exhibit other problems that are not yet characterized. Nevertheless, they are currently the best option for studying the role of GADD34 even though we cannot discount the possibility that these abnormalities could have systemic consequences. Future endeavors employing *Gadd34*-floxed mice may provide a better understanding of the role of this protein in various tissues, including the mechanism of translational control in rd16 mouse retinas (Starr and Gorbatyuk, 2019).

7.3. CHOP KO mice

CHOP (also known as GADD153), a bZIP transcription factor, is strongly induced by ER stress (Wang and Ron, 1996). It is upregulated by the PERK pathway, although other UPR pathways may also contribute to its expression. It is a pro-apoptotic factor that promotes the transcription of several stress-related genes in response to stress (Bartlett et al., 1992; Ron and Habener, 1992; Wang et al., 1996). CHOP-deficient mice exhibit no abnormalities in development and display reduced apoptosis due to a lack of repression of the anti-apoptotic protein BCL-2, which could contribute to CHOP-mediated apoptosis (McCullough et al., 2001). Despite this fact, apoptosis still occurs in *Chop*$^{-/-}$ animals with ongoing ER stress, suggesting that other CHOP-independent mechanisms of cell death are activated in response to ER stress.

7.4. ATF4 KO mice

ATF4 KO mice show abnormalities in perinatal and postnatal development (Masuoka and Townes, 2002). Around 70% of animals die between embryonic day 17.5 and P14, and the remaining 30% survive until adulthood but display growth retardation and severe micropthalmia. Therefore, we and other research groups have used ATF4 hemizygous animals to validate role of this UPR marker.

8. Translational apparatus and control of protein synthesis

8.1. 5’ cap and IRES translation

Eukaryotic protein synthesis occurs through two modes of translation that coexist in cells: canonical or 5’-cap-dependent translation and non-canonical translation requiring an internal ribosome entry site (IRES) sequence located on the 5′ untranslated region (UTR) of mRNA. The difference between the two modes relies on their utilization of the 5’ cap initiation complex. The first mode is responsible for 85–90% of all synthetized proteins. The second mode requires a reduced subset of initiation factors and accounts for up to 10–15% of the remaining proteins (Komar and Hatzoglou, 2015; Leppek et al., 2018). Translation is generally achieved in three steps: initiation, elongation, and termination. Due to our interest in the initiation step of translation in healthy and diseased retinas, we focus primarily on this step.

Initiation of 5’ cap-dependent translation occurs through multiple steps including mRNA activation, scanning, ATG recognition, and joining to the 60S ribosomal subunit for further elongation (Figure 2). The TC is formed when GTP-bound eIF2 binds the initiator Met-tRNA (Barrieux and Rosenfeld, 1977; Kaempfer et al., 1978; Lorsch and Dever, 2010; Walton and Gill, 1976). Upon activation, the TC interacts with the 40S ribosomal subunit and other translation initiation factors, including eIF1, eIF1A, and the eIF3 complex (13 subunits from a-m) (Phan et al., 2001; Valasek et al., 2001). Together, these components form the 43S pre-initiation complex (PIC). All factors in the PIC are important for start codon recognition (Lorsch and Dever, 2010). The 43S PIC is then recruited to the 5’ prime end of a 7-methyl guanosine (m^7G) cap of an mRNA by the eIF4F complex (Lorsch and Dever, 2010). The eIF4F complex consists of the cap binding protein eIF4E (Sonenberg et al., 1978), the helicase eIF4A (Lorsch and Herschlag, 1998), and the scaffolding protein

eIF4G (Tarun et al., 1997). eIF4G creates a loop in the entirety of the mRNA by binding the poly A-tail and m^7G cap, which are located at the 3' and 5' regions of a typical mRNA, respectively (Le et al., 1997; Tarun and Sachs, 1996). Once recruited to the mRNA, the PIC scans for a start codon in an ATP-dependent manner (Walton and Gill, 1976). When the anti-codon for Met-tRNA is found and bound in the P, or peptidyl, site of the ribosome, the GTP associated with eIF2 is hydrolyzed, releasing a phosphate in the process (Marcus and Feeley, 1966; Merrick, 1979). This process is mediated by eIF5, the GTPase-activating protein for eIF2 (Asano et al., 1999). For the translation elongation step to begin, the 60S ribosomal subunit must join the complex, which requires the displacement of several factors including eIF2-GDP, eIF1A, eIF3, eIF1, and eIF5 (Kearse and Wilusz, 2017). Recruitment of the 60S ribosomal subunit to the complex utilizes GTP, a process mediated by eIF5B (Asano et al., 1999).

Most mechanisms that negatively regulate translation target components of the initiation complex, which benefits cells energetically. Several steps in translation utilize high-energy phosphates in the form of ATP or GTP. Stopping translation before these hydrolyzation events is critical for the survival of energy-starved cells (Kearse and Wilusz, 2017). The best studied mechanisms of protein synthesis inhibition involve the regulation of eIF2 and eIF4E (Gingras et al., 1999; Sonenberg and Hinnebusch, 2009; Taniuchi et al., 2016). Following a cellular stressor such as nutrient deprivation, viral infection, or ER stress, one or both of these factors can be targeted to reduce translation rates (Sonenberg and Hinnebusch, 2009). Control of protein synthesis through these two factors has been a focus of our resent research (Starr and Gorbatyuk, 2019; Starr et al., 2018).

IRES mediates translation initiation independently of the cap through binding eIF3. Similar to 5' cap-dependent translation, eIF3 controls assembly of mRNA with a 40S ribosome and formation of an IRES RNA-40S-eIF3 TC. In addition to varied eIFs, IRES translation also requires IRES trans-acting factors, the role of which is still under investigation. Such RNA chaperones could remodel the IRES structure to prepare a landing platform for the ribosome. The IRES element is commonly located on the 5' UTR of RNA. Recruitment of the internal ribosome by IRES-containing mRNAs may be promoted by environmental changes favoring bypassing the 5′ cap region to keep up with protein expression when cap-dependent translation is weakened (Leppek et al., 2018). Such conditions could be cellular stress, mitosis, or apoptosis, resulting in reduced global cap-dependent translation. Cells may also increase the translation of certain proteins during programmed cell death. Ten to 15% of mammalian mRNAs are predicted to contain an IRES element (Leppek et al., 2018). Over 100 proposed IRES-containing eukaryotic mRNAs have been identified (Mokrejs et al., 2010). Among them are varied transcription (ATF4, NF-KB, C-JUN) and translational (eIFs) factors, chaperones (Grp78, HSP70, HSP90), growth factors (FGF-1/2, PDGF, VEGF, IGF2), apoptosis inhibitors (XIAP, Bcl-xL, Bcl2), apoptosis activators (Apaf1), and other regulatory molecules. Although the evidence for IRES-regulated mRNA translation was found more than a decade ago, the importance of eukaryotic RNA structure for IRES activity has only been discovered for some RNA structures and cellular IRESs.

Several well-studied mechanisms of non-canonical translation provide clues as to how *ATF4* mRNA is regulated. Normally, genes with multiple uORFs with AUG start codons allow

translation to begin, but downstream sequences have certain properties that make the ribosome stall, preventing the translation of downstream reading frames. The reason for the stall is often due to the existence of regions of RNA that form stable hairpins shortly after the start codon(Kearse and Wilusz, 2017). Although the mechanism that results in re-initiation at the downstream ORF is also a mystery, it likely involves a well-studied set of factors. Canonical translation requires Met-tRNA to be brought to the 43S PIC by eIF2. The anti-codon on Met-tRNA binds the triplet AUG. Therefore, when stress results in the phosphorylation of eIF2α, the PIC must find another way to initiate translation. A mechanism known as non-AUG translation is a process that occurs in all cells at a lesser frequency than canonical translation. One mechanism of non-AUG translation involves eIF2α (Komar et al., 2005) or eIF2D (Dmitriev et al., 2010) interacting with the PIC and binding non-AUG start sites. Interestingly, these factors do not require GTP to initiate translation, which differs from eIF2-mediated initiation or translation elongation (Dmitriev et al., 2010; Kearse and Wilusz, 2017; Komar et al., 2005). In addition, both of these factors are upregulated following cellular stress, consistent with a potential role of ATF4 activation. Interestingly, translation of BiP, another protein whose mRNA has uORFs, depends on eIF2A (Starck et al., 2016), further suggesting a role for eIF2A and non-AUG initiation in ER stress.

8.2. Two modes of regulation of 5’ cap-dependent translation

Protein synthesis requires cells to expend a great amount of energy, and the translation process is tightly regulated (Hinnebusch, 2017; Hinnebusch and Lorsch, 2012; Ryoo and Vasudevan, 2017; Sonenberg and Hinnebusch, 2009). Two major modes of translational control are currently known (Figure 4). In one approach, PERK phosphorylates and activates eIF2α during ISR. In the other approach, the phosphorylation state of translational repressors, eIF4E-binding proteins (4E-BP1, 2, and 3), is altered (Gingras et al., 1999; Gingras et al., 1998). Interestingly, ATF4 elevation during ER stress could connect both pathways via back loop-mediated control of phosphorylated eIF2α and the direct transcription of 4E-BPs as it has been shown in tissue culture (Han et al., 2013) and *Drosophila* (Ryoo and Vasudevan, 2017) systems. Recent research demonstrates that both mechanisms are dysfunctional in mice with IRD (Kunte et al., 2012; Lin et al., 2018; Punzo et al., 2009; Starr et al., 2018). Phosphorylated eIF2α prevents the eIF2 complex from directing Met-tRNA to the pre-initiation complex, resulting in translational inhibition. We and other investigators observe elevated phosphorylated eIF2α in the retinas of mice with IRD (Athanasiou et al., 2017b; Kunte et al., 2012; Starr et al., 2018). Despite this fact, the role of eIF2α in retinal pathogenesis has not been addressed until recently.

8.2.1. Regulation of protein synthesis through phosphorylated eIF2α—

Phosphorylated eIF2α can stop the global production of protein synthesis to allow cells to recover from accumulation of misfolded proteins during acute stress (Figure 4). Interestingly, varied animal models of retinal degenerative diseases and neurodegenerative disorders, including PD and AD, exhibit chronic activation of phosphorylated eIF2α along with a reduced translational rate. Therefore, we became interested in the role of phosphorylated eIF2α in controlling the translational rate during chronic stress. Our previous study indicates that the primary point of translational control in IRD may not occur

through eIF2α (Starr et al., 2018). That is, we found that although PERK is responsible for phosphorylating eIF2α, it does not play a major role in regulating protein synthesis in degenerating retinas with chronic UPR activation. Furthermore, using two genetic approaches—systemic GADD34 KO and photoreceptor-specific conditional PERK KO—we demonstrate that altering phosphorylated eIF2α levels in rd16 mice is insufficient to delay retinal degeneration (Starr and Gorbatyuk, 2019). Nevertheless, multiple research groups report that PERK-mediated modulation of eIF2α and downstream signaling may be a viable strategy for treating neurodegenerative diseases (Athanasiou et al., 2017a; Comitato et al., 2019).

8.2.2. Regulation of protein synthesis through eIF4E—Global rates of protein synthesis in the retina have not been assessed until recently. Our group was the first to demonstrate chronic inhibition of translation in various models of IRD (Starr et al., 2018) (Figure 5). This study fueled our interest in further investigating the molecular control of protein synthesis in degenerating retinas (Starr and Gorbatyuk, 2019; Starr et al., 2019; Starr et al., 2018).

In 1978, Sonenberg et al. discovered that eIF4E is the m^7G cap binding protein of the heterotrimeric eIF4F complex (Sonenberg, 2008; Sonenberg et al., 1978) and the canonical rate-limiting initiation factor. Thus, by negatively regulating eIF4E, cells can shut off synthesis of the vast majority of proteins (Gingras et al., 1998; Sonenberg, 2008; Sonenberg and Hinnebusch, 2009) (Figure 4). Depending on their hyper- or hypo-phosphorylated status, 4E-BPs can interact with eIF4E and prevent it from joining the cap-binding complex, reducing protein synthesis (Gingras et al., 1999; Gingras et al., 1998). The more Ser/Thr sites become phosphorylated, the weaker the affinity of 4E-BPs for eIF4E (Gingras et al., 1998). Also, 4E-BP1 phosphorylation is downregulated in both rd16 and rd10 mouse retinas (Starr et al., 2018). Despite advances in our knowledge of translation inhibition in neurodegeneration (Jan et al., 2018; Ma et al., 2013; Mercado et al., 2018; Moreno et al., 2012; Radford et al., 2015; Sharma et al., 2018), it is unclear whether a decline in protein synthesis is protective or whether increasing translation rates could be a viable neuroprotective strategy in IRD. Therefore, we conducted a study to decipher the role of translational attenuation in degenerating retinas during the course of IRD (Starr et al., 2019) using a comprehensive approach including applying pharmacological compounds, inhibiting protein synthesis, overexpressing constitutively active (i.e., less phosphorylated) 4E-BP1 in wild-type retinas via AAV gene delivery, and genetically ablating 4e-BP1/2 in the retinas of rd16 mice. For the first time, we reported that restoring protein synthesis rates delays retinal degeneration in mice (Starr et al., 2019).

The activity of 4E-BPs is regulated by mTOR phosphorylation. The mechanistic target of mTOR is a kinase that is coined the master regulator of protein synthesis and cellular metabolism (Chen, 2004; Sandsmark et al., 2007). mTOR is a kinase that forms the core of two complexes known as mTOR complex 1 (Kim et al., 2002; Nojima et al., 2003) and 2 (Jacinto et al., 2004; Sarbassov et al., 2004) (mTORC1 and mTORC2), which are involved in the regulation of protein synthesis and autophagy, respectively. mTOR forms a complex with multiple proteins including regulatory-associated protein of mTOR (Raptor), DEP domain-containing mTOR-interacting protein (DEPTOR), proline-rich AKT1 substrate 1

(PRAS40), and mammalian lethal with SEC13 protein 8 to form mTORC1 (Figure 6). Each of these proteins regulates the activity of mTOR in some way. Raptor promotes the phosphorylation of mTORC1 targets (Hara et al., 2002; Kim et al., 2002), whereas DEPTOR inhibits mTOR (Liu et al., 2010; Peterson et al., 2009). PRAS40 is a target of mTOR and a positive intermediate of mTORC1 signaling (Fonseca et al., 2007). Various external stimuli signal for the activation of mTOR through phosphorylation at multiple sites. Interestingly, we and other investigators observe downregulation of mTOR in degenerating retinas (Lin et al., 2018; Punzo et al., 2009; Starr et al., 2018). Moreover, the stimulation of the insulin/mTOR pathway delays cone death in a mouse model of RP (Punzo et al., 2009).

One well-studied activator of mTORC1 is protein kinase B, or AKT, a serine/threonine protein kinase (Inoki et al., 2002). Many external stimuli, which are often growth factors, initiate signaling cascades that converge to activate AKT (Burgering and Coffer, 1995), making it a central mediator of metabolic signaling. The general model of AKT activation involves a growth factor or hormone, such as insulin, that activates a receptor tyrosine kinase (Burgering and Coffer, 1995). Full activation of AKT is not achieved until it is phosphorylated at Ser473 by PDK2 or mTOR (Alessi et al., 1997; Partovian and Simons, 2004; Rane et al., 2001; Zhang et al., 2012). When AKT is active, it phosphorylates and alters the activity of several key players in many signaling cascades. For example, AKT activates mTORC1 by phosphorylating and inhibiting tuberous sclerosis 1 and 2 (TSC1/2), key negative regulators of mTORC1 (Gao and Pan, 2001; Inoki et al., 2002; Zhang et al., 2003a). When no longer inhibited by TSC1/2, mTORC1 promotes cell growth and division. To regulate translation, mTOR directly phosphorylates regulators of protein synthesis, including 4E-BPs (Gingras et al., 1999; Gingras et al., 1998) and S6 kinase (Garami et al., 2003). We demonstrated that the pAKT axis is downregulated in degenerating retinas of mouse models of IRD (Starr et al., 2018), and others validated the AKT gene transfer approach to rescue degenerating photoreceptors (McDougald et al., 2019).

9. Current therapeutic strategies for neuroprotection from degenerating photoreceptors

Currently, there are no therapies that effectively cure IRD. Thus, supportive care is the main approach to managing these diseases. Some evidence indicates that antioxidant vitamins slow IRD progression (Fahim, 2018). Recent studies show that 20 mg β-carotene, a less toxic form of vitamin A, increases scotopic and photopic b-wave ERG amplitudes (Rotenstreich et al., 2013). Also, the concentration of docosahexaenoic acid in red blood cells is associated with the rate of RP progression (Berson et al., 2010; Berson et al., 2004). As smoking and UV light are believed to be causative factors for retinal degeneration, precautions such as sunglasses are recommended for RP patients. Retinal prostheses have recently been designed to manage end-stage patients and hold promise for improving their quality of life. While these approaches may help manage RP, gene and stem cell therapy are the only currently available options for slowing down the rate of IRD progression. Since the first FDA-approved clinical trial for RPE65-associated LCA, several other clinical trials with IRD patients have begun (Vazquez-Dominguez et al., 2019), including those testing the use of AAV gene delivery and pharmacological compounds targeting ABCA4, CHM, CNGA3,

CNGB3, MERTK, PDE6B, RPE65, RLBP1, RPGR, RS1, CEP290, and non-syndromic RP. Due to our interest in AAV-mediated gene transfer, we generated a double-mutant R585, 588A AAV vector that shows better transduction in the eye compared with other wild-type and mutant viruses (Gorbatyuk et al., 2019). Our laboratory is also investigating a new generation of viruses (Gorbatyuk et al., 2019) that could target the UPR-associated markers ATF4 and 4e-BP1 in mice with IRD and ongoing UPR activation.

9.1. UPR as a target in retinal degeneration

Suppression of chronic UPR activation as a therapeutic strategy was validated in different preclinical animal and cellular models of retinal degeneration. We demonstrated that AAV-mediated delivery of Grp78/BiP protein, a UPR marker, protects P23H *RHO* transgenic rats from photoreceptor deterioration and vision decline (Gorbatyuk et al., 2010). Later, another group found that BiP prevents rod opsin aggregation *in vitro* (Athanasiou et al., 2012). A more recent study proposes that pharmacological interventions against pathogenic ER stress should promote a favorable ratio of BiP to its disease-causing client protein (Vitale et al., 2019). Therefore, future experiments should determine the BiP-to-mutant rhodopsin ratio that provides therapeutic effects in degenerating retinas.

The FDA-approved 4-phenylbutyrate (PBA) is another chaperone validated for mutant rhodopsin folding in *vitro* (Mendes and Cheetham, 2008). P23H RHO folding is improved in SK-N-SH cells expressing the P23H-GFP opsin treated with 4-PBA. Additionally, this chaperone, together with Hsp90 inhibitor and 17-AAG compound, was recently tested *in vitro* and *in vivo* (Aguila et al., 2014); rats expressing the R135L rod opsin treated with HSP90 inhibitor in combination with 17-AAG show an improvement in P135L RHO mislocalization compared with wild-type rats. In 661W cells, 4-PBA reduces thapsigargin-induced elevations in CXCL10 and CCL2 expression and diminishes ER stress (Zhu et al., 2017). Recently, the ability of 4-PBA to improve P23H *RHO* folding and reduce ER stress was directly tested in mice (Qiu et al., 2019); treatment with this molecule significantly reduces the number of apoptotic cells and normalizes the autophagy flux-to-proteasome activity ratio, resulting in photoreceptor survival. Treatment with curcumin also improves the folding and proper localization of newly synthetized mutant rhodopsin in P23H *RHO* rats as well as retinal morphology, physiology, and gene expression (Vasireddy et al., 2011).

Over the course of IRD, other retinal cells, such as RPE and retinal ganglion cells, could also degenerate through activation of the ER stress response, suggesting that an AAV-mediated approach targeting UPR reprogramming could also be applied to these cell types. For example, overexpression of p58IPK (McLaughlin et al., 2018), GRP78 (Ha et al., 2018), or X-box binding protein 1 (Yang et al., 2016a) promotes retinal ganglion cell survival, whereas overexpression of GRP78/BIP increases RPE viability under ER stress (Ghaderi et al., 2018). In human RPE cells expressing mutant L22P RPE65 protein, application of 4-BPA chaperone in combination with a low temperature rescues enzymatic activity and may be a promising “protein repair therapy” that could enhance the efficacy of gene therapy (Jin et al., 2016).

Small molecules such as integrated stress response inhibitor (ISRIB) have been validated in patient keratoconic fibroblasts (Soiberman et al., 2019); inhibition of the ISR relieves many

hallmarks of the keratoconic phenotype in affected cells, suggesting that targeting the ISR through ISRIB could have therapeutic potential. This molecule, however, has not been extensively tested in animal models of IRD. Our unpublished data from T17M *RHO* transgenic mice show that application of ISRIB does not improve rod function. However, this treatment slows down cone functional loss, suggesting that future experiments are required to carefully investigate the therapeutic potential of ISRIB.

Finally, a mini-peptide targeting ATF4, H2-MRAKWRKKRMRRLKRKRRKMRQ RSK-OH, was validated in an animal model of oxygen-induced retinopathy (Geng et al., 2018). Although different from IRD, this model is associated with ATF4 elevation (Wang et al., 2013). Thus, it would be interesting to test this peptide in preclinical animal models of IRD known to show ATF4 upregulation. This approach could be particularly valuable when large cDNA insertions, such as those coding for CEP290 or RPGR (290 and 113 kD, respectively), would render AAV gene delivery problematic due to instability and difficulties in maintaining a recombinant vector.

Conclusion:

Pharmacologically based therapies targeting a chronic ER stress response alone or in a combination with gene therapy could be valuable neuroprotective strategies for degenerating retinas.

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List of abbreviations

PERK	Pancreatic endoplasmic reticulum kinase-like endoplasmic reticulum kinase
IRE1	Inositol-requiring kinase/endoRNase 1
ATF6	Activating transcription factor 6
GRP78	Glucose-regulated protein 78
BiP	Binding immunoglobulin protein
eIF2α	Eukaryotic transcription factor 2α
ATF4	Activating transcription factor 4
CHOP	C/EBP homologous protein
GADD153	Growth arrest and DNA damage inducible gene 153
GADD34	Growth arrest and DNA damage inducible gene 34
PP1	Protein phosphatase 1

XBP1	X box-binding protein 1, transcription factor
4eIF-BPs	Eukaryotic translation initiation factor 4E-binding proteins
IRD	Inherited retinal degeneration
RP	Retinitis pigmentosa
LCA	Leber’s congenital amaurosis
TRB3	Tribbles homolog 3 protein
ERAD	Endoplasmic reticulum-associated degradation
eIF4E	Eukaryotic translation initiation factor 4E
mTOR	Mammalian target of rapamycin
AKT	Protein kinase B
UPR	Unfolded protein response
ISR	Integrated stress response
TM	Tunicamycin

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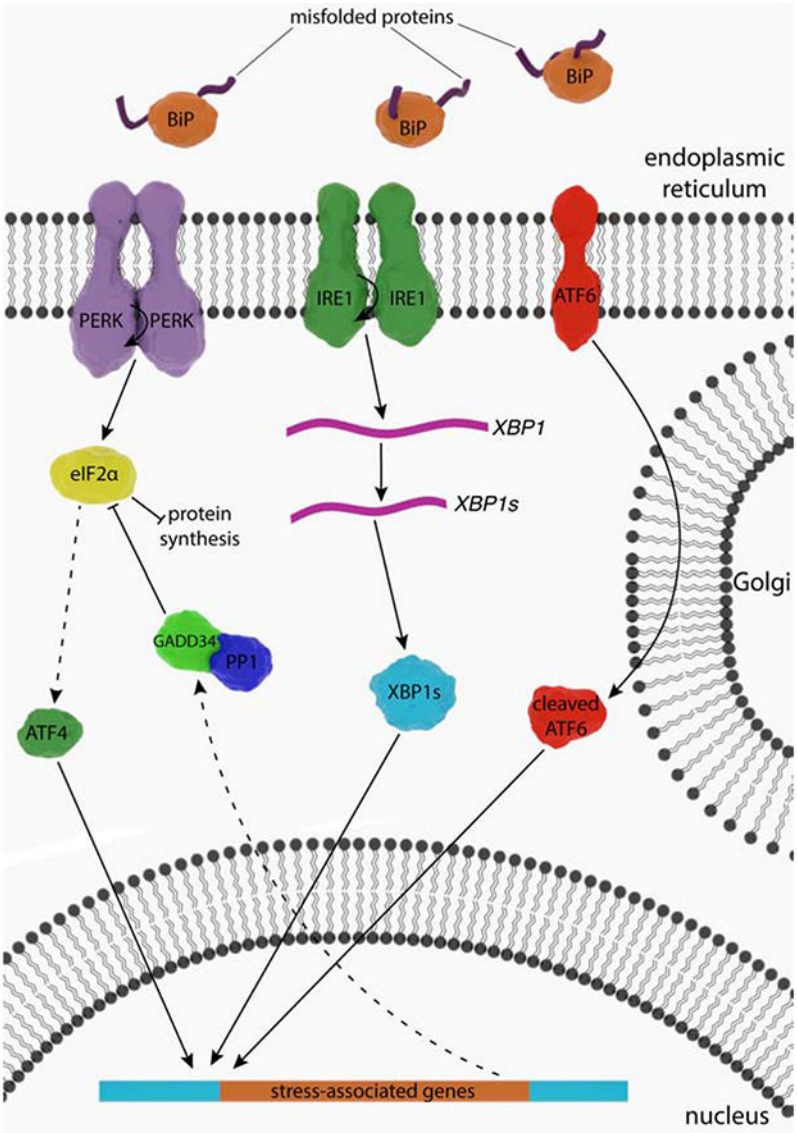

Figure 1.

The UPR. Schematic depicting signaling through the three ER transmembrane proteins—PERK, ATF6 and IRE—during ER stress. BiP dissociation results in activation of all three membrane proteins. PERK attenuates protein synthesis through phosphorylation of eIF2α. IRE1 and ATF6 proteins activate specialized transcriptional programs to help alleviate ER stress. IRE1 phosphorylation results in unconventional splicing of XBP1 mRNA, which promotes transcription of stress-induced genes.

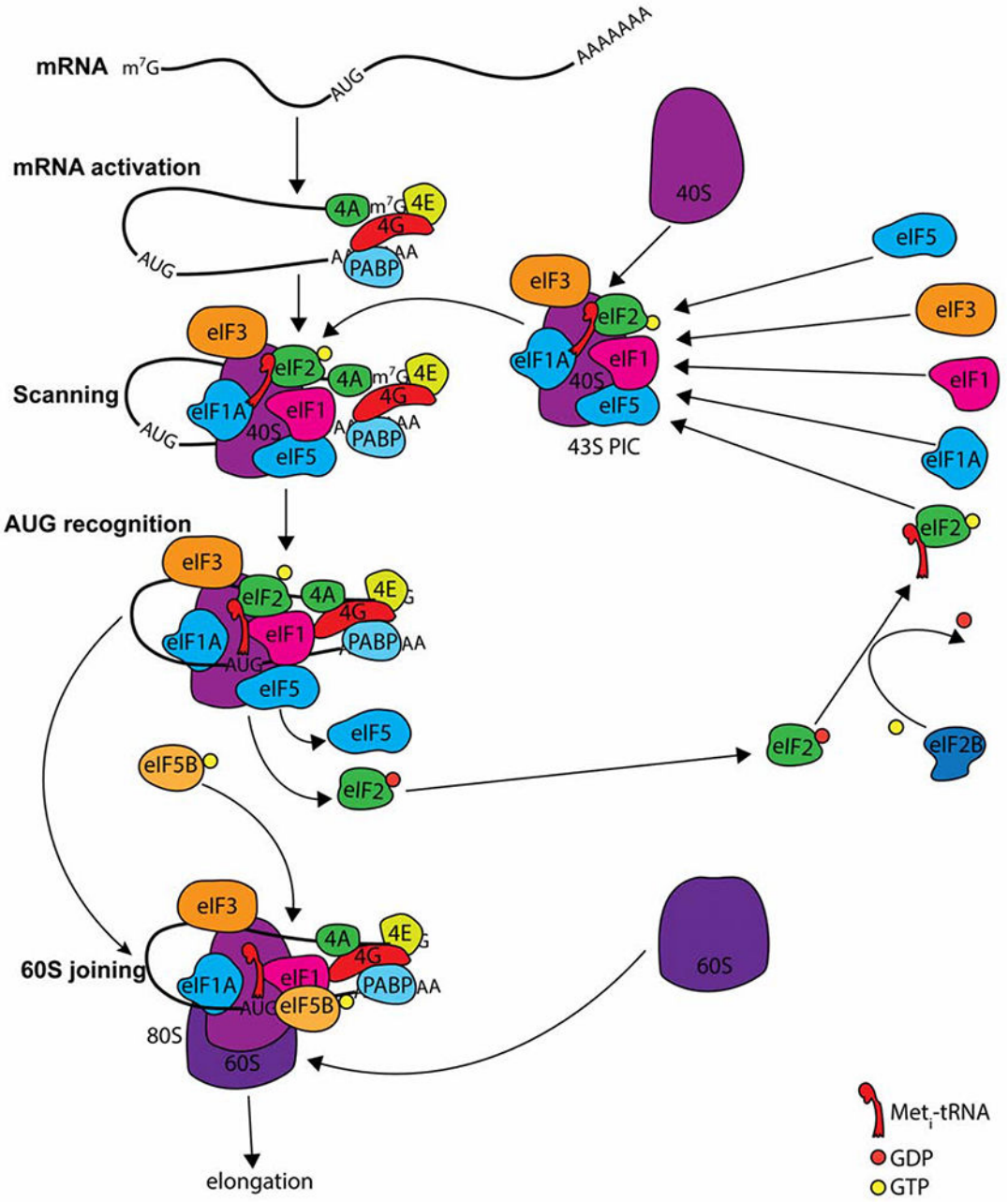

Figure 2.

Depiction of translation initiation. Many factors are involved in protein synthesis regulation. Step 1: Formation of the 43S PIC when Met-tRNA$_i^{Met}$ is delivered by eIF2 to the P site of the 40S ribosomal subunit. Step 2: Recruitment of the 43S complex to the 5' end of the mRNA by eIF3 and eIF4 factors. mRNAs are activated by the eIF4F complex (4E, 4G, and 4A) and Poly A binding protein (PABP). Multiple factors (eIFs 1, 1A, 2, 3, 5) join the 40S ribosome to generate the 43S PIC. eIF2 brings the initiator Met-tRNA to the complex. Step 3: Scanning of the 5' UTR and recognition of the AUG codon. The complex scans while eIF1 and 1A keep the complex inactive. When the AUG is found, GTP on eIF2 is hydrolyzed in a process mediated by eIF5, and eIF2-GDP leaves the complex. eIF2-GDP

must be reactivated to eIF2-GTP by eIF2B for eIF2 to begin another round of initiation. Step 4: Assembly of the 80S ribosome. eIF5B promotes joining of the 60S ribosome to form the first peptidyl bond, which is followed by elongation. Adapted from Hinnebusch AG, *Trends in Biochemical Sciences*, 2017.

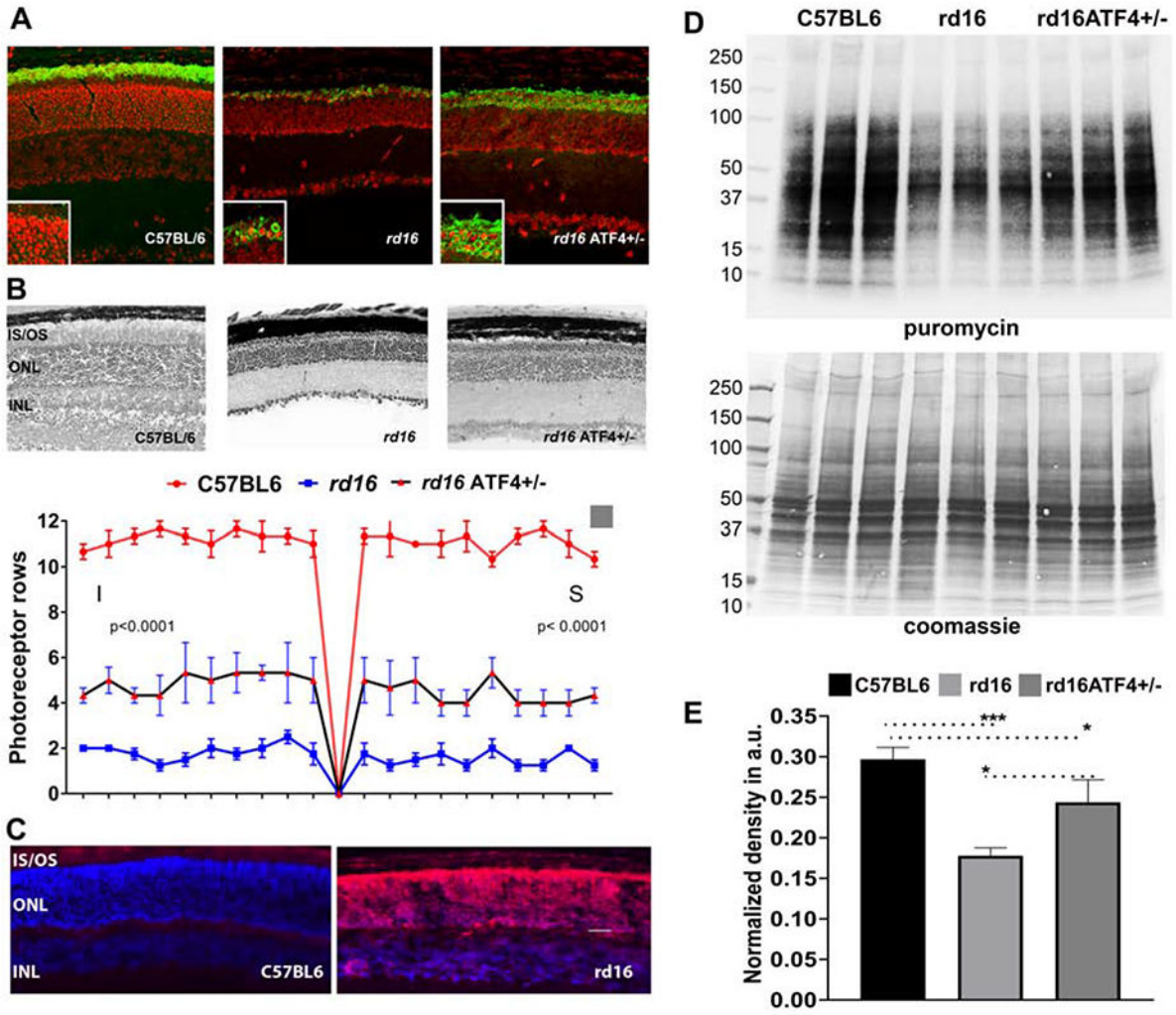

Figure 3.

Molecular mechanisms of retinopathy in rd16 mice. Immunohistochemical analysis of C57BL6, rd16, and rd16 *ATF4*$^{+/-}$ retinas show mislocalization of rhodopsin in rd16 retinas at P18 (unpublished data). Detection of rhodopsin (green) was performed using primary anti-rhodopsin antibody ID4. Propidium iodide was used to stain retinal cell nuclei (red) (A). Delay of photoreceptor cell death in rd16 *ATF4*$^{+/-}$ retinas. H&E-stained retina sections are shown in the upper panel, and counts of photoreceptor rows are shown in the bottom panel (B). P15 rd16 retinas show significant accumulation of adenylyl cyclase (red) in the ONL. Based on the mechanism proposed by Nakao et al., this mislocalization could contribute to the retinal pathophysiology of rd16 mice (C). Study of the molecular mechanisms responsible for the delay of retinal degeneration in *rd16 ATF4*$^{+/-}$ retinas demonstrates enhanced synthesis of proteins in general (D) and rhodopsin in particular (A). Protein synthesis was assessed by the SUnSET method (Starr et al., 2019). C57BL6, *rd16*, and *rd16* ATF4$^{+/-}$ mice were intraperitoneally injected with puromycin at a dosage of 0.04 μmol/g body mass. After 30 min of puromycin injection, retinas were harvested. Retinal proteins with incorporated puromycin were extracted in RIPA buffer, and their concentrations were estimated. Protein (60 μg) was separated by SDS-PAGE and transferred to a PVDF

membrane, which was then probed with anti-puromycin antibody. A secondary antibody specific for IgG2a was also applied. As a loading control, membranes were stained with Coomassie blue after washing with distilled water (D). The relative densities of entire lanes were measured using ImageJ software. Puromycin densities were normalized to their corresponding Coomassie densities (E).

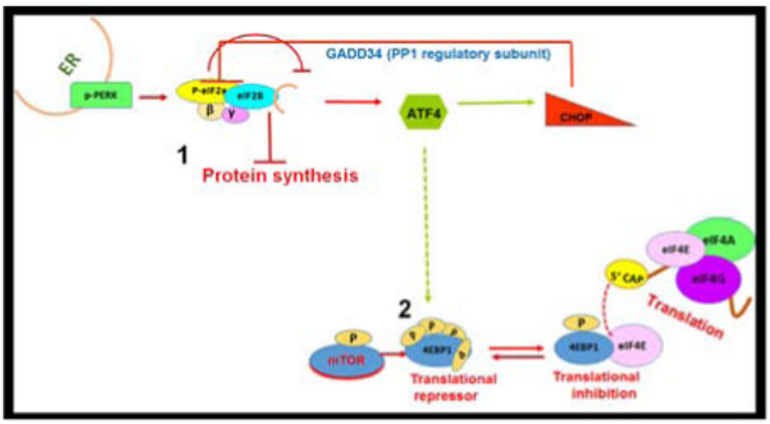

Figure 4.

Two modes of translational control in photoreceptors. The first mode operates through eIF2α. Phosphorylation of eIF2α leads to translational attenuation during the ER stress response (1). The second mode regulates protein synthesis through eIF4-BP, a translational repressor that binds to eIF4 in its hypo-phosphorylated form and has a reduced binding affinity when is hyper-phosphorylated (2). ATF4 elevation during ER stress could connect both pathways via back loop-mediated control of phosphorylated eIF2α and the direct transcription of 4E-BPs.

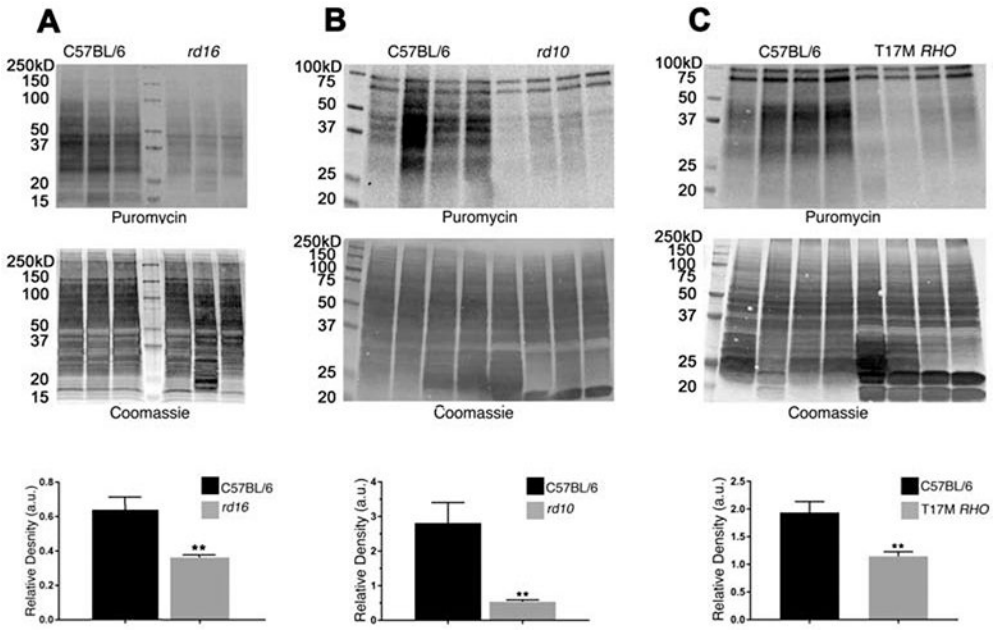

Figure 5.

Translational attenuation in retinas of various models of IRD. Measurement of newly synthesized polypeptides using the SUnSET method shows translational attenuation in the retinas of rd16 mice at P15 (A and B), T17M *RHO* mice at P15 (C and D), and rd10 mice at P20 (E and F). Published with copyright permission from *Cell Death and Disease* (2018, May 1;9(5):484).

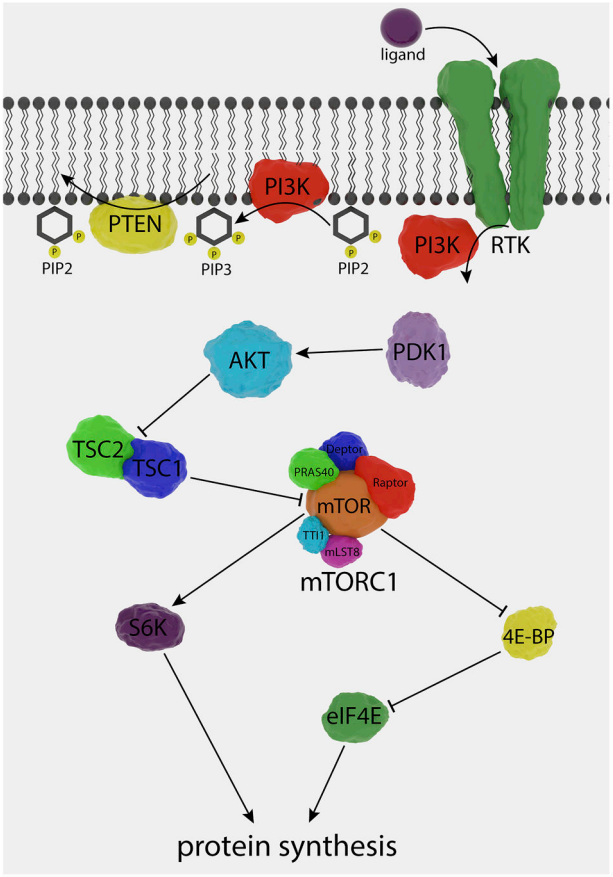

Figure 6.

mTORC1 regulation of protein synthesis. mTOR is a heavily regulated kinase that promotes cell growth and division following cell receipt of nutrients or growth factors. This schematic depicts a growth factor resulting in AKT and PDK1 activation by PI3K. AKT inhibits TSC1/2, enabling mTOR activation. mTOR regulates protein synthesis through S6K and 4E-BPs.