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Review

Endoplasmic reticulum stress in human photoreceptor diseases

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ABSTRACT

Photoreceptors are specialized sensory neurons essential for light detection in the human eye. Photoreceptor cell dysfunction and death cause vision loss in many eye diseases such as retinitis pigmentosa and achromatopsia. Endoplasmic reticulum (ER) stress and Unfolded Protein Response (UPR) signaling have been implicated in the development and pathology of heritable forms of retinitis pigmentosa and achromatopsia. We review the role of ER stress and UPR in retinitis pigmentosa arising from misfolded rhodopsins (RHO) and in achromatopsia arising from genetic mutations in Activating Transcription Factor 6 (ATF6).

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Contents

1. Introduction

1.1. Retina, rods, and cones

The human retina lines the posterior concavity of the eye and is dedicated to sensing, processing, and sending visual information collected from the environment to the brain. Photoreceptors are specialized sensory neurons in the outer nuclear layer of the retina that detect light and activate retinal circuitry. Two types of photoreceptors, rods and cones, are found in vertebrates including man (Sung and Chuang, 2010). Rod photoreceptors have slender, rod-shaped, modified cilia, termed outer segments, and comprise the majority of photoreceptors in the retina. Rods are activated by low intensities of light and are responsible for vision under dim and nocturnal conditions. By contrast, cone photoreceptors have a conical outer segment and are much less common than rods but – in humans – are highly enriched in the macula region of the retina, our point of highest visual acuity and special resolution. Cones are activated by higher intensities of light and mediate diurnal and color vision, the latter by subspecialization into different wavelength sensitivities. Many human blinding diseases arise when rods and/or cones are damaged or dysfunctional.

Photoreceptors produce unique proteins to transduce photonic stimuli into electrical signals and to maintain their structural integrity and lamination in the neuroretina (Sung and Chuang, 2010). Photoreceptors turn over many of these proteins through a daily process involving “shedding” of their outer segment tips to remove damaged proteins as well as to enable neighboring retinal pigment epithelial cells to recycle essential nutrients back to the photoreceptors (Sung and Chuang, 2010). Photoreceptors expend significant amounts of energy to perform these essential biosynthetic tasks and are metabolically the most active cells in the human body (Sung and Chuang, 2010; Wong-Riley, 2010).

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1.2. Endoplasmic reticulum organelle

The endoplasmic reticulum (ER) is an organelle dedicated to biosynthesis, folding, and assembly of membrane and secreted proteins, lipid and sterol metabolism, and free calcium storage (Alberts, 2008). Pathologic and environmental conditions that disrupt ER functions lead to ER stress (Hetz and Mollereau, 2014; Hiramatsu et al., 2015; Wang and Kaufman, 2016). To alleviate ER stress, cells activate the Unfolded Protein Response (UPR) (Walter and Ron, 2011; Wang and Kaufman, 2016). In mammals, the UPR is controlled by three ER resident transmembrane proteins: IRE1, PERK, and ATF6 (Walter and Ron, 2011; Wang and Kaufman, 2016). When activated by ER stress, IRE1, PERK, and ATF6 initiate intracellular signal transduction pathways that turn on transcriptional programs that enhance ER function by increasing ER size, ER protein folding enzymes and chaperones, and degradation of damaged proteins. PERK signaling also attenuates ribosome assembly on mRNAs so that protein translation is decreased. By reducing the metabolic demand of protein folding and enhancing the functional capacity of the ER, the UPR enables cells to adjust to and survive periods of ER stress. If ER stress persists despite these actions, UPR signaling "switches" to promote cell death by activating the intrinsic apoptosis machinery.

ER stress and UPR signaling are molecular pathologic mechanisms found in a wide variety of eye diseases (Kroeger et al., 2014; Zhang et al., 2014, 2015; Zode et al., 2011). Here, we review the role of ER stress and UPR in the development of two photoreceptor diseases: retinitis pigmentosa and achromatopsia.

2. ER stress in retinitis pigmentosa

Retinitis pigmentosa is a retinal degenerative disease that affects an estimated 1.5 million people worldwide (Berson, 1993). Clinically, the disease is characterized by night blindness and loss of peripheral vision due to degeneration of the rod photoreceptors that progressively worsens to damage central vision over the course of years by a secondary loss of the cone photoreceptors (Berson, 1993). Retinitis pigmentosa is a genetically heterogeneous disease with autosomal dominant, autosomal recessive, and X-linked subtypes (Dryja and Li, 1995). Mutations in rhodopsin (*RHO*) are a common genetic cause of autosomal dominantly inherited retinitis pigmentosa, and these patients experience progressive loss of rod photoreceptors which will eventually also lead to loss of cones (Dryja et al., 1990; Dryja, 1992).

Rhodopsin (RHO) is a small 348 amino acid, G-protein-coupled transmembrane receptor protein exclusively expressed by rods (Palczewski, 2006). When covalently linked to 11-cis-retinal, RHO responds to light to initiate the phototransduction cascade that generates electrical signals in the neuroretina (Palczewski, 2012). RHO is essential for photoreceptor function and survival, and RHO knockout mice ($Rho^{-/-}$) develop retinal degeneration very early in life (Humphries et al., 1997). Almost 200 different *RHO* mutations have been found in retinitis pigmentosa patients. Many of these mutations introduce missense changes that cause the mutant RHO protein to misfold in the ER (Chiang et al., 2012, 2014; Illing et al., 2002; Kaushal and Khorana, 1994; Sung et al., 1991).

The proline to histidine mutation at position 23 (P23H) of rhodopsin (Rho^{P23H}) is the most common cause of heritable retinitis pigmentosa in North America accounting for 10% of adRP patients (Dryja et al., 1991; Dryja and Li, 1995). Mutant Rho^{P23H} protein extensively aggregates *in vitro* and fails to traffic efficiently out of the ER in rod photoreceptors (Saliba et al., 2002). Rho^{P23H} causes ER stress and activates UPR in transgenic animal models of retinitis pigmentosa prior to overt photoreceptor cell death (Kroeger et al., 2014; Lin et al., 2007). Most recently, a P23H rhodopsin knock-in mouse ($Rho^{P23H/+}$) was created that closely recapitulated the spatial distribution and temporal progression of photoreceptor cell death and vision loss found in patients with the same mutation (Sakami et al., 2011). When ($Rho^{P23H/+}$) were crossed with *ER Stress-Activated Indicator* (*ERAI*) mice, a transgenic reporter mouse line that produces fluorescent XBP1-Venus fusion protein when the IRE1 branch of the UPR is activated (Iwawaki et al., 2004), robust fluorescent signal was selectively seen in rod photoreceptors in $Rho^{P23H/+}$ mice (Chiang et al., 2015). Consistent with increased reporter activity, levels of spliced *Xbp-1* mRNA, XBP1 protein, and transcriptional targets of XBP1s were all significantly elevated in retinas of $Rho^{P23H/+}$ mice (Chiang et al., 2015). Increased IRE1 signaling through XBP1 generation was observed prior to photoreceptor cell loss in $Rho^{P23H/+}$ mice (Chiang *et al.*, 2015). However, no activation of c-Jun N-terminal kinase, IRE1-dependent mRNA decay, or signaling via the PERK arm of the UPR was observed in $Rho^{P23H/+}$ mice at these ages (Chiang et al., 2015). These findings demonstrate that Rho^{P23H} causes ER stress *in vivo* in rods. Furthermore, the physiologic ER stress caused by Rho^{P23H} activates a "partial" or "selective" UPR in photoreceptors of $Rho^{P23H/+}$ mice that is dominated by IRE1's generation of XBP1. By contrast, pharmacologic ER stress caused by tunicamycin or thapsigargin activates all UPR signaling pathways simultaneously.

What is the function of XBP1 generation in photoreceptors of $Rho^{P23H/+}$ mice? Many of XBP1′ target genes, including those found to be upregulated in the retinas of $Rho^{P23H/+}$ mice, encode components of the ER-associated protein degradation (ERAD) machinery (Chiang et al., 2015; Lee et al., 2003; Shoulders et al., 2013). P23H rhodopsin's propensity to misfold in the ER and its robust production makes it a prime target for ERAD in photoreceptors. Indeed, Rho^{P23H} was found to be heavily ubiquitinated when immunoprecipitated from photoreceptors of $Rho^{P23H/+}$ mice (Chiang et al., 2015). Furthermore, miniscule steady state levels of Rho^{P23H} protein were found in photoreceptors of $Rho^{P23H/+}$ mice ($<5\%$ the levels of wild-type RHO protein in rods) despite comparable levels of Rho^{P23H} and wild-type *RHO* mRNA levels (Chiang et al., 2015). These findings reveal robust elimination of Rho^{P23H} protein from rods by ERAD. Given that RHO protein is essential for photoreceptor function and survival, the disruption of RHO protein homeostasis found in $Rho^{P23H/+}$ mice may underlie the molecular pathology of retinitis pigmentosa.

Important mechanistic questions to investigate about the pathogenesis of retinitis pigmentosa arising from RHO protein misfolding include: 1. What are the precise ERAD components that efficiently target Rho^{P23H} for retrotranslocation from the ER and proteasomal degradation? 2. Does the loss of RHO protein in rods cause the retinal degeneration found in $Rho^{P23H/+}$ mice? 3. Does the small amount of Rho^{P23H} protein that escapes degradation also cause retinal degeneration found in $Rho^{P23H/+}$ mice?

3. ER stress in achromatopsia

Achromatopsia is an autosomal recessive vision disorder that affects 1 in 33,000 people in the United States. This blinding disease is characterized by cone photoreceptor dysfunction and degeneration. Patients with incomplete achromatopsia may have some color vision while those with complete achromatopsia can only see black, white, and shades of gray. Achromatic patients experience photophobia, nystagmus, and significantly impaired visual acuity. Symptoms typically manifest at birth or within the first few months of life. Mutations in cone phototransduction genes, GNAT2, PDE6C, PDE6H, CNGA3, and CNGB3 are found in ~80–90% of patients with achromatopsia (Chang et al., 2009; Kohl et al., 1998, 2000, 2012; Thiadens et al., 2009). Recently, a novel achromatopsia disease gene, *ATF6*, was identified in patients with