COMPLEMENT SYSTEM AND THE EYE

Purushottam Jha, Puran S. Bora, Jeong-Hyeon Sohn, Henry J. Kaplan, and Nalini S. Bora.

1. INTRODUCTION

The complement system is a key component of natural immunity and consists of a large group of plasma proteins that play a central role in the defense against infection and in modulation of inflammatory responses. 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.

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. The alternative pathway provides a rapid, antibody-independent route of C 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. 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 protein (MBL), with mannose and N-acetyl glucosamine residues present in abundance in bacterial cell walls.

Complement is a powerful defense system that has the potential to damage host tissue. A critical step in the complement activation sequence is formation of the C3 convertases. These proteases activate the third (C3) complement component, resulting in generation and deposition of the major opsonic fragments C3b and C4b on the cell membrane. In addition, the convertases promote assembly of the membrane attack complex (MAC). Thus, it is essential that the formation and function of C3 convertases be carefully regulated so that the opsonic activity of C3b and the cytolytic activity of MAC are directed against foreign cells and not to self-tissue. The host must be protected from inadvertent activation of complement on its own tissue.
Decay Accelerating Factor (DAF, CD55) and Membrane Cofactor Protein (MCP, CD46) are two important membrane-bound regulatory proteins that downregulate the complement cascade by regulating two critical enzymes — C3 and C5 convertases\textsuperscript{10-14}. Membrane Inhibitor of Reactive Lysis (MIRL, CD59) has the capacity to regulate the assembly and activity of MAC\textsuperscript{15-16}. Crry is a widely distributed complement regulatory protein (CRP) in rodents and has both decay-accelerating and co-factor activities. It controls complement activation at the critical step of C3 convertase formation\textsuperscript{17-20}. Tissue distribution studies have shown that CD59 is a widely distributed protein in rodents also\textsuperscript{21,22}. Recently, MCP and DAF have also been identified in rodents.

2. COMPLEMENT AND OCULAR PROTECTION

Sohn et al.\textsuperscript{23} demonstrated that the functionally active complement system is present in the normal eye because anterior chamber injection of zymosan induced severe anterior uveitis. Immunohistologic staining of the normal rat eye revealed that, even when there was no inflammation, low levels of iC3b and MAC were present. These results suggested that the complement system is active at a low level in the normal eye and may provide immediate protection against various pathogens. Sohn et al.\textsuperscript{23} also demonstrated that intraocular complement regulatory proteins tightly regulate this spontaneous complement activation. Control of complement activation at the level of C3 convertase was sufficient to prevent complement-mediated intraocular inflammation.

3. COMPLEMENT AND OCULAR DISEASES

Inappropriate activation of complement has been reported to play an important role in the pathogenesis of various diseases, including ocular ones.

3.1. Complement and Corneal Disease

Several investigators have shown that membrane-bound complement regulatory proteins (CRPs) — MCP, DAF, Crry, and CD59 — are differentially expressed in the normal human and rodent eyes\textsuperscript{24-26}. All of these proteins are very strongly expressed in the corneal epithelium and the limbus, as well as on the central cornea. This overexpression is very 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 that can remove CRPs from ocular cell surfaces. The bacterially induced loss of CRPs on the cornea could lead to damage of ocular tissue by autologous complement activation in the course of complement attack on pathogens. Complement activation is believed to play an important role in ulceration of the human cornea induced by Gram-negative bacteria\textsuperscript{27}. Cleveland and associates\textsuperscript{28} demonstrated