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Mechanistical retinal drug targets and challenges☆

Kai Kaarniranta [a,b,c,*], Heping Xu [d,e,**], Anu Kauppinen [f]

[a] Department of Ophthalmology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland
[b] Department of Ophthalmology, Kuopio University Hospital, Kuopio, Finland
[c] Department of Molecular Genetics, University of Lodz, Lodz, Poland
[d] Centre for Experimental Medicine, The Wellcome-Wolfson Institute of Experimental Medicine, Queen's University Belfast, Belfast, UK
[e] Aier School of Ophthalmology, Central South University, China
[f] School of Pharmacy, University of Eastern Finland, Kuopio, Finland

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ABSTRACT

The retina is constantly exposed to light that increases reactive oxygen species in retina. Oxidative stress, inflammation and neurodegeneration are the major contributors in the most common retinal diseases, such as age-related macular degeneration (AMD), glaucoma and diabetic retinopathy (DR). Emerging developments and research for novel therapy targets and drug delivery to the posterior segment offer a promising future for the treatment of retinal diseases including rare hereditary diseases. In this review we discuss about promising mechanistical retinal drug targets. Vascular endothelial growth factor (VEGF) signaling and anti-VEGF treatments are excluded.

1. Introduction

The mature retina is organized into three nuclear layers; ganglion cell layer (GCL), inner nuclear layer (INL) and outer nuclear layer (ONL) that are interconnected by synapses [Fig. 1]. Retinal ganglion cells (RGCs) form the most inner layer of retinal cells. Their axons form the optic nerve and transmit visual information into the visual cortex. RGCs undergo apoptotic cell death in glaucoma and other optic neuropathies [1]. The mechanisms of RGC death are still a matter of intense investigation, and several factors including growth factor deprivation and oxidative stress have been proposed to participate in RGC degeneration in glaucoma. Rod and cone photoreceptors of the ONL are the light sensing cells of the eye that are responsible for black/white and colour vision respectively. The photoreceptors initiate the phototransduction, which leads to the action potential in retinal ganglion cells. The retinal pigment epithelial (RPE) cells are situated between the photoreceptor cells and the choroid [Fig. 1]. The RPE cells are vitally important for vision by maintaining the viability of photoreceptor cells [2–4]. Daily phagocytosis of photoreceptor outer segments (POS) and their degradation in RPE cell lysosomes (heterophagy) are critical for visual cycle and maintaining vision [4–6]. RPE cells are phagocytically the most active cells in the whole body, uptaking and degrading up to 10% of the POS daily. 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 [2]. These phagosomes fuse with lysosomes to form phagolysosomes. Lysosomal acid hydrolases degrade the outer segment material that is re-used in photoreceptors. The degradation process is critically controlled by acidification of lysosomes with vacuolar-type H + -ATPases (V-ATPase) [7]. Decreased lysosomal enzyme activity evokes an accumulation of lipofuscin, increases oxidative stress and protein aggregation and enhances RPE degeneration. We discuss about promising drug targets that coincide with normal cellular homeostasis in retina.

2. Targeting phagocytosis

Phagocytosis processes comprise recognition and binding, internalization, and finally digestion of POS discs in lysosomes [8; Fig. 2]. [9,10]. Initially, the integrin ITGAV-ITGB5 ($\alpha V\beta 5$) regulates the binding

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* Correspondence to: K. Kaarniranta, Department of Ophthalmology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland.
** Correspondence to: H. Xu, Centre for Experimental Medicine, The Wellcome-Wolfson Institute of Experimental Medicine, Queen's University Belfast, Belfast, UK.
E-mail addresses: kai.kaarniranta@uef.fi (K. Kaarniranta), heping.xu@qub.ac.uk (H. Xu).

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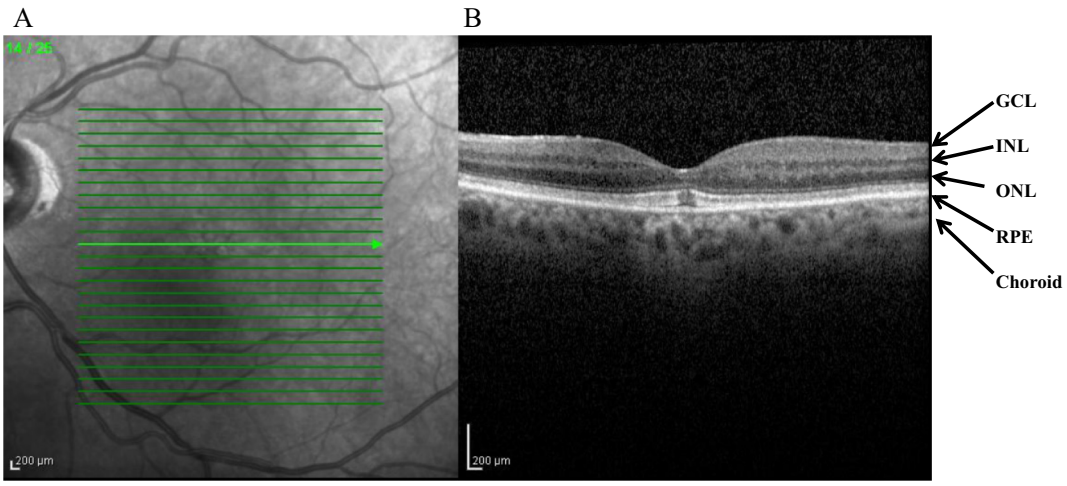

Fig. 1. (A) Optical coherent tomography A-scan and (B) B-scan from macula. Abbreviations: GCL, ganglion cell layer; INL, inner nuclear layer; ONL, outer nuclear layer; RPE, retinal pigment epithelium.

process [11,12]. Subsequently, MERTK (c-mer proto-oncogene tyrosine kinase) enhances the POS ingestion [13,14]. MERTK phosphorylates protein tyrosine kinase 2 during the binding process and links the signaling between integrin ITGAV-ITGB5 and MERTK [15,16]. Efficiency of phagocytosis varies according to circadian rhythm which is controlled by MFGE8 (milk fat globule-EGF factor 8 protein [17]). It is widely accepted that defects in phagocytosis are detrimental to photoreceptors and RPE [13,14,18]. It has been documented that decrease of integrin ITGAV-ITGB5 associates with the accumulation of lipofuscin in RPE cell lysosomes. Lipofuscin is a heterogenous protein-lipid-carbohydrate aggregate which includes toxic fluorophores such as, *N*-retinylidene-*N*-retinylethanolamine (A2E) compound. Lipofuscin toxic compounds disturb lysosomal membrane stability, inhibits mitochondrial respiration and accelerate RPE degeneration [18]. Thus, regulatory proteins of POS phagocytosis are critical pharmaceutical targets to maintain retinal homeostasis. In addition, for improving the POS clearance, many modulators of visual cycle have been developed in order to treat various retinal diseases [Fig. 2]. These agents were designed to inhibit retinoid isomerase [retinal pigment epithelium-specific 65 kDa protein (RPE65)], the rate-limiting enzyme of the visual cycle, based

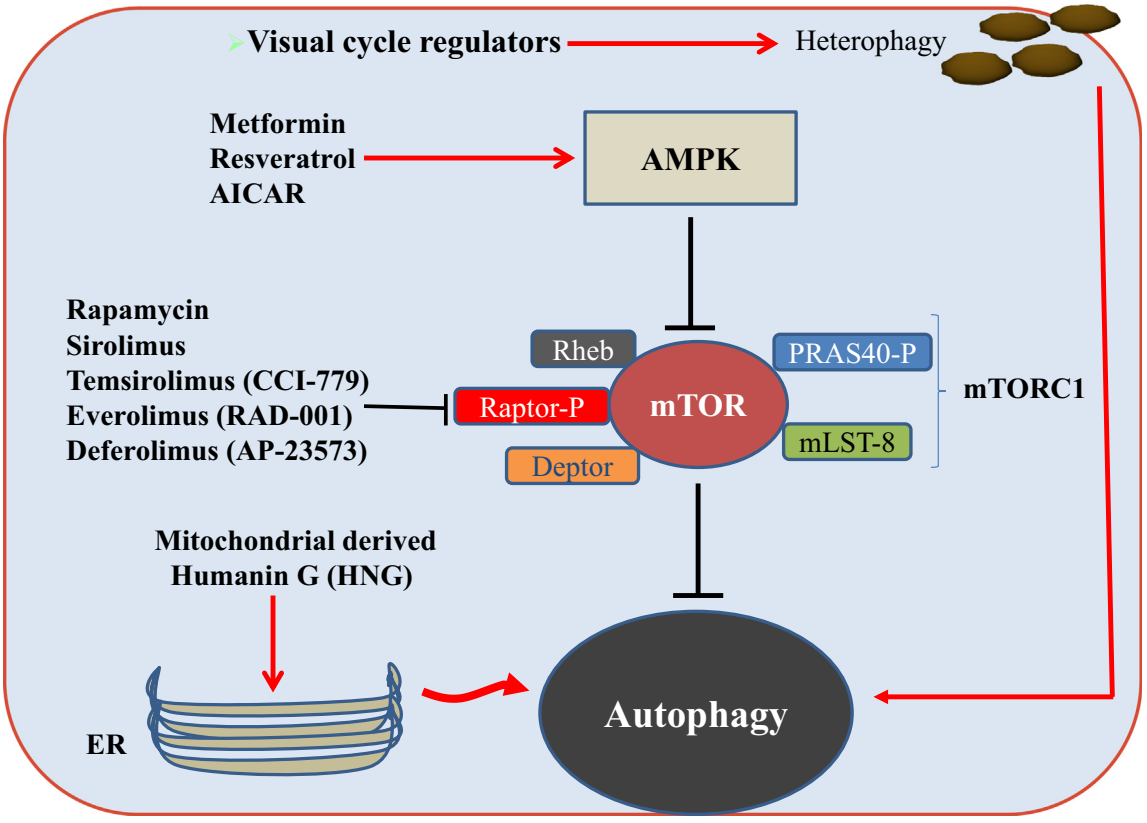

Fig. 2. Schematic presentation of RPE drug targets for phagocytosis, AMPK, mTOR and autophagy. Abbreviations: AICAR, adenosine analogue 5-aminoimidazole-4-carboxamide ribonucleoside; AMPK, adenosinemonophosphate-activated protein kinase; ER, endoplasmic reticulum; mLST-8, target of rapamycin complex subunit LST8; mTOR, mechanistical target of rapamycin; mTORC1, mechanistical target of rapamycin complex 1; PRAS40-P, Phospho proline-rich Akt substrate of 40kDa; Rheb, Ras homolog enriched in brain.

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