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Review

The role of complement system in ocular diseases including uveitis and macular degeneration

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Abstract

In the normal eye, the complement system is continuously activated at low levels and both membrane-bound and soluble intraocular complement regulatory proteins tightly regulate this spontaneous complement activation. This allows protection against pathogens without causing any damage to self-tissue and vision loss. The complement system and complement regulatory proteins control the intraocular inflammation in autoimmune uveitis and play an important role in the development of corneal inflammation, age-related macular degeneration and diabetic retinopathy. The evidence derived from both animal models and patient studies support the concept that complement inhibition is a relevant therapeutic target in the treatment of various ocular diseases. Currently, several clinical trials using complement inhibitors are going on. It is possible that, in the near future, complement inhibitors might be used as therapeutic agents in eye clinics.

Keywords: Complement; Eye; Corneal inflammation; Uveitis; Age related macular degeneration; Diabetic retinopathy

1. Introduction

The complement system is a key component of innate immunity. It consists of a large group of plasma and membrane bound proteins that play a central role in the defense against infection and in the modulation of immune and inflammatory responses (Atkinson and Frank, 1980; Ross, 1986; Muller-Eberhard, 1988; Frank and Fries, 1991). The complement system can be activated via three distinct pathways namely, the classical, the alternative and the lectin pathways and complement activation triggers a sequence of biological reactions (Atkinson and Frank, 1980; Ross, 1986; Muller-Eberhard, 1988; Frank and Fries, 1991; Reid, 1986; Morgan and Harris, 1999; Thiel et al., 1997). The classical pathway can be activated by immune complexes or by substances such as C-reactive protein, and the complement components involved include C1, C2, C4 and C3 (Muller-Eberhard, 1988; Frank and Fries, 1991). The alternative pathway provides a rapid, antibody-independent route of complement activation and amplification. The alternative pathway directly activates C3 when it interacts with certain activating surfaces (e.g. zymosan, lipopolysaccharides) and involves C3, Factor B, Factor D and properdin (Reid, 1986; Morgan and Harris, 1999). The activation of the lectin pathway is also independent of immune complex generation and can be achieved by interaction of certain serum lectins, such as mannose binding lectin (MBL), with mannose and *N*-acetyl glucosamine residues present in abundance in bacterial cell walls (Thiel et al., 1997).

Activated complement is a double-edged sword that not only helps defend the host against pathogens, but also has the potential to inflict damage to self-tissues (Liszewski et al., 1996; Atkinson and Farries, 1987). Thus, it is critical for the body to maintain a balance between complement activation and complement inhibition (Atkinson and Farries, 1987). To protect the host from destructive effects of complement-mediated damage, complement activation is tightly regulated by the complement regulatory proteins—CRegs (Morgan and Harris, 1999). CRegs can be categorized into two classes—membrane bound and soluble proteins. Decay accelerating factor (DAF, CD55), membrane cofactor protein (MCP, CD46), complement receptor 1 (CR1, CD35), and membrane inhibitor of reactive lysis (MIRL, CD59) are important membrane bound CRegs. DAF regulates the activation of C3 and C5 by preventing the formation of C3 and

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C5 convertases and by accelerating the decay of these convertases (Lublin and Atkinson, 1987; Nicholson-Weller, 1992). MCP down regulates the complement cascade by acting as a cofactor for Factor I-mediated cleavage of C3b (Liszewski et al., 1991, 1996; Liszewski and Atkinson, 1992). CR1 has both DAF and MCP functions (Krych-Goldberg and Atkinson, 2001). CD59 regulates the assembly and function of membrane attack complex—MAC (Holguin and Parker, 1992; Watts et al., 1990). Crry (5I2 antigen) is a membrane bound CReg that is present in rodents only and has both decay accelerating and co-factor activities. It controls complement activation at the critical step of C3 convertase formation (Kim et al., 1995a; Takizawa et al., 1994; Molina et al., 1992). Tissue distribution studies have shown that both Crry and CD59 are widely distributed proteins in rodents (Li et al., 1993; Powell et al., 1997; Qian et al., 2000). DAF and MCP have also been identified in rodents (Spicer et al., 1995; Miwa et al., 1998). C1 inhibitor (C1INH), C4 binding protein (C4bp), complement Factor H (CFH), and complement Factor I (CFI), are some of the important soluble CRegs. C1INH regulates C1 whereas C4bp catalyses the cleavage of C4b by CFI. CFH acts as a cofactor for CFI-mediated cleavage of C3b and also has decay accelerating activity against the alternative pathway C3 convertase, C3bBb. Soluble forms of MCP, DAF, CR1, CD59 and Crry have been reported to be present in various biological fluids. These soluble forms may be the products resulting from proteolysis, alternative splicing of mRNA, or post-translational modification (Wheeler et al., 2002; Nonaka et al., 1995; Nickells et al., 1994).

2. Complement and ocular protection

Several reports in the literature have suggested the presence of functionally active classical and alternative complement pathways in the cornea, aqueous humor, tears and retina (Mondino and Brady, 1981; Mondino and Rao, 1983; Bora et al., 1993; Willcox et al., 1997). Various proteins which regulate the activation of the complement system, such as C1 inhibitor, DAF, MCP, CD59, Factor I and Factor H, have been reported to be present in various ocular tissues, tears, aqueous and vitreous humor (Willcox et al., 1997; Bora et al., 1993). We have reported that a functionally active complement system is present in normal rodent eye (Sohn et al., 2000a). It was further demonstrated in this report that the complement system is continuously active at a low level in the normal rodent eye, and intraocular CRegs present in the intraocular fluid as well as on the cell membrane tightly regulate this spontaneous complement activation (Sohn et al., 2000a,b). Control of complement activation at the level of C3 convertase was sufficient to prevent complement-mediated intraocular inflammation (Sohn et al., 2000a).

3. Complement and ocular diseases

The presence and activation of complement has been suggested to play a crucial role in the pathogenesis of a large number of diseases, including ocular diseases (Thurman and Holers, 2006).

3.1. Complement and corneal disease

The ocular surface that consists of the cornea and the conjunctiva, is constantly exposed to the external environment, therefore is in contact with a variety of pathogenic microorganisms and inflammatory antigens. The complement system plays an important role in protection of the cornea from these insults. Components of both the classical and alternative pathways of complement (C1, C4, C2, C3, C5, C6, C7, properdin and Factor B) are present in normal cornea. It has been suggested that the cornea has the capability to activate the complement cascades in response to bacterial infection (Mondino and Sumner, 1990; Mondino et al., 1996). Cleveland and associates demonstrated that depletion of C3 by cobra venom factor (CVF) renders the normally resistant DBA/2 mice susceptible to corneal infection with *Pseudomonas aeruginosa* (Cleveland et al., 1983; Hazlett and Berk, 1984). However, C5 deficient mice are still resistant to corneal *P. aeruginosa* infection indicating that the complete lytic pathway of complement is not essential for host resistance towards this gram-negative bacterium. These findings suggest that the functions associated with C3 such as opsonization and regulation of phagocytosis, may be critical in protection of the cornea from bacterial infection (Cleveland et al., 1983; Hazlett and Berk, 1984).

Although the complement system is critical for the protection of the cornea from infection, spontaneous complement activation can cause damage to the corneal tissue after the infection is cleared. To protect from this complement-mediated damage, the cornea expresses membrane bound CRegs such as MCP, DAF, Crry and CD59 (Bora et al., 1993; Bardenstein et al., 1994; Sohn et al., 2000a). These CRegs are heavily expressed in the corneal epithelium at the limbus, as well as in the central cornea. High expression of CRegs is crucial for the protection of cornea because the cornea is constantly being challenged by a variety of substances, including infectious organisms that produce phospholipase and other enzymes, which can remove CRegs from ocular cell surface (Cocuzzi et al., 2000). This bacterially induced loss of CRegs on the cornea could lead to the damage of ocular tissue by autologous complement activation during the course of complement attack on pathogens.

3.2. Complement and autoimmune uveitis

Uveitis is broadly defined as inflammation of the uvea (comprising choroids, iris and ciliary body), and is responsible for almost 3% of blindness in the United States. Each year, 17.6% of active uveitis patients experience a transient or permanent loss of vision. The study of uveitis is complicated by the fact that it encompasses a wide range of underlying etiologies. It may be idiopathic, associated with systemic diseases, or resulting from a variety of infectious agents. Anatomically, uveitis is classified as anterior (iritis, iridocyclitis), intermediate, posterior (vitritis, retinitis, choroiditis) or pan. Anterior uveitis (AU) is the most common form of uveitis and accounts for approximately 75% of cases. The most common form of anterior uveitis is of unknown (i.e. idiopathic) etiology (Bora and Kaplan, 2007). In a