CHAPTER 3

Bacterial Complement Escape
Ilse Jongerius, Sanjay Ram and Suzan Rooijakkers*

Abstract

Complement activation is a crucial step in our innate immune defense against invading bacteria. Complement proteins can quickly recognize invading bacteria and subsequently label them for phagocytosis or kill them by direct lysis. In order to survive in the human host, bacterial pathogens have evolved a number of excreted and membrane-bound proteins that interfere with several steps of the complement cascade. In this chapter we summarize the most successful complement-modulating strategies by human bacterial pathogens.

Introduction

The complement system is a major mediator of the innate immune system, our first line of defense against invading micro-organisms. The complement consists of more than thirty proteins in plasma and on cell surfaces and its activation results in a quick and effective defense against invading microbes. An important eradication strategy is the opsonization of foreign substances with C3b and iC3b which marks them for uptake by neutrophils via complement receptors (CR). Furthermore, Gram-negative bacteria can be directly killed via the formation of C5b-9, the membrane attack complex (MAC). The complement system also forms a bridge between the innate and adaptive immune system since C3d, the degradation product of C3b and iC3b, facilitates antigen presentation to B-cells.

The complement system comprises three different activation routes to recognize extrinsic substances (Fig. 1): the classical (CP), the lectin (LP) and the alternative (AP) pathway. The CP is activated by binding of C1q to IgG or IgM molecules bound to the microbial surface. The C1q-attached serine protease Cls in turn cleaves C4 resulting in formation of the anaphylatoxic peptide C4a and C4b. Then C4b molecule covalently binds to the bacterial surface due to exposure of its internal thioester that reacts with hydroxyl (creating an ester bond) or amino groups (creating an amide bond). Then C2 binds to surface-bound C4b whereupon it is cleaved by activated C1s to form the CP C3 convertase C4b2a.

The LP is highly similar to the CP and its activation also results in the formation of C4b2a. The recognition molecules of the LP are mannan-binding lectin (MBL) and ficolins (L-, H- or M-ficolin). These lectins are structurally similar to C1q although they recognize microbial sugar patterns instead of immune complexes. MBL and ficolins recognize neutral sugars (preferentially mannose, N-acetylglucosamine (GlcNAc) and fucose) when presented in a repetitive manner such as on the surface of a range of microbes. MBL and ficolins are associated with MBL-associated serine protease (MASP)-1, MASP-2, MASP-3 and a nonprotease small MBL-associated protein (sMAP or MAP19). MASP-2 is the only protease known to be responsible for cleavage of C4 and C2 to generate the C3 convertase C4b2a. Other less well-defined functions of MASPs are activation of the AP by direct cleavage of C3 by MASP-1 and activation of the coagulation system by MASP-2.

*Corresponding Author: Suzan Rooijakkers—Medical Microbiology, HP G04.614, University Medical Center Utrecht, The Netherlands. Email: s.h.m.rooijakkers@umcutrecht.nl

The AP is either activated by spontaneous hydrolysis of the internal thioester bond in C3 (forming C3(H₂O)) or by covalent attachment of C3b to bacterial surfaces via the CP and LP. Factor B binds to both surface-bound C3b and fluid-phase C3(H₂O) and is in turn cleaved by factor D to form a fluid-phase C3 convertase C3(H₂O)Bb or a surface-bound C3bBb complex.\(^7\)\(^8\)

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Figure 1. Schematic overview of the complement system. Complement activation can occur via three different pathways. The antibody-dependent Classical Pathway starts when C1q in the C1q-C1r-C1s complex recognizes antibodies that are bound to the microbial surface. In the Lectin Pathway, Mannose Binding Lectin (MBL) and Ficolins recognize microbial sugar patterns and activate the MBL-associated serine protease 2 (MASP-2). Both C1s and MASP-2 can cleave complement proteins C4 and C2 to generate the CP/LP C3 convertase: C4b2a. Within this complex, C4b is covalently (*) attached to the microbial surface. The Alternative Pathway C3 convertase (C3bBb) is generated after binding of factor B (fB) to surface-bound C3b or fluid-phase C3(H₂O). Factor B is subsequently cleaved by factor D (fD) to generate C3bBb. Both C3 convertases C4b2a and C3bBb cleave C3 into covalently bound C3b (*) and an anaphylatoxin C3a. C3b contributes to phagocytosis, antigen presentation and formation of CS convertases, C4b2a3b and C3bBb3b. C5 convertases cleave C5 into an anaphylatoxin C5a and C5b, which forms a complex with complement proteins C6, C7, C8 and C9 to generate the membrane attack complex (MAC) and mediate microbial lysis.