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Review

Defects in retinal pigment epithelial cell proteolysis and the pathology associated with age-related macular degeneration

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ABSTRACT

Maintenance of protein homeostasis, also referred to as "Proteostasis", integrates multiple pathways that regulate protein synthesis, folding, translocation, and degradation. Failure in proteostasis may be one of the underlying mechanisms responsible for the cascade of events leading to age-related macular degeneration (AMD). This review covers the major degradative pathways (ubiquitin-proteasome and lysosomal involvement in phagocytosis and autophagy) in the retinal pigment epithelium (RPE) and summarizes evidence of their involvement in AMD. Degradation of damaged and misfolded proteins via the proteasome occurs in coordination with heat shock proteins. Evidence of increased content of proteasome and heat shock proteins in retinas from human donors with AMD is consistent with increased oxidative stress and extensive protein damage with AMD. Phagocytosis and autophagy share key molecules in phagosome maturation as well as degradation of their cargo following fusion with lysosomes. Phagocytosis and degradation of photoreceptor outer segments ensures functional integrity of the neural retina. Autophagy rids the cell of toxic protein aggregates and defective mitochondria. Evidence suggesting a decline in autophagic flux includes the accumulation of autophagic substrates and damaged mitochondria in RPE from AMD donors. An age-related decrease in lysosomal enzymatic activity inhibits autophagic clearance of outer segments, mitochondria, and protein aggregates, thereby accelerating the accumulation of lipofuscin. This cumulative damage over a person's lifetime tips the balance in RPE from a state of para-inflammation, which strives to restore cell homeostasis, to the chronic inflammation associated with AMD.

Contents

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1. Introduction to proteostasis and proteolysis

Maintenance of protein homeostasis, recently coined "Proteostasis", involves multiple integrated pathways that regulate protein synthesis, folding, translocation, and degradation. Proteostasis is essential for preserving cellular function under both normal conditions and following conditions that upset the balance, for instance, exposure to environmental stressors or biological aging. A deficiency in cellular proteostasis has been associated with multiple age-related degenerative disorders (Marques et al., 2015) and has particularly devastating consequences in post-mitotic cells, such as neurons and the retinal pigment epithelium (RPE), where cell replacement to maintain tissue integrity and function is very limited. This review will examine pathways of degradation in the RPE and discuss the implications to age-related macular degeneration (AMD) when there is failure in this key part of proteostasis.

There are two main proteolytic machineries in eukaryotic cells that are an essential component of quality control: 1) the ubiquitin-proteasome system (UPS), and 2) the lysosomal/autophagosomal degradation system (Ciechanover, 2012; Ciechanover and Stanhill, 2014). These are separate pathways with their own unique characteristics, but they also share similar major steps. Both systems recognize and actively select the material for degradation, and when the proteins have been degraded, the end products, i.e. amino acids, are recycled (Wong and Cuervo, 2010). In both systems, molecular chaperones play important roles in the recognition and selection of the proteins or organelles to be degraded (Kaarniranta et al., 2009; Kaarniranta et al., 2010; Reggiori et al., 2012). An auxiliary degradation system that is present in the RPE involves the daily phagocytosis and degradation of the outer tips of photoreceptors, which is a fundamental process in disc renewal and maintenance of visual function. As will be explained in detail, there is some overlap between the molecules used for autophagy and those involved in phagocytic degradation of photoreceptor outer segments.

The basic molecular details of the UPS and lysosomal/autophagy degradation system have been developed from studies in cultured cells and by comparing WT and transgenic mice lacking specific proteins that are involved in proteolysis. Manipulation of these model systems to mimic conditions associated with AMD, such as stressors associated with oxidation or cytokines, provided a rational basis for inferring the contribution of proteolytic dysfunction in AMD. More recent work in tissue from human donors with and without AMD have provided key evidence either refuting or confirming results from model systems. Continued work in model systems, coupled with validating specific hypotheses in tissue from human donors with AMD, will provide a more accurate and detailed picture of how failure in degradative pathways contribute to AMD pathology.

Failure in proteostasis, which can be initiated when the degradative system is overwhelmed, may be one of the underlying mechanisms responsible for the cascade of events leading to the AMD phenotype. This review will cover the major players in each proteolytic system of the RPE, summarize evidence of their involvement in AMD, and highlight areas requiring more detailed study. Finally, we propose a model that includes defects in RPE proteolysis and the consequent cumulative damage as a potential mechanism underlying AMD pathology.

2. Phagocytosis in the retinal pigment epithelial cells

The RPE serves many physiological roles that are crucial to maintaining homeostasis of the retina. Phagocytosis is one of its most important functions; however, gaps remain in our understanding of the molecular details of this process. The RPE is one of the most active phagocytic cell types in the body, phagocytosing and degrading 10% of total photoreceptor volume daily (Kevany and Palczewski, 2010).

The process of photoreceptor disc shedding and renewal and the role of RPE in phagocytizing the shed discs have been known since the work of Young and colleagues (Young, 1967; Young and Droz, 1968; Young and Bok, 1969). Phagocytosis of the shed discs is essential to the survival of photoreceptor cells; several lines of evidence link abnormal RPE phagocytic function to degenerative diseases of the retina (Sparrow et al., 2010; Mustafi et al., 2011). A close proximity of photoreceptor outer segments (OS) and the RPE is required for the phagocytic process to take place (Williams and Fisher, 1987).

The process of phagocytosis exhibits a circadian rhythm (La Vail, 1976; Besharse et al., 1977; Young, 1977, 1978; O'Day and Young, 1978; Fisher et al., 1983; Immel and Fisher, 1985; Bobu and Hicks, 2009) and can be divided into five distinct stages: 1) recognition and attachment of the OS; 2) ingestion of the OS; 3) formation of the phagosome, (4) fusion with lysosomes; and finally, 5) digestion (Fig. 1). It is now recognized that abnormalities at any stage of this process or to the phagocytosis machinery can lead to disease, ranging from early-onset retinal dystrophies, such as retinitis pigmentosa or Usher's syndrome, to aging diseases affecting the central retina, such as AMD (Nandrot, 2014).

A number of molecules that are essential in recognition, binding and internalization of OS have been identified (Kevany and Palczewski, 2010; Caberoy et al., 2010). The RPE cells can recognize phosphatidylserine "eat me" signals that trigger phagocytic uptake (Wu et al., 2006; Ruggiero and Finnemann, 2014). In various phagocytic cell types, phosphatidylserine can be detected via several membrane receptors, such as brain-specific angiogenesis inhibitor 1 (BAI1), which helps in recognition and engulfment (Park et al., 2007). Members of the T cell immunoglobulin mucin domain (TIM) family of proteins, such as TIM1, TIM 3 and TIM4 mediate phosphatidylserine binding (Freeman et al., 2010). Following phosphatidylserine binding, stabilin 2 also helps to promote engulfment by interacting with PTB domain-containing engulfment adaptor protein 1 (GULP) and thymosin β4 (Park et al., 2008). In addition, several ligands that are bridging molecules, such as milk fat globule EGF factor 8 (MFGE8), protein S and GAS6 also participate in the clearance process (Fricker et al., 2012; Li, 2013). There are a growing number of recognition molecules (Poon et al., 2014), for which a function in RPE phagocytosis remains to be