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Review

Relationship between the complement system, risk factors and prediction models in age-related macular degeneration

Nalini S. Bora*, Bharati Matta, Valeriy V. Lyzogubov, Puran S. Bora

Department of Ophthalmology, Jones Eye Institute, Pat and Willard Walker Eye Research Center, University of Arkansas for Medical Sciences, 4301 West Markham, Little Rock, AR 72205, USA

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ABSTRACT

Studies performed over the past decade in humans and experimental animals have been a major source of information and improved our understanding of how dysregulation of the complement system contributes to age-related macular degeneration (AMD) pathology. Drusen, the hall-mark of dry-type AMD are reported to be the by-product of complement mediated inflammatory processes. In wet AMD, unregulated complement activation results in increased production of angiogenic growth factors leading to choroidal neovascularization both in humans and in animal models. In this review article we have linked the complement system with modifiable and non-modifiable AMD risk factors as well as with prediction models of AMD. Understanding the association between the complement system, risk factors and prediction models will help improve our understanding of AMD pathology and management of this disease.

1. The complement system

The complement system is a major component of the innate immunity and provides a first line of defense by modulating immune and inflammatory responses especially when the adaptive immune system of the host has yet to fully develop (Atkinson and Frank, 1980; Morgan and Harris, 1999; Bora et al., 2008, 2011; Dzik, 2010). Complement system is now known to play an important role in adaptive immune responses involving T and B cells and serves as a bridge between innate and adaptive immunity (Kemper and Atkinson, 2007; Walport, 2001a,b). Furthermore, the complement system has been shown to play an important role in maintaining tissue homeostasis and cellular integrity as well as in tissue regeneration (Ricklin et al., 2010).

Complement system consists of a network of approximately forty plasma and membrane bound proteins (Atkinson and Frank, 1980; Ross, 1986; Muller-Eberhard, 1988). Complement proteins circulate in an inactive form but in response to various stimuli, they get activated in a cascading manner via three well defined pathways namely, the classical, the alternative and the lectin pathways (Atkinson and Farries, 1987; Liszewski and Atkinson, 2011, 1992; Sacks and Zhou, 2012). Complement activation via these pathways (Fig. 1) involves a series of initiation, cleavage and amplification steps where complement proteins interact with one another in a tightly regulated manner (Liszewski and Atkinson, 2011, 1992; Sacks and Zhou, 2012).

Complement activation generates multiple activation products with potent biological activity and these biologically active molecules promote and perpetuate immune and inflammatory reactions (Bora et al., 2008; Muller-Eberhard, 1988; Kemper and Atkinson, 2007). The low level of complement activation is beneficial to the host because it provides immune surveillance against foreign particles (cell, bacteria and viruses) and facilitates removal of potentially damaging particles such as immune complexes, abnormal cells (apoptotic cells) and cellular debris from the body (Bora et al., 2008; Kondos et al., 2010). Additionally, a moderately activated complement system plays a role in organ regeneration and protection including protection of the eye (Sohn et al., 2000a; Rutkowski et al., 2010). However, the fact that the activated complement cannot discriminate between self-tissues and foreign particles; unregulated complement activation has the potential to cause substantial damage to self-tissues leading to various diseases including ocular diseases (Köhl, 2006; Sohn et al., 2000a,b, 2007).

In order to maintain the proper physiological state, cell and tissue integrity and prevent immunopathology, it is necessary for the host that the complement system is appropriately regulated so that there is targeted activation against the foreign particles only. Several regulatory mechanisms in the form of complement

* Corresponding author at: Department of Ophthalmology, Jones Eye Institute, University of Arkansas for Medical Sciences, 4301 West Markham, Mail Slot 523, Little Rock, AR 72205, USA. Tel.: +1 501 686 8293; fax: +1 501 686 8316.
E-mail address: nbora@uams.edu (N.S. Bora).

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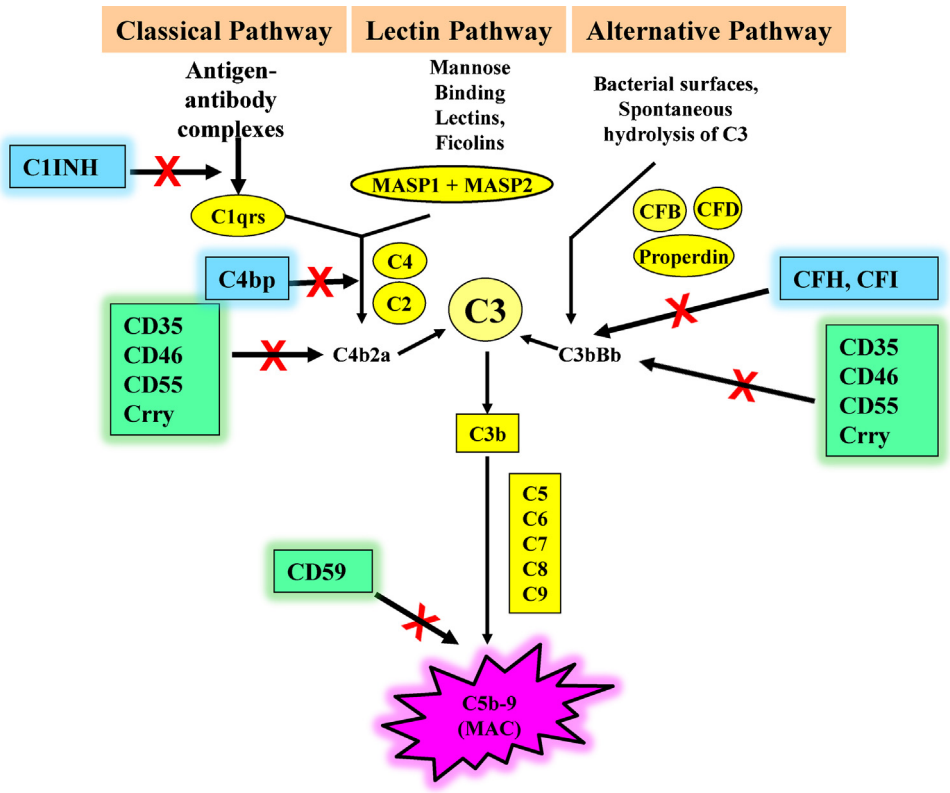

Fig. 1. Schematic diagram shows complement activation pathways and complement regulatory proteins (CRegs). The site of action of membrane bound CRegs (green boxes) and soluble CRegs (blue boxes) are shown with red X.

regulatory proteins (CRegs) are in place that allows the host cells to limit complement activation and formation of complement activation products on their surface (Morgan and Harris, 1999; Bora et al., 2008). CRegs regulate complement system at multiple levels (Fig. 1) by regulating the progression of complement activation (Atkinson and Farries, 1987; Morgan and Harris, 1999; Bora et al., 2008) or by regulating the function of various biologically active molecules generated during complement activation (Morgan and Harris, 1999; Bora et al., 2008). CRegs can be classified in two categories – (1) CRegs bound to the surface of host cells (Morgan and Harris, 1999; Bora et al., 2008); (2) CRegs present in the plasma and body fluids as soluble proteins (Morgan and Harris, 1999; Bora et al., 2008). Examples of membrane bound CRegs (Fig. 1) include Decay Accelerating Factor (DAF, CD55), Membrane Cofactor Protein (MCP, CD46), Complement Receptor 1 (CR1, CD35), Membrane Inhibitor of Reactive Lysis (MIRL, CD59) and Crry. Crry is present in rodents only (Molina, 2002; Ricklin et al., 2010; Morgan and Harris, 1999). C1 inhibitor (C1INH), C4 binding protein (C4bp), complement factor H (CFH), and complement factor I (CFI), are example of soluble CRegs (Fig. 1). Soluble forms of CD55, CD46, CD35, CD59 and Crry are also present in various body fluids such as blood, seminal fluid, urine, tears and intraocular fluid (Sohn et al., 2000a,b).

2. Age-related macular degeneration (AMD)

In age-related macular degeneration (AMD) there is loss of the central vision in people over the age of 50 (Coleman et al., 2008; Zarbin, 2004; Zarbin and Rosenfeld, 2010; Hageman et al., 2005; Mullins et al., 2000). Macular degeneration is characterized by damage to or loss of photoreceptor and/or retinal pigment epithelium (RPE) within the macular region of the retina (Campochiaro, 2000; de Jong, 2006). AMD is a progressive chronic degenerative disease. Two major clinical phenotypes of AMD are recognized–a non-exudative (dry-type), and an exudative (wet-type). Dry AMD is characterized by the presence of drusen (large extracellular deposits) and RPE abnormalities including geographic atrophy (degeneration of RPE). Wet AMD is characterized by choroidal neovascularization (CNV), RPE or neuronal retinal detachment, retinal hemorrhage and fibrous scarring (Lim et al., 2012; Woo et al., 2009; Visual impairment and blindness, Word Health Organization). Wet AMD usually develops after dry AMD (Donoso et al., 2006; de Jong, 2006; Ambati and Fowler, 2012) and catastrophic vision loss is more frequently associated with wet AMD.

3. Complement and dry AMD

With aging, chronic inflammation develops locally as a result of continuous complement activation via the alternative pathway. Complement activation is one of the major factors responsible for drusen formation in dry-type AMD (Hageman et al., 2008). It has been suggested that complement activation leads to RPE atrophy and photoreceptor degeneration (Hageman et al., 2001; Johnson et al., 2001; Anderson et al., 2010). This leads to alterations in Bruch's membrane, drusen formation and the accumulation of sub-RPE deposits. RPE atrophy and cellular debris in sub-RPE space in turn activate the complement system. This vicious cycle results in further damage to RPE cells and the retina.

Several members of the complement system such as CD46, CD35 (CR1), C5, C6, C9, C8 have been reported to be present in drusen (Johnson et al., 2001; Nussenblatt and Ferris, 2007). Complement activation products such as C3a, C3b, iC3b and C3dg, C3c, C5a, C5b-9 (MAC; membrane attack complex) have also been detected within drusen (Nozaki et al., 2006; Johnson et al., 2001; Nussenblatt and Ferris, 2007). In addition, C-reactive protein, lipofuschin, etc. present within drusen are capable of activating the complement system (Sparrow et al., 2012). Oxidative stress also activates the complement system (Hart et al., 2004). Oxidized products of RPE lipofuschin pigments have been reported to activate the alternative