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Review

The link between morphology and complement in ocular disease

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ABSTRACT

The complement system is a vital component of the immune-priveliged human eye that is always active at a low-grade level, preventing harmful intraocular injuries caused by accumulation of turnover products and controlling pathogens to preserve eye homeostasis and vision. The complement system is a double-edged sword that is essential for protection but may also become harmful and contribute to eye pathology. Here, we review the evidence for the involvement of complement system dysregulation in age-related macular degeneration, glaucoma, uveitis, and neuromyelitis optica, highlighting the relationship between morphogical changes and complement system protein expression and regulation in these diseases. The potential benefits of complement inhibition in age-related macular degeneration, glaucoma, uveitis, and neuromyelitis optica are abundant, as are those of further research to improve our understanding of complement-mediated injury in these diseases.

1. Introduction

The human eye lies protected in the bony orbit of the skull. The eye can be anatomically separated into two compartments: the anterior segment (including the cornea, iris, lens, and anterior and posterior chamber) and the posterior segment (the remainder of the eye) (Fig. 1) (Kolb, 1995). The immune-privileged eye can be divided into a vascularized part, the uvea, and an avascular part (the rest of the eye). The normal eye contains a number of different factors that protect it from dangerous insult. One of these is the tightly regulated complement system which is continuously activated at a low level, protecting the various ocular compartments (Perez and Caspi, 2015; Stein-Streilein, 2008; Streilein, 1999, 2003; Taylor, 2016). The eye is further protected by blood-ocular barriers consisting of tight junctions in the uvea, the endothelial cells of the inner retinal capillaries, and the cornea (Campbell and Humphries, 2012).

In the healthy eye, the continuous flow of soluble immunomodulating molecules in the aqueous humor, including growth factors such as TGF-β2 and neuropeptides, suppresses various immune cells, keeping resident immune cells quiescent and migrating immune cells outside the retinal barrier (Perez and Caspi, 2015; Taylor, 2016; Taylor et al., 1992). Pigmented epithelial cells produce these soluble factors, and corneal and retinal cells have membrane-bound immunoregulating molecules that cause apoptosis of immune cells invading the intraocular space (Sugita et al., 2006; Sugita et al., 2009; Taylor, 2016). Thus, immunosuppressive factors, complement system proteins, and resident immune cells all contribute to the elimination of foreign pathogens and waste products without damaging the healthy ocular tissue. If these ocular barriers are broken or downregulated, the eye becomes susceptible to dangerous insults, and invading non-resident immune cells can cause tissue damage.

2. Cornea

The fibrous cornea is the avascular, alymphatic and transparent protective barrier covering the anterior ocular surface (Fig. 1). It is about 0.5 mm in thickness and protects the eye against injury and infections, although its main purpose is to transmit and focus light into the eye (Ramos et al., 2015). The external, anterior convex surface of the cornea is covered by a tear film, and the internal posterior concave cornea faces the aqueous humor. The cornea can be divided into five main components: the most superficial, anterior stratified epithelium cell layer, Bowmańs layer, and, the strong middle collagen fibril-rich stroma (constituting 90% of the cornea) interspersed with keratinocytes and the internal endothelium. The crystalline structures of the stromal collagen fibrils (predominantly types I, III, V, VI, and XII) are separated by keratinocyte-derived proteoglycans (Di Girolamo, 2011; Ramos et al., 2015). The cornea is endowed with stromal dendritic and epithelial Langerhans cells as well as macrophages (Hamrah and Dana, 2007; Hamrah et al., 2003).

Among the components of complement, the normal human cornea has been shown to express C1q, C2, C3, C4, C5, C6, and C7, as well as properdin, factor B, and plasminogen (Mondino and Hoffman, 1980; Mondino et al., 1980), as detected by immunofluorescent staining and

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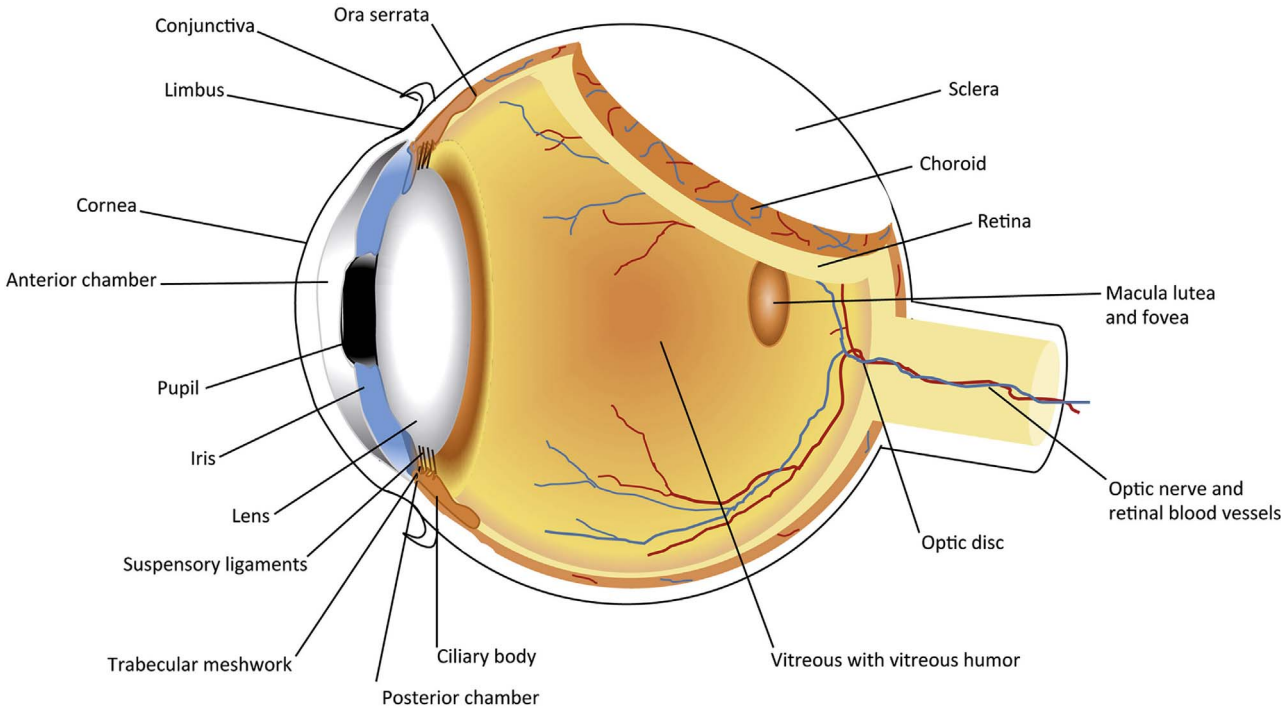

Fig. 1. Sagittal section of the human eye. The human eye comprises several functional layers, which can be divided into an external fibrous layer (sclera, limbus, cornea, and conjunctiva), a middle vascular layer (the uvea: iris, ciliary body, and choroid), and an internal sensorineural layer (vitreous humor, retina, and optic nerve). The anterior part of the ocular surface of the eye is covered by the transparent cornea, which merges with the opaque sclera at the limbus. The anterior chamber of the eye is divided from the posterior chamber by the iris, with the central pupil in front of the lens. Ciliary processes secrete the aqueous humor into the posterior chamber, from which it flows into the anterior chamber and drains out of the eye via the trabecular meshwork. The inside of the eye globe is occupied by the spherical, transparent, almost avascular and gelatinous vitreous humor. The vitreous is adherent to the lens, ciliary body, and retina (ora serrata and optic disc), keeping the retina in place and pressing it against the choroid. The macula, with its central fovea, is the area of the retina responsible for fine detail and central vision. The pigmented, highly vascularized choroidal tissue is positioned between the retinal pigment epithelium and sclera in the posterior segment of the eye. The optic nerve head is the exit of ganglion cell axons as well as entry and exit of the retinal artery and vein.

by hemolytic CH_{50} activity. Known regulators of the complement system found in the cornea are C1 inhibitor (C1-INH) and factor H (Mondino and Sumner, 1984), as well as membrane cofactor protein (MCP or CD46), decay accelerating factor (DAF or CD55), and protectin (CD59) (Table I) (Bardenstein et al., 1994; Bora et al., 1993).

3. Limbus

The corneal edge, or limbus, located at the corneoscleral junction, is a band that encircles the peripheral cornea (Fig. 1). It is a transitional zone between the cornea and the conjunctiva and the cornea and sclera. The limbus consists of cells derived from its adjacent tissues; hence, it is built up from a diverse collection of cells along its depth and around the edge of the limbus (Ramos et al., 2015; Thoft and Friend, 1983). In addition, limbal stem cells maintain and renew the corneal epithelium cell layers (Ahmad et al., 2006; Ramos et al., 2015). The corneal limbus contains blood vessels as well as lymphatic markers and lymphatic vessels (Birke et al., 2010; Gausas et al., 1999; Nakao et al., 2012; Narumi et al., 2014; Smolin, 1989), and the corneal limbal epithelium expresses membrane-bound complement regulators such as CD46, CD55, and CD59 (Table 1) (Bardenstein et al., 1994; Bora et al., 1993; Cocuzzi et al., 2000).

4. Sclera

The most external layer of the eye is the fibrous sclera (Fig. 1), a white opaque collagen-enriched (type I, III, V and VI) layer that helps to maintain the shape of the eye; the muscles attached to it control eye movement (Watson and Young, 2004). The sclera can be divided into the episclera, the scleral stroma, and the internal pigmented lamina fusca sclerae, melding into the uveal tract (choroid and ciliary body). Its collagen fibrils vary in thickness and are abundantly occupied by diverse proteoglycans, influencing solute and nutrient diffusion from the uvea and choroid, since most of the sclera (with the exception of the episclera) is avascular (Keeley et al., 1984; Young, 1985). The densely vascularized episclera contains fibroblasts, macrophages and lymphocytes (Schlereth et al., 2016), which can act as antigen-presenting cells. Although vascularized, the sclera does not contain any true lymphatic vessels, but specific markers for the lymphatic vascular endothelium (lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1 +)) are expressed on CD68 + macrophages (Schlereth et al., 2014). The scleral tissue has been shown to contain complement system proteins such as C1, C4, C2, C3, C5, and C6, as well as factor B and immunoglobulin G (IgG) and IgM, as determined by radial immunodiffusion (Brawman-Mintzer et al., 1988, 1989). Complement factor H has also been detected in scleral tissue (Table 1) (Mandal and Ayyagari, 2006).

5. Conjunctiva

The conjunctiva is an thin, translucent mucus secreating membrane. It runs from the limbus over the anterior sclera and turns antriorly to line the eyelids (Fig. 1). The conjunctiva is vascularized and containg lymphatic vessles (Chen, 2009; de Andrade et al., 2016; Stewart et al., 2015; Yucel et al., 2009). The conjunctival tissue can be divided into the bulbar area (on the eye surface) and the palpebral area (lining the posterior surface of the eyelids), with the forniceal area in between (de Andrade et al., 2016; Stewart et al., 2015). The superficial conjunctival epithelium contains mucin-producing goblet cells, which together with lymphoid cells and resident T-cells (Bose et al., 2017; Gipson, 2004, 2016) play a key role in the ocular defense and immunological protection of the tear film. Lubrication sustains a healthy tear film as well as aiding the movement of the eyelids and eyeball (Gipson, 2004, 2016). The conjunctiva expresses cell-surface regulatory proteins such as CD55 and CD59 (Table 1) (Bardenstein et al., 1994; Bora et al., 1993)