European Journal of Pharmacology ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Full Length Article

Targeting the complement system for the management of retinal inflammatory and degenerative diseases

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ARTICLE INFO

Article history:
Received 27 October 2015
Received in revised form
12 January 2016
Accepted 1 March 2016

Keywords:
Age-related macular degeneration
Diabetic retinopathy
Glaucoma
Uveoretinitis
Inflammation
Complement
Treatment

ABSTRACT

The retina, an immune privileged tissue, has specialized immune defense mechanisms against noxious insults that may exist in diseases such as age-related macular degeneration (AMD), diabetic retinopathy (DR), uveoretinitis and glaucoma. The defense system consists of retinal innate immune cells (including microglia, perivascular macrophages, and a small population of dendritic cells) and the complement system. Under normal aging conditions, retinal innate immune cells and the complement system undergo a low-grade activation (parainflammation) which is important for retinal homeostasis. In disease states such as AMD and DR, the parainflammatory response is dysregulated and develops into detrimental chronic inflammation. Complement activation in the retina is an important part of chronic inflammation and may contribute to retinal pathology in these disease states. Here, we review the evidence that supports the role of uncontrolled or dysregulated complement activation in various retinal degenerative and angiogenic conditions. We also discuss current strategies that are used to develop complement-based therapies for retinal diseases such as AMD. The potential benefits of complement inhibition in DR, uveoretinitis and glaucoma are also discussed, as well as the need for further research to better understand the mechanisms of complement-mediated retinal damage in these disease states.

1. The retina – an immune privileged tissue

The retina is essential for perception of vision. Light enters the eye through the cornea and iris and passes through the vitreous body to project onto the retina where the light signal is converted into electric impulses (Fig. 1A). The visual cycle occurs at the interface between the retina and retinal pigment epithelium (RPE), leading to the depolarization of photoreceptors (the rods and the cones). The electrical impulses converge via bipolar cells and ganglion cells onto the optic nerve, and then into the visual cortex (Fig. 1B). The inner retinal cells obtain nutrients and oxygen from the retinal circulation (Fig. 1C), whereas the outer retinal layers (which consists of the outer nuclear layer (ONL), photoreceptor inner segment (IS), and outer segment (OS)) are avascularized and nutrients and oxygen are supplied by the choroidal circulation (Fig. 1B). To ensure good visual function, this complex and sophisticated structure must be maintained throughout life, and even a minor perturbation may cause devastating visual impairment.

The eye has special mechanisms to protect the retina from exogenous and endogenous insults, which not only reduces the risk of infection, but also prevents inappropriate immune responses, thereby reducing the risk of inflammation–mediated retinal damage. Firstly, the retina is protected by physical barriers. The blood retina barrier (BRB) is formed by tight junctions between vascular endothelial cells (inner BRB, iBRB) and RPE cells (outer BRB, oBRB), and ensures that pathogens, circulating cells and molecules do not freely pass into the retinal parenchyma. The BRB also sequesters retinal antigens within the intraocular compartment avoiding T cell activation, a phenomenon called immunological ignorance (Avichezer et al., 2003; Forrester et al., 2008; Forrester et al., 2010; Forrester and Xu, 2012). Secondly, the retina has no lymphatic system. Therefore, when the retina suffers from any insult, the endogenous alarmins are unlikely to be detected by circulating or choroidal antigen presenting cells (APCs) if the BRB is intact. Thirdly, the retina has a sophisticated immune regulatory system orchestrated by retinal cells, including various neurons and RPE cells (Streilein, 1999; Streilein et al., 2002; Wenkel and Streilein, 2000). These retinal cells express immune modulators that can suppress immune cell activation. Examples of the immune modulatory mechanisms include (but are not limited to) the CD200-CD200R (Dick et al., 2003) and CX3CL1-CX3CR1 (Combadiere et al., 2007) pathway, thrombospondin-1, TGF-β, CTLA4, CTLA2, and various complement inhibitors (Horie et al., 2010; Kawazoe et al., 2012; Mochizuki et al., 2013; Sugita et al.,

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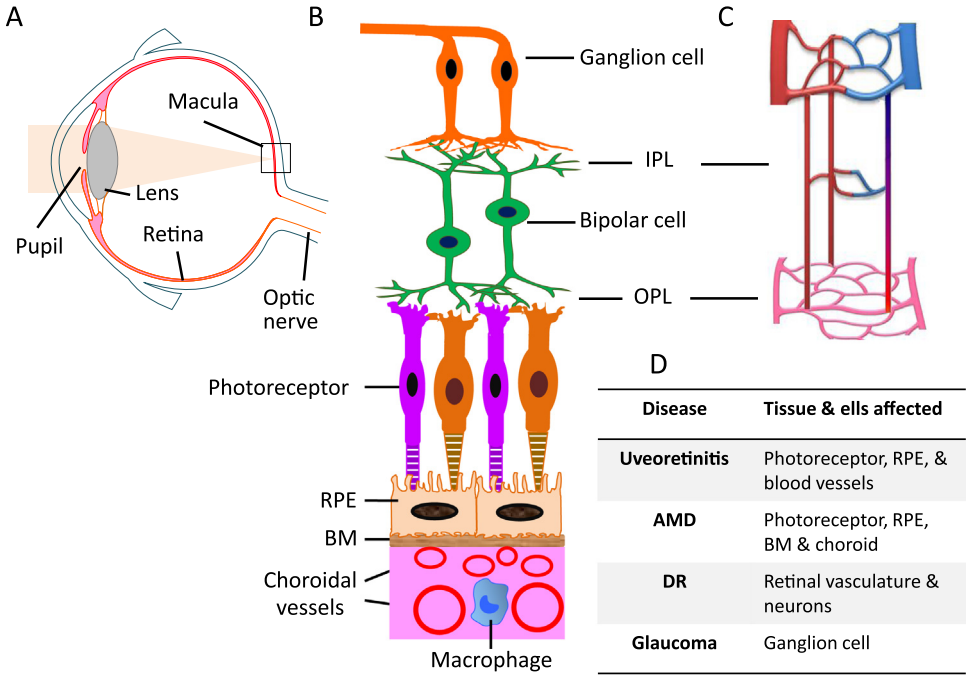
http://dx.doi.org/10.1016/j.ejphar.2016.03.001



Disease	Tissue & ells affected
Uveoretinitis	Photoreceptor, RPE, & blood vessels
AMD	Photoreceptor, RPE, BM & choroid
DR	Retinal vasculature & neurons
Glaucoma	Ganglion cell

Fig. 1. Retinal neuronal and vascular structure and retinal disease. A, diagram of a human eye. Light passes through the pupil and is focused by the lens onto the macula of the retinal layer at the back of the eye. B, the retina consists of three layers of neurons, photoreceptor, bipolar, and ganglion cells. The RPE monolayer together with Bruch's membrane (BM) form the outer blood retinal barrier that separates the neuroretina from the choroid. Choroidal circulation provides oxygen and nutrients to the outer retina. C, the retina has an interconnected network of three vascular layers located in the ganglion cell/nerve fibre layer, inner plexiform layer (IPL), and outer plexiform layer (OPL). D, retinal tissue and cells that are affected under different disease conditions.

2009; Zamiri et al., 2005). Mechanisms to induce the death of infiltrating immune cells through Fas ligand (FasL) and Tumor Necrosis Factor-related apoptosis-inducing ligand (TRAIL) pathways also exist in the retina (Ferguson and Griffith, 1997; Ferguson and Griffith, 2007; Kazama et al., 2008). Furthermore, ocular fluids contain immunoinhibitory molecules such as TGF-β2 and neuropeptides, including α-melanocyte-stimulating hormone and vasoactive intestinal peptide (Taylor, 1996; Taylor and Lee, 2010). The retina, therefore, represents an immune privileged tissue (Forrester et al., 2008; Gregerson, 1998; Streilein et al., 2002).

Despite being an immune privileged tissue, both retinal neurons and the vascular system may degenerate in conditions such as diabetic retinopathy (DR), age-related macular degeneration (AMD), uveoretinitis and glaucoma (Fig. 1D). Although the initial triggers of different diseases may differ, the retinal immune response following the initial insult shares many common pathways. Such inflammatory response secondary to retinal damage critically contributes to further neuronal and vascular degeneration in the aforementioned sight-threatening diseases. Here, we review the current knowledge on how the retinal innate immune system responds to insults with a strong focus on the complement system, and further discuss how the knowledge can be applied to developing complement based therapy.

2. Tissue insults, inflammation and disease – the concept

The central role of the immune system is to protect the host from exogenous and endogenous insults. When a tissue suffers from non-infectious noxious insults, a cell-autonomous response is initiated for stressor elimination or stress adaptation. This may include the upregulation of the autophagy pathway, the initiation of DNA repair, and the induction of chaperones to help to prevent protein misfolding (the adaptation response). The adaptation response is especially important for aging and diabetes. In addition, a non-cell-autonomous response may also be initiated wherein stressed cells release cytokines, chemokines and growth factors that affect neighbouring cells within the tissue, promoting tissue level adaptation. In the literature, this tissue autonomous response (cell-autonomous or non-cell-autonomous) is often called "inflammation" when inflammatory cytokines and chemokines are released by stressed cells.

Although many cells can detect tissue stress, this function is performed most efficiently by specialized sensory cells, such as tissue resident macrophages. Thus, pathogens and generic stressors such as hypoxia and oxidized lipids/proteins are primarily delegated to macrophages. Tissue macrophages may orchestrate tissue level defence and adaptations by releasing inflammatory mediators, including complement components. If the level of insult exceeds the repair capacity of tissue macrophages, they may recruit circulating immune cells to sites of damage. A low-level of tissue insult may initiate a protective para-inflammation (Chovatiya and Medzhitov, 2014; Medzhitov, 2008). When the stress persists for a sustained period of time, the affected tissue may mal-adapt leading to loss of function. In addition, the immune system may respond inappropriately to tissue stress due to genetic and epigenetic modifications resulting in dysregulated para-inflammation (chronic inflammation). Tissue pathology (disease) may occur as a result of tissue mal-adaptation or immune dysregulation.

3. Retinal innate immune defence and disease

As an immune privileged tissue, circulating immune cells are not able to enter the retina to deal with endogenous insults under normal physiological conditions. However, the retina has a unique immune defence system consisting of innate immune cells and the complement system. The retina contains at least three types of innate immune cells: microglia, perivascular macrophages, and dendritic cells (DCs) (Forrester et al., 2010; Xu et al., 2009). Although both perivascular macrophages and microglia express

Please cite this article as: Xu, H., Chen, M., Targeting the complement system for the management of retinal inflammatory and degenerative diseases. Eur J Pharmacol (2016), http://dx.doi.org/10.1016/j.ejphar.2016.03.001