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Review

Bacterial complement evasion

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Abstract

The human complement system is elemental to recognize bacteria, opsonize them for handling by phagocytes, or kill them by direct lysis. However, successful bacterial pathogens have in turn evolved ingenious strategies to overcome this part of the immune system. In this review we discuss the different stages of complement activation sequentially and illustrate the immune evasion strategies that various bacteria have developed to evade each subsequent step. The focus is on bacterial proteins, either surface-bound or excreted, that block complement activation. The underlying molecular mechanism of action and the possible role in pathophysiology of bacterial infections are discussed.
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1. Introduction

The complement system is an essential and effective part of the innate immune system. It can rapidly recognize and opsonize bacteria for phagocytosis by professional phagocytes or kill them directly by membrane perturbations. Therefore it is to no surprise that bacteria have evolved a whole array of highly specific complement-modulating strategies. In this way bacteria can either stop or delay the detrimental effects of an innate immune attack, thereby creating a window of opportunity to divide and create a microenvironment that allows an even better survival. The human complement system consists of more than thirty proteins in plasma and on cells. The complement system is organized in three different initiation pathways that all converge at one step: the cleavage of the central complement protein C3 (Walport, 2001a,b). The three different complement pathways are represented by the classical (CP), the lectin (LP) and the alternative (AP) pathway. These pathways consist of different recognition molecules to sense a foreign substance. After recognition, these pathways use similar activation mechanisms to generate C3 convertases, the enzymes that cleave C3. The attachment of C3b to acceptor cells is necessary to initiate phagocytosis, formation of the membrane attack complex (MAC) and enhancement of humoral responses to antigens (Gasque, 2004).

In this overview we have divided the activation steps of the complement system in the following sequential phases: 'initial steps' (2), 'convertases' (3), 'C3 and its degradation products' (4), 'the terminal pathway' (5), 'host regulators' (6) and 'receptors' (7). In these chapters, the bacterial inhibitors that have been identified for these subsequent steps will be discussed.

2. Modulation of the initial steps

The primary step in complement activation is the binding of recognition molecules to the microbe. For the classical pathway this is achieved through the binding of C1q to IgG or IgM that is specifically bound to the surface of the microbe (Duncan and Winter, 1988). C1q is complexed with two serine proteases, C1r and C1s (Sim and Laich (2000)). When the globular heads of C1q bind to an activator, the associated C1r undergoes auto activation and activates C1s. Activated C1s then cleaves C4 to generate C4b and the anaphylatoxic peptide C4a. Exposed within the C4b is a highly labile internal thiol ester, which is able to react with hydroxyl groups (creating an ester bond) and amino groups (creating an amide bond) (Law and Dodds, 1997). C2 binds to surface-bound C4b and activated C1s of the nearby C1 complex cleaves C2 to release the small C2b fragment and form the classical pathway C3 convertase, C4b2a.

The lectin pathway (LP) is highly analogous to the CP and its activation also results in formation of C4b2a (Matsushita and Fujita, 2001). However, the recognition molecules for the

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lectin pathway recognize microbial sugars instead of immune complexes. The recognition molecules of the LP are mannan-binding lectin (MBL) and ficolin (L-, H- or M-ficolin) (Fujita, 2004). These lectins are structurally similar to C1q. MBL binds in a Ca^{2+}-dependent manner to the target via its C-type lectin domains, which recognize neutral sugars (preferentially mannose, *N*-acetylglucosamine and fucose) on the surfaces of a range of microorganisms, such as *Neisseria* and *Leishmania* species (Holmskov et al., 2003). L-Ficolin binds GlcNAc and peptidoglycan. In circulation, both MBL and ficolins are associated with several proteases called MBL-associated serine proteases (MASPs) (Matsushita et al., 2000). MASP-1, MASP-2 and MASP-3 are structurally similar to C1r and C1s. However, only MASP-2 is known to cleave complement components C4 and C2 and thereby generate C4b2a.

The alternative pathway (AP) mainly functions as an amplification loop of the CP and LP after surface-bound C3b is created. However, it can also be spontaneously activated by hydrolysis of the internal thioester bond in C3 (0.005%/min) (Sahu and Lambris, 2001), forming the so-called $C3H_2O$. Just like particle-bound C3b, this $C3H_2O$ can participate in the formation of the AP C3 convertase. Both surface-bound C3b and $C3H_2O$ can bind factor B. The resulting complexes are recognized by factor D (Xu et al., 2001). Unlike other complement serine proteases that are present as zymogens in the serum, factor D circulates in its active form. Factor D cleaves factor B to release Ba and yield the activated $C3H_2O$ Bb complex, an unstable fluid-phase C3 convertase, or a surface-bound C3bBb complex.

Bacteria have evolved several modulators of these initial steps in complement activation. So far no inhibitors of the lectin pathway components have been described but, since this pathway has been discovered only recently, we envision that bacterial modulators will emerge in the coming years.

Although many biological roles have been attributed to *Staphylococcal protein A* (*SpA*), its capacity to bind the Fc part of IgG is still the most established one (Silverman et al., 2005). SpA is a type I membrane protein that is bound to the cell wall of *Staphylococcus aureus* via its C-terminal cell-wall-binding region X. In the N-terminal half of the protein are its IgG-binding domains E, D, A, B, and C. Through binding of IgG, protein A blocks Fc-receptor mediated phagocytosis but is also a highly efficient complement activation modulator by interfering with binding of C1q (Verhoef et al., 2004; Forsgren et al., 1966; Goward et al., 1993). SpA is surface-bound, but can also be released in the surrounding environment during growth of the peptidoglycan layer to which it is attached. A second IgG-binding protein has been reported in *S. aureus* called *Sbi* (Zhang et al., 1998). The protein consists of 436 amino acids and exhibits an immunoglobulin-binding specificity similar to protein A. Its role in complement modulation remains to be established.

In other bacteria, proteins with similar functions have been described. *Protein G*, a bacterial cell wall protein with comparable affinity for IgG, was isolated from group G streptococci. With a molecular weight of 30 kDa, Protein G was found to bind all human IgG subclasses but also rabbit, mouse, and goat IgG. On the IgG molecule, the Fc part appears mainly responsible for the interaction with protein G, although a low degree interaction was also recorded for Fab fragments. IgM, IgA, and IgD, however, showed no binding to protein G (Bjorck and Kronvall, 1984). By the same group, *Protein L* was isolated from the surface of the anaerobic bacterium *Peptostreptococcus magnus* (Bjorck, 1988). Although this protein binds both IgM and IgG, it seems to have no affinity for the Fc-part of immunoglobulins but rather for Fab parts. A role in complement inhibition could not be demonstrated and its role is more likely as a B-cell superantigen (Genovese et al., 2003).

The majority of group A streptococci (GAS) express, next to the well known M proteins, structurally similar M-related proteins, *Mrp* and *Enn*, which have been described as IgG- and IgA-binding proteins. Subsequent analysis of phagocytosis by flow cytometry indicates that, if present, both *mrp* and *emm* gene products contribute to phagocytosis resistance by decreasing bacterial binding to granulocytes (Podbielski et al., 1996). GAS also produce two immunoglobulin-degrading enzymes: the streptococcal cysteine proteinases, *IdeS* and *SpeB*, that both cleave IgG specifically in the hinge region, and thus removing the entire Fc region from IgG molecules that are attached to the bacterium (Von Pawel-Rammingen and Bjorck, 2003).

Similarly, staphylococci hinder IgG-mediated effector functions by the excretion of *Staphylokinase* (*SAK*). *S. aureus* expresses several plasminogen (PLG)-binding receptors at their surface and this surface-bound PLG can be activated into plasmin (PL) by SAK. Surface-bound PL has the ability to cleave both IgG and C3b. Recently we showed that PL, formed by the conversion of PLG by SAK at physiological concentrations, leads to opsonin removal. PL cleaves human IgG from the bacterial cell wall leading to impaired phagocytosis by human neutrophils (Rooijakkers et al., 2005a). PL cleaves IgG at position Lys 222, and thus removes the entire Fc fragment, including the glycosylation site (Asn 297) necessary for recognition by C1q thereby inhibiting the activation of the classical pathway of complement.

A similar strategy is employed by a protease from *Porphyromonas gingivalis*, a pathogen in human periodontitis. The *prtH gene* encodes a 97-kDa active protease, which degrades C3 and IgG. An allelic exchange mutant of *P. gingivalis*, in which the prtH gene was inactivated, is less virulent in a mouse model of bacterial invasiveness. Also, in comparison with its parent strain, the mutant strain is less able to degrade C3 and accumulates significantly greater numbers of molecules of C3b and iC3b on the bacterial surface during complement activation, resulting in increased phagocytosis by human neutrophils as compared to the wild type suggesting a function of the prtH gene product may be important in evasion of host defense mechanisms (Schenkein et al., 1995).

Also, bacteria can target C1 itself. The fish pathogen *Aeromonas salmonicida*, encodes a 40 kDa C1q-binding outer membrane protein. This *40 kDa porin* binds C1q in an antibody independent process, and its in vivo role in serum resistance was established. The 40 kDa porin gene and/or protein was present in all the A. salmonicida typical or atypical strains tested (Merino et al., 2005). Two excreted enzymes from

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