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Review

Cellular and molecular mechanisms of age-related macular degeneration: From impaired autophagy to neovascularization

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ABSTRACT

Age-related macular degeneration (AMD) is a complex, degenerative and progressive disease involving multiple genetic and environmental factors. It can result in severe visual loss e.g. AMD is the leading cause of blindness in the elderly in the western countries. Although age, genetics, diet, smoking, and many cardiovascular factors are known to be linked with this disease there is increasing evidence that long-term oxidative stress, impaired autophagy clearance and inflammasome mediated inflammation are involved in the pathogenesis. Under certain conditions these may trigger detrimental processes e.g. release of vascular endothelial growth factor (VEGF), causing choroidal neovascularization e.g. in wet AMD. This review ties together these crucial pathological threads in AMD.

Contents

Abbreviations: A2-E, N-retinylidene- N-retinylethanol-amine; AGE, advanced glycation end products; AIM2, Absent in melanoma; AMD, age-related macular degeneration; Aβ, amyloid β; ATP, adenosine tri-phosphate; BACE1, β-secretase; BMDM, bone-marrow derived macrophages; Bm, Bruch's membrane; DAMP, danger-associated molecular pattern; D, drusen; FAK, focal adhesion kinase; HIF-1α, hypoxia-inducible factor-1α; HMGB1, high mobility group box 1; HNE, hydroxynonenal; HRE, hypoxia responsive element; Hsp60, heat shock protein 60; IFN, interferone; IL, interleukin; L, lipofuscin; LPR, leucine-rich repeat; MAPK, mitogen activated protein kinase; MDA, malondialdehyde; MerTK, Mer tyrosine kinase; MFG-E8, milk fat globule-EGF8; NBD, nucleotide-binding domain; NF-κB, nuclear factor-κB; NIK, NF-κB inducing kinase; NLR, NOD-like receptor; PAMP, pathogen-associated molecular pattern; PKC, protein kinace C; POS, photoreceptor outer segment; PYD, pyrid domain; RCS, Royal College of Surgeons; RIG-1, retinoic acid-inducible gene-1; RLR, retinoic acid-inducible gene-1 receptor; ROS, reactive oxygen species; RPE, retinal pigment epithelium; TNF, tumour necrosis factor; TRX, thioredoxin; TXNIP, redox-sensitive thioredoxin-interacting protein; VEGF, vascular endothelial growt factor; VEGFR, vascular endothelial growth factor receptor; VHL, von Hippel–Lindau tumor suppressor protein.

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1. Introduction

Age-related macular degeneration (AMD), the decline in macular function from the degenerative alterations, is the leading cause of visual impairment in the western world. As the name suggests, the disease becomes more common with increasing age. There are approximately 50 million elderly people suffering from AMD around the world and this number is expected to double during the next 20 years and thus it represents a major public health issue (Gordois et al., 2012; Pascolini et al., 2004). The disease affects the most sensitive area of the ocular fundus, the macula, the region responsible for sharp central vision, which is needed to identify letters, numbers, facial features, border surfaces, angles and colors. AMD can be divided into two distinct forms: dry AMD (atrophic) and wet AMD (exudative) (Figs. 1 and 2). A total of 80% of patients suffer from the dry form of AMD for which no efficient treatment exists today, although some observational studies have indicated that omega-3 fatty acids may be beneficial in the prevention of AMD (Arnold et al., 2013; Kaarniranta and Salminen, 2009; Merle et al., 2011; Reynolds et al., 2013). Wet AMD development is strongly associated with the upregulation of vascular endothelial growth factor (VEGF) and this represents the principal therapy target for inhibiting the detrimental neovascularization process i.e. by intravitreal administration of ranibizumab or bevacizumab or VEGF Trap (CATT Research Group et al., 2011; Heier et al., 2011; IVAN Study Investigators et al., 2012; Klettner and Roider, 2009b).

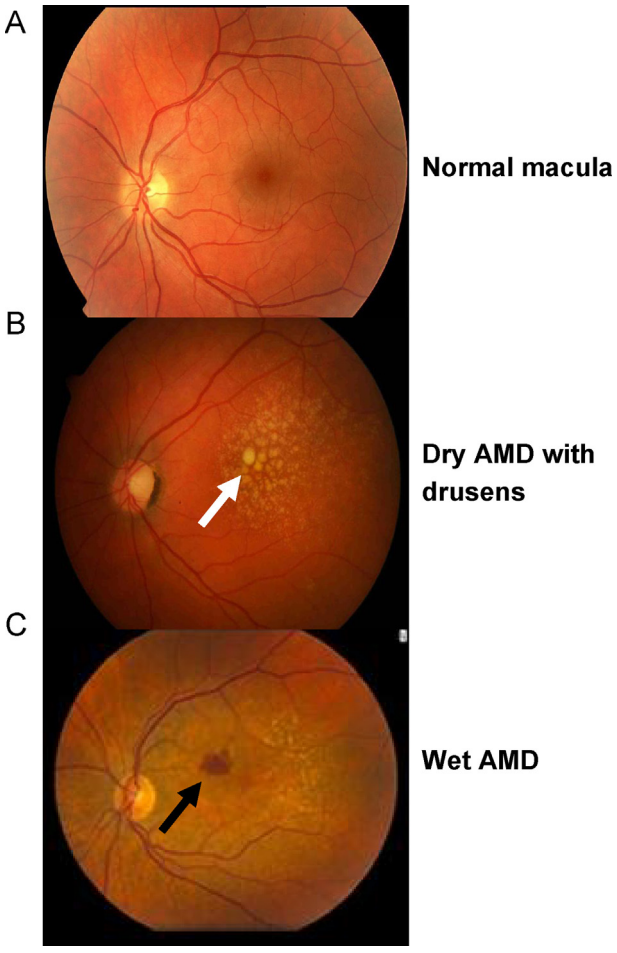

Fig. 1. Color photograph from (A) normal healthy macula, (B) drusen (white arrow) -rich dry AMD macula and hemorrhagic wet (black arrow) AMD.

AMD is a complex disease of the eye with a multifactorial etiology including aging, family history, smoking, high blood pressure, obesity, hypercholesterolemia and arteriosclerosis (Kaarniranta et al., 2011). At the tissue level, degenerative alterations in the photoreceptor layer (rod and cones), the retinal pigment epithelium (RPE) and choriocapillaris have been observed in AMD cases (Bhutto and Lutty, 2012; Kinnunen et al., 2012). The loss of vision primarily involves a progressive degeneration and cell death of the neuroepithelial RPE cells, which subsequently exerts adverse effects on the rod and cones. The RPE cells are exposed to chronic oxidative stress due to their high levels of oxygen consumption, their exposure to the lipid peroxidation products derived from the photoreceptor outer segments and the constant presence of light stimuli. Many oxidatively damaged molecules accumulate in macula area e.g. carboxyethylpyrrole, malondialdehyde, 4-hydroxynonenal, and advanced glycation endproducts and these are all molecular sources of oxidative stress (Blasiak and Szaflik, 2011; Cai et al., 2012; Crabb et al., 2002; De La Paz and Anderson, 1992; Glenn et al., 2009; Handa, 2012; Klettner, 2012; Schutt et al., 2003; Uchiki et al., 2012; Yoon et al., 2012). In senescent RPE cells, the ability to respond to the increased oxidative stress is reduced of; one sign of this impairment is the increased accumulation of autoxidative lipofuscin in lysosomes of RPE cells and extracellular drusen formation between the space of RPE and Bruch's membrane (Figs. 1 and 2; Jarrett and Boulton, 2012; Kaarniranta and Salminen, 2009). In addition to oxidative stress and protein aggregation, immunologic processes are involved in the pathogenesis of AMD, including the generation of inflammatory related molecules in Bruch's membrane, recruitment of macrophages, dendritic cells, complement activation and microglial activation in the macular area (Hageman et al., 2001; Kinnunen et al., 2012; Mettu et al., 2012; Penfold et al., 1990; Tuo et al., 2012; Wang et al., 2009a,b; Zhou et al., 2006).

2. Retinal pigment epithelial cells

The apical plasma membrane microvilli of the postmitotic RPE cells is in contacts with the outer segment tips of rods and cones and the interphotoreceptor matrix in the posterior retinal pole (Fig. 2). There is adhesion between the RPE cells and photoreceptors which maintains outer segment alignment (Marmorstein et al., 1998). Each RPE cell is faces around 20–50 photoreceptor cells (Winkler et al., 1999). The average of RPE cell density is about 4000 cells/mm^2 at the fovea, decreasing toward the