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Review

Lysosomes: Regulators of autophagy in the retinal pigmented epithelium

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ABSTRACT

The retinal pigmented epithelium (RPE) is critically important to retinal homeostasis, in part due to its very active processes of phagocytosis and autophagy. Both of these processes depend upon the normal functioning of lysosomes, organelles which must fuse with (auto)phagosomes to deliver the hydrolases that effect degradation of cargo. It has become clear that signaling through mTOR complex 1 (mTORC1), is very important in the regulation of lysosomal function. This signaling pathway is becoming a target for therapeutic intervention in diseases, including age-related macular degeneration (AMD), where lysosomal function is defective. In addition, our laboratory has been studying animal models in which the gene (*Cryba1*) for βA3/A1-crystallin is deficient. These animals exhibit impaired lysosomal clearance in the RPE and pathological signs that are similar to some of those seen in AMD patients. The data demonstrate that βA3/A1-crystallin localizes to lysosomes in the RPE and that it is a binding partner of V-ATPase, the proton pump that acidifies the lysosomal lumen. This suggests that βA3/A1-crystallin may also be a potential target for therapeutic intervention in AMD. In this review, we focus on effector molecules that impact the lysosomal–autophagic pathway in RPE cells.

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Contents

Lysosomes are cellular organelles that modulate various processes such as autophagy and heterophagy, plasma membrane repair, cholesterol homeostasis and cell death (Xu and Ren, 2015). The number, size and content of lysosomes vary in different cell types. The distribution of lysosomes within the cell is determined by the nutrient sensing machinery at the lysosomal membrane, and is an important factor in lysosomal catabolic function. In this review, we focus on the effector molecules present in retinal pigmented epithelial (RPE) cells that impact the lysosomal–autophagic pathway.

1. Retinal pigmented epithelium (RPE)

The RPE is a single layer of cells interposed between the neurosensory retina and Bruch's membrane (Strauss, 2005). En

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face, RPE cells assume a hexagonal, cobblestone-like appearance. The cells are highly polarized and contain abundant melanin granules that absorb scattered light, thereby reducing photo-oxidative stress on the retina (Beatty et al., 1999). In addition, the RPE has several other functions that are crucial to the retina's functional integrity. Perhaps its most important function is the phagocytosis of shed photoreceptor outer segments (POS) and the subsequent degradation and recycling of their molecular components for re-use in the visual cycle (Young and Bok, 1969; Bok, 1993). Apical microvilli of the RPE extend around the POS and ingest shed rod and cone outer segment discs into the RPE as membrane bound phagosomes. These phagosomes fuse with lysosomes to form phagolysosomes. The acid hydrolases from the lysosomes digest the outer segment material, critical components of which are returned to the photoreceptors for re-use. In a related process, called autophagy, damaged intra-cellular components including organelles, protein aggregates, and membranes are packaged into autophagosomes, which like phagosomes, fuse with lysosomes to effect cargo degradation.

2. Lysosomes and autophagy

Much is now known about the molecular mechanisms of autophagosome formation (Mizushima and Komatsu, 2011; Yang and Klionsky, 2010; Rubinsztein et al., 2012), however, we know less about the end stages of macroautophagy, particularly the role of lysosomes in the degradation of autophagosome contents (Shen and Mizushima, 2014). The process is different from micro-autophagy and chaperone-mediated autophagy, where cellular materials to be degraded are directly delivered to the lysosomes, independent of autophagosomes (Kaushik and Cuervo, 2012). Therefore, lysosomes are indispensible in the degradation and recycling processes of all three major autophagy types.

Lysosomes are the major digestive organelle in eukaryotic cells (Saftig, 2006). Lysosomes have a lipid bilayer membrane with an acidic lumen containing over 60 acidic hydrolases, each capable of degrading specific substrates (Settembre et al., 2013). The acidification of lysosomes is established by vacuolar-type H^+-ATPases (V-ATPase) (Sun-Wada et al., 2003; Mindell, 2012) which are multi-subunit complexes, composed of a peripheral V_1 domain that hydrolyzes ATP and an integral V_0 domain, that translocates protons from the cytoplasm to the lumen (Toei et al., 2010).

Lysosomal dysfunction may result from abnormal functioning of any of the myriad of proteins required for maintaining lysosomal homeostasis. However, in each case, the disease phenotype and tissue (s) affected can be different. Therefore, the mechanisms by which lysosomal function is regulated in the RPE may be unique. RPE cells are not only among the most active phagocytic cells in the body, continuously phagocytosing shed POS, but also are post-mitotic cells with high metabolic activity, where a high rate of autophagy would be expected. Therefore, lysosomal-mediated removal of waste products in the RPE is essential to insure functional integrity of the neural retina. The lysosomal degradation pathway declines with age in the human brain, contributing to the pathogenesis of neurodegenerative diseases (Cuervo and Dice, 2000; Nixon, 2013). While RPE lysosomal dysfunction is now thought to be a significant risk factor for age-related macular degeneration (AMD), our knowledge of how such abnormalities contribute to the disease process remains limited (Kaarniranta et al., 2013). In 1 year old rats with a spontaneous mutation in the *Cryba1* gene (encoding for βA3/A1-crystallin) (Sinha et al., 2008), electron microscopy (EM) showed large aggregates of lipofuscin-like material (arrows in Fig. 1A) and a large vacuole containing many degenerated cellular organelles (arrowheads in Fig. 1A) associated with inefficient lysosomal clearance (Zigler et al., 2011). Interestingly, similar structures are also seen in EM sections of the fovea from a 95-year old male patient with geographic atrophy (Fig. 1B). Therefore, understanding the lysosomal-mediated clearance mechanisms in the RPE may help to understand the pathophysiology of AMD.

In the RPE, lysosomes degrade both extracellular (POS) and intracellular (autophagy) material. Recently, it has become very clear that lysosomes and mTORC1 signaling are interconnected (Bar-Peled and Sabatini, 2014; Betz and Hall, 2013; Puertollano, 2014). An elegant study demonstrated that lysosomal positioning within the cell regulates mTORC1 signaling (Korolchuk et al., 2011) while another showed that long starvation periods lead to mTORC1 reactivation and thereby formation of proto-lysosomes with reformation into mature lysosomes (Yu et al., 2010).

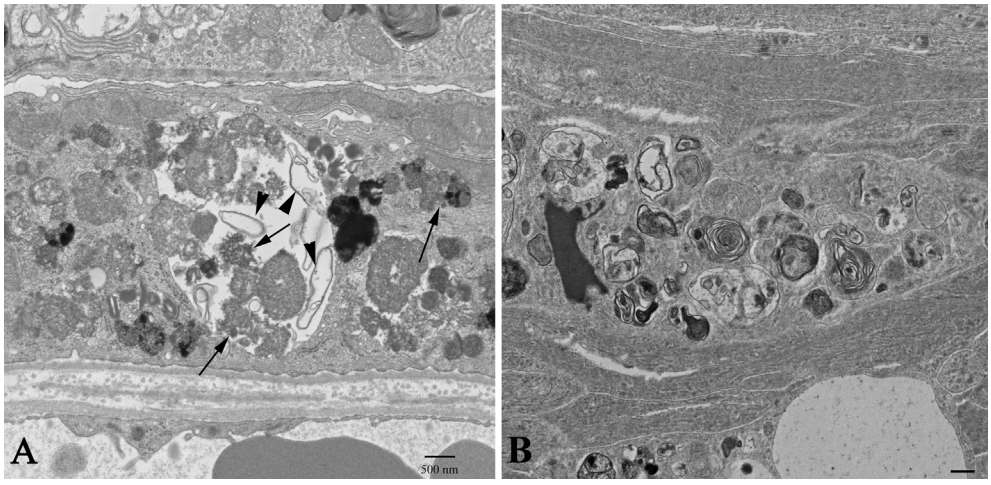

Fig. 1. Effects of Lysosomal dysfunction on RPE cell ultrastructure. Transmission electron microscopy (TEM) was used to compare the cellular ultrastructure of the RPE in the Nuc1 rat (A) and a 95-year old human subject with geographic atrophy (B). Nuc1 is a spontaneous mutation in *Cryba1*, the gene encoding βA3/A1-crystallin, a lysosomal protein in RPE cells that participates in lysosomal-mediated clearance. The Nuc1 RPE at 1 year of age shows a large vacuole containing both partially degraded cellular organelles (arrowheads) and lipofuscin-like aggregates (arrows). The RPE from the foveal region of a 95-year old geographic atrophy subject (B) shows similar changes in the fibro-cellular formation located above Bruch's membrane near the area of atrophy. Scale bar = 500 nm.

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