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Review

Complement evasion of pathogens: Common strategies are shared by diverse organisms

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Abstract

Infectious diseases represent a major health problem. Based on the limited efficacy of existing drugs and vaccines and the increasing antibiotic resistance new strategies are needed to fight infectious diseases. A better understanding of pathogen–host interaction is one important aspect to identify new virulence factors and antimicrobial and anti-inflammatory compounds utilized by pathogens represent an additional source for effective anti-inflammatory compounds. Complement forms a major defense line against invading microbes, and pathogens have learned during evolution to breach this defense line. The characterization of how pathogens evade complement attack is a rapidly developing field of current research. Pathogens mimic host surfaces and bind host complement regulators. Similarly pathogens utilize a number of complement inhibitory molecules which help to evade complement attack and which display anti-inflammatory activity. The molecular identification of these molecules, as well as the functional characterization of their roles at the pathogen–host interface is an important and emerging field of infection biology. In addition, pathogens utilize multiple sets of such regulators as redundancy and multiplicity is important for immune and complement evasion. Here we summarize the current scenarios of this emerging field which identifies multiple virulence factors and complement evasion strategies, but which at the same time reveals common mechanisms for immune and complement defense.

Keywords: Human; Complement; Bacterial infections

1. Introduction

Infectious diseases represent a major health, social and economic problem. Although treatment and management of microbial infections has improved during the last decades, the increase in antimicrobial resistance, the emergence of new pathogens and re-emergence of known pathogens form a major threat for health systems in all countries of the world (Fauci, 2006).

Antimicrobial agents in the form of antibiotics and vaccines are generally used to fight microbes and pathogens. However the limited efficacy of existing antibiotics, the increasing antibiotic resistance of both hospital and community acquired pathogens and the availability of suboptimal vaccines represent major health problems. Therefore new strategies are crucial for fighting infectious diseases. Development of new antimicrobial substances requires a better characterization of pathogen-encoded virulence factors and a more detailed understanding of pathogen–host interaction.

The complement system of the vertebrate host forms a powerful immune barrier. Upon entry of a foreign invader, this defense system is activated within seconds. The activated complement system generates a finely regulated and very potent antimicrobial response. Thus, in order to establish an infection, pathogens need to inhibit, control and prevent complement recognition and inhibit effector function. Many pathogens have evolved the means to control host complement response and to this end pathogens utilize multiple evasion strategies to interfere with and to inactivate the powerful complement attack. Analyses of complement evasion strategies used by pathogenic microbes is an active research area and multiple complement evasion strategies have been characterized in recent years.

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In several studies, the proteins encoded by the pathogen, which are essential for this immune escape, were identified as novel virulence factors, representing interesting targets for immune interference (Dobrindt et al., 2004). Complement and immune evasion strategies at first seem both diverse and unique for each pathogen. However, detailed functional characterization of the escape strategies identifies common features and mechanisms of complement escape.

All microbes and pathogens including Gram-negative and Gram-positive bacteria, pathogenic fungi, multicellular organisms, as well as parasites and viruses are attacked and targeted by the complement systems of their hosts. While non-pathogenic microbes are normally recognized and eliminated by the activated complement system, pathogens utilize strategies to evade this type of host immune recognition and immune defense.

The multiple complement and immune evasion strategies used by the wide range of microbes are covered in recent reviews (Zipfel et al., 2002; Hillman, 2004; Kraiczy and Würzner, 2006; Mark et al., 2007; Rooijakkers and van Strijp, 2007). In this review we focus on the common mechanisms which are emerging for complement escape of pathogens.

2. Host complement defense and pathogen complement evasion

2.1. Host complement defense

The complement system is part of the innate immune defense of a vertebrate host, which forms a major and early barrier for invading microbes and pathogens. Upon entry of an invader, complement is promptly activated and attacks by opsonization and target lysis (Walport, 2001). In addition, the activated complement system induces inflammatory reactions which initiate additional cellular effector functions of both the innate and adaptive immune response (Kemper and Atkinson, 2007).

2.2. Pathogen complement evasion

As every pathogen is recognized and attacked by the immune system, successful pathogens have developed strategies to evade host defense. In recent times multiple pathogen-specific proteins have been isolated which mediate escape from complement attack. Additional novel molecules are currently being identified which mediate this type of complement escape. The detailed molecular and functional analyses of the individual proteins revealed diverse mechanisms in avoiding immune recognition as well as inhibition of complement effector mechanisms. Nevertheless, common principles of complement disguise and immune evasion strategies used by microbes are emerging.

The intriguing part of this development is the complex nature of the interaction and the diversity of the response. Given the powerful role of complement in immune defense a pathogen, in order to establish an infection, must overcome this immediately acting first line of host defense. Therefore pathogens have developed escape strategies to evade complement attack. The current research in this field shows that a single pathogen may utilize multiple strategies and molecules to evade host complement attack. An expanding number of pathogens encode host complement regulator binding proteins as well as complement inhibitors. Although these molecules are diverse in nature and sequence, they have evolved to inactivate the same type of host immune attack. Human pathogens, represent a highly diverse group of organism. Gram-negative and Gram-positive bacteria, human pathogenic fungi, multicellular organisms, parasites and viruses all face the same conserved and constant complement attack as part of the host innate immune response. An intriguing aspect of this expanding field of complement evasion is the realisation that it is possible to extrapolate the conserved principles of escape, despite the diversity of escape strategies and the variability of the individual proteins. We here summarize the common aspects of this fascinating and rapidly developing research field.

2.3. Selected examples

For several pathogens the complement evasion strategies are relatively well understood in molecular terms, and therefore we have chosen to extrapolate the basic principles and mechanisms of complement escape by focusing on a selected group of pathogens. These well-characterized pathogens include:

Streptococcus pyogenes, also known as Group A streptococcus, is a strictly human pathogen. *S. pyogenes* is a common cause of pharyngeal, skin, and soft-tissue infections. This pathogen, which is responsible for a wide variety of diseases, including scarlet fever, pharyngitis and impetigo, is transmitted via the upper respiratory tract or damaged skin (Courtney et al., 2002, 2006). The immune defense of *S. pyogenes* has been studied in detail and the M protein, which is attached to the cell surface, acts as virulence factor and binds multiple soluble host plasma proteins. Additional proteins such as Fba and ScpA are exposed on the surface of streptococci, which also bind and acquire host complement components (Cunningham, 2000).

Streptococcus pneumonia (or pneumococcus) is a human pathogen causing diseases such as otitis media, meningitis, bacteremia and pneumonia. Several antibiotic-resistant strains are currently identified and vaccines are not completely protective against infection (Tuomanen et al., 1995). Recently the pneumococcal surface protein C (PspC; also termed CbpA, HIC, PbcA, SpsA and Sp2190) has been described and expression studies identified this protein in all analyzed clinical isolates. The PspC genes show a high level of sequence variability (Lopez, 2006).

Borrelia burgdorferi. The Lyme disease-causing spirochete *B burgdorferi s.l.* is transmitted to mammalian hosts by bites from ticks of the Ioxodes family (Fikrig and Narasimhan, 2006). Complement escape of the spirochetes is largely due to complement disguise, which is mediated by specific surface proteins, termed complement regulator acquiring surface proteins (CRASP), that bind soluble host complement regulators (Kraiczy et al., 2001). Borrelia survive and are adapted to the immune response of diverse hosts, including humans, deer, rodents and lizards.

Staphylococcus aureus. *S. aureus* is a very common human pathogen that causes a wide range of infections and is associated with septic arthritis. The bacterium expresses multiple cell surface proteins and secretes additional proteins that target innate and adaptive immune defenses of the host (Van Belkum et al., 2002).

Pseudomonas aeruginosa is an opportunistic pathogen that causes life-threatening infections in humans, including pneumonia and blood stream infections. This Gram-negative bacterium is a major cause of hospital-acquired infections especially in immunocompromised patients (Lyczak et al., 2000).

Candida albicans is the most important human pathogenic yeast and causes disseminated infections. The yeast form represents a common saprophyte in healthy individuals, which resides mainly on the skin, oral cavity, urogenital and gastrointestinal tracts. However, *C. albicans* can cause systemic infections predominantly in immunocompromised or granulocytopenic patients (Pfaller and Wenzel, 1990).

These diverse pathogens all have the ability to inactivate the complement system and to survive in an immunocompetent host. Each individual pathogen uses a distinct set of surface proteins for complement evasion. The functional characterization of these complement escape proteins shows similar features in terms of binding, interaction profiles and function.

3. Mechanisms of complement evasion and molecules involved

Pathogens facing the host complement system exploit multiple strategies to interfere with this type of innate immune recognition and effector function. They express diverse and multiple surface proteins and secrete additional molecules to avoid and disrupt complement attack and recognition by the innate immune system. Common conserved features include: (i) secretion of proteases, (ii) complement disguise and (iii) expression of complement inhibitors.

3.1. Inactivation by proteases

By secretion of proteases, pathogens control their environment in the infected host. Secreted proteases inactivate complement activation products, such C5a. Group B *streptococci* express a cell surface C5a endopeptidase (ScpB) that cleaves and inactivates C5a, providing a significant advantage for mucosal colonization. Streptococci utilize additional surface proteins, such as streptococcal plasmin receptor (Plr) which, by capturing and binding C5a with high affinity, inhibits the biological effects of C5a on human neutrophils.

Similarly, the Gram-negative bacterium *P. aeruginosa* secretes active proteases in the form of alkaline protease and elastase that cleave C3b and thus inhibit C3b deposition and complement activation at the bacterial surface (Hong and Ghebrehiwet, 1992; Schmidtchen et al., 2003). In addition, LPS variants of *P. aeruginosa* which are expressed at the pathogen surface interfere with C3b deposition (Schiller and Joiner, 1986; Engels et al., 1985).

3.2. Complement disguise

All microbes and pathogens face the same complement system in their human hosts, and each pathogen has developed a means to inactivate this type of immune defense. Attachment of soluble host complement regulators to the surface of the pathogen is a common complement escape mechanism. A large number of pathogens, ranging from Gram-negative (*B. burgdorferi*, *s.l.*, *E. coli*, *P. aeruginosa*, *Neisseria gonorrhoeae* and *N. meningitidis*) and Gram-positive (*S. pyogenes* and *S. pneumoniae*) bacteria, fungi (*Candida albicans*, *Aspergillus fumigatus*) to multicellular eukaryotic organisms and parasites (*Echinococcus granulosis* and *Onchocerca volvulus*), and viruses (HIV, Herpes virus, West Nile virus), use highly similar complement escape strategies. Each of these pathogens bind soluble host complement regulators, including Factor H, factor H-like 1 (CFHL-1), factor H-related 1 (CFHR-1) and C4BP to their surface (Zipfel et al., 2002; Sandin et al., 2006; Meri et al., 2002a,b; Diaz et al., 1997; Gulati et al., 2005; Jarva et al., 2005; Rambach et al., 2005; Chung et al., 2006). Specific examples are listed in Table 1. The number of identified CRASP, for **c**omplement **r**egulator **a**cquiring **s**urface **p**roteins, is constantly growing. The detailed characterization of these immune escape proteins in terms of protein–protein interaction and functional studies identify highly conserved mechanisms of complement escape. Attached to the surface of the pathogen the host complement regulators CFH, CFHL1 and C4BP maintain cofactor activity for inactivating C3b and C4b and thus restrict complement activation.

3.3. Complement escape proteins are polymorphic

Several of these complement escape proteins are polymorphic and show strain specific variation. The M protein of *S. pyogenes* is a dimeric coiled-coiled surface protein and represents one intensively studied virulence factor. The M protein is encoded in the Mga regulon and the gene numbers and sequence differ between individual bacterial strains and between clinical isolates. *S. pyogenes* strains can express one, two or three members of the M protein family (Ribardo and McIver, 2006), which are termed M, Mrp and Enn. As the Mga regulon includes several genes involved in complement inhibition, involvement of these conserved gene clusters in pathogenicity can be assumed (Fig. 1) (Iannelli et al., 2002).

3.4. Sequence diversity

The M protein of *S. pyogenes* shows high antigenic variation, particularly in the N-terminal, solvent exposed, hypervariable region, which is ~50 residues long. Despite this extraordinary sequence diversity these proteins retain the ability to specifically bind host ligands necessary for immune escape. This N-terminal region is strain-specific and includes a binding region for the host regulator C4BP. Thus this hypervariable region of the M proteins derived from several streptococcal isolates combines two important features necessary for host immune evasion: conserved binding of the host complement inhibitor C4BP which allows

Table 1
General features of complement escape proteins of pathogens

Feature	Example	Complement escape protein	Comments
1. CRASP proteins are polymorphic	*S. pyogenes*	M protein family??	
	S pneumonia	PspC	
	Borrelia burgdorferi	CRASP 1	
2. One single CRASP protein binds multiple host proteins	*S. pyogenes*	M protein	
	Borrelia burgdorferi ss	BbCRASP1–BbCRASP5	
	B. hermisii	BhCRASP1	
	C. albicans	CaCRASP1	
3. CRASP proteins have multiple functions	*S. pyogenes*	M protein	Complement evasion Phagocytosis resistance Antiphagocytic
	Borrelia burgdorferi	CRASP1	Complement inhibition Serum resistance
4. Simultaneous expression	*S. pyogenes*	Expression of M protein emm enp and Fba	
	Borrelia burgdorferi ss	Simultaneous expression of CRASP1 to CRASP5	

complement evasion, and sequence variability which generates antigenic variation to evade protective IgG mediated immunity (Persson et al., 2006).

The pneumococcal surface protein C (PspC, also termed CbpA, SpsA, PbcA, SP2190 and HIC) is a major pneumococcal virulence factor. The gene is found in all clinical isolates analyzed so far and shows a high level of sequence variability. Members of the PspC gene family are encoded either by single or by two tandem copy genes and show high sequence variations. PspC proteins have a common structure and organization; based on the different anchor sequences, two subgroups with a total of 11 different PspC protein subtypes were identified. The classical PspC proteins (subtypes 1 to 6) are choline-binding proteins (CBPs) and constitute subgroup 1. The C-terminal choline-binding domain (CBD) attaches the classical PspC proteins non-covalently to the cell wall via an interaction with the phophorylcholine of lipoteichoic and teichoic acids. The second subgroup, representing atypical or PspC-like proteins (subtypes 7 to 11) such as Hic (PspC11.4), is anchored in a sortase-dependent manner to the peptidoglycan of the cell wall by an LPXTG motif. The N-terminal regions of the first PspC subgroup show a common structure and organization. All these proteins have a leader peptide and an N-terminal domain which is followed by either one or two single repeated domains (termed R1 and R2) and a proline-rich sequence. PspC mediates pneumococcal adherence by binding the extracellular, immunoglobulin-like (Ig-like) domains (also known as secretory component) of the polymeric immunoglobulin receptor (pIgR). The specific binding to the human Ig-like ectodomain D3 and D4 of the secretory component (SC) occurs through hexapeptide motifs located in the direct repeats R1 and R2 of PspC. One R domain is sufficient for binding to the SC of pIgR, to free SC or SC as part of secretory IgA.

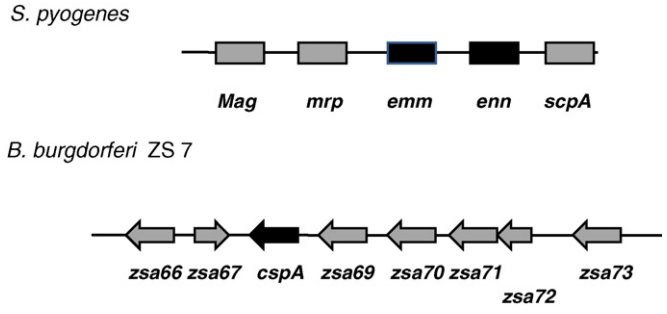

Fig. 1. Genomic organization of the Mga regulon of *S. pyogenes* and the CRASP gene locus of *B. burgdorferi* strain ZS7. *S. pyogenese* utilizes the M protein as a major virulence factor which binds multiple host proteins. The M protein-encoding gene is contained in the Mga regulon which encodes several genes involved in pathogenicity. The product of the Mga gene controls expression of several other genes involved in virulence. The genes of the Mga regulon can vary in number and can encode one, two or three genes of the M protein family, termed mrp, emm and enn. Linear genomic structure of the gbb54 gene cluster on plasmid lp54 of *B. burgdorferi* strain ZS7. Open reading frames of homologous genes are indicated by arrows. The complement Factor H and CFHL-1 binding CRASP1 protein is encoded by the CspA gene (black).

3.5. CRASPs are highly polymorphic and show sequence diversity

The Lyme disease causing spirochete *Borrelia* species, and in particular the serum resistant strains, express surface CRASP proteins which bind host complement and immune regulators. Borrelial CRASP are similar to streptococcal M proteins and represent well-characterized virulence factors that bind host complement components. Depending on the strain studied, up to five distinct surface proteins have been identified, which are termed CRASP1 to CRASP5. *Borrelia* CRASP1 shows substantial strain-specific sequence diversity, despite a similar/conserved genomic structure and organization. The CRASP1 gene and the additional orthologs are located in tandem on the bacterial genome (Wallich et al., 2005) (Fig. 1). CRASP1 of *B. burgdorferi* strain ZS7 is localized on the linear 54 kb plasmid (lp54) and gives rise to the orthologous gbb 54 gene family. The genome of *B. burgdorferi* strain ZS7 has eight gbb 54 family genes (zsa66, zsa67, cspA (encoding CRASP-1) zsa69, zsa70 zsa 71, zsa72 and zsa 73) encoded in tandem (Wallich et al., 2005).

3.6. A single immune escape protein binds multiple host proteins

Streptococcal M proteins, pneumococcal PspC proteins and borrelia CRASP bind multiple host proteins. A single *streptococcal* M protein binds multiple host plasma proteins including CFH, CFHL1, CFHR3, C4BP, IgA, IgB, fibrinogen, fibronectin, kininogen, plasminogen and albumin (Table 2). This interaction confers immune evasion during different phases of infection. The streptococcal Fba protein binds Factor H, CFHL1 and fibronectin, and, in some streptococcal strains, is co-expressed with M or M-like proteins (Pandiripally et al., 2003; Carlsson et al., 2003).

Similar to *S. pyogenes*, the PspC surface protein of *S. pneumonia*, which confers complement evasion and which serves multiple functions in virulence, binds Factor H, the human secretory immunoglobulin A (sIgA) and the human polymeric Ig receptor, and mediates both attachment of pneumococci to human cells and invasion (Hammerschmidt et al., 2007).

CRASP-1 of *Borrelia hermsii* has been shown to bind CFH, CFHL-1 and plasminogen (Rossmann et al., 2007). CRASP proteins of *Borrelia* bind multiple complement regulators and are sub-divided based on the binding profile. Group I proteins BbCRASP-1 and BbCRASP-2 bind Factor H and CFHL1, but not CFHR1. In contrast group II proteins, BbCRASP-3, BbCRASP-4 and BbCRASP-5, bind Factor H, CFHR1, but not CFHL1 (Haupt et al., 2007). In addition, CRASP-1 isolated from the relapsing fever-transmitting spirochete *B. hermsii* shows multiple binding specificity for Factor H, CFHR1 and plasminogen (Rossmann et al., 2007).

Two factor H binding proteins from *P aeruginosa* and *Candida albicans* have recently been identified and cloned. Although the two genes from these different pathogen species lack any sequence identity or regions of homology, both recombinant proteins, termed pseudomonas CRASP-1 and candida CRASP-1, bind Factor H and also the coagulation protease plasminogen. Plasminogen is an inactive protease which, when converted to plasmin, cleaves fibrinogen and fibrin. Plasminogen bound to each of these CRASP can be converted to proteolytically active plasmin. This example identifies two additional pathogen encoded surface proteins which bind host plasma proteins of the complement and the coagulation cascade (Kunert et al., submitted for publication; Poltermann et al., 2007). The dual or even multiple roles of surface attached complement regulators and coagulation proteinases are outlined in Fig. 2.

3.7. Pathogen complement binding proteins have multiple functions

The evidence above shows that pathogen-encoded complement escape proteins have multiple and different binding sites for various host proteins and that one single pathogen protein binds simultaneously several different host regulators. Thus, during infection, one single surface protein is able to control several steps and interfere with multiple cascades, including complement and coagulation, as well as mediating immune evasion, tissue destruction and adhesion to host cells.

In several cases it was shown that attached plasminogen, is converted to active plasmin either by host encoded activators (urine plasminogen activator, tissue plasminogen activator) or by bacterial encoded proteins (staphyoloccsin, etc.). Simultaneous binding of host complement regulators and the coagulation protease plasminogen, and the generation of active plasmin, allows control of the coagulation cascade and permits interaction with the extracellular matrix. Extracellular matrix degradation is required for tissue invasion and likely for organ tropisms. Thus it is probable that attached plasminogen serves multiple functions in pathogen defense, tissue invasion and localisation.

Table 2
Examples of surface proteins of pathogenic microbes that bind complement components and additional host proteins

Species	Pathogen surface protein	Interacting host complement components	Other bound host proteins
1. *S. pyogenes*	M Protein	Factor H, CFHL1 C4BP	Plasminogen Fibronectin Thrombin Fibrinogen IgA, IgG, Kininogen
	Fba	Factor H, CFHL1	Fibronectin
	ScpB, C5a peptidase	C5a	Fibronectin
2. *S. pneumonia*	PspC	Factor H,	C3, sIgA Polymeric Ig receptor
3. *Borrelia burgdorferi sl*	BbCRASP1	Factor H, CFHL1	
	BbCRASP3	Factor H, CFHR1	
	BhRASP1	Factor H	Plasminogen
4. *S. aureus*	EfB	C3	Fibrinogen
	SSL	C5	IgA
5. *P. aeruginosa*	PaCRASP/Tuf	Factor H, CFHR1	Plasminogen
6. *Candida albicans*	CaCRASP1	Factor H	Plasminogen

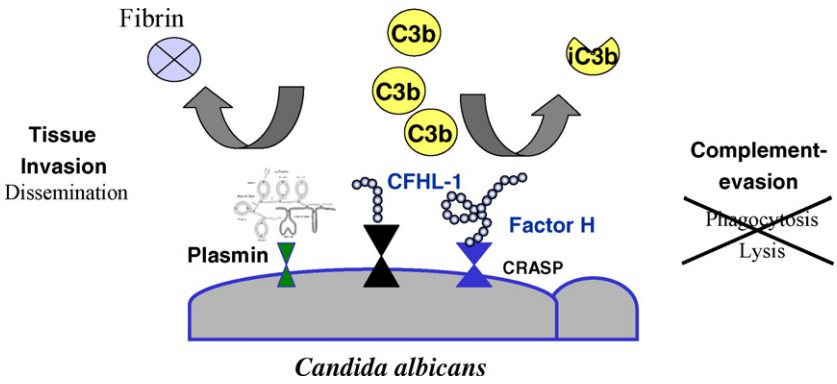

Fig. 2. Human pathogenic Yeast *C. albicans* utilizes CRASP proteins to bind host complement regulators and plasminogen. Attached to the surface of the yeast Factor H and CFHL-1 and C4BP act as cofactors and aid in the inactivation of C3b and C4b. Similarly, plasminogen is bound to the pathogen surface proteins, converted to the proteolytically active protein plasmin which cleaves fibrinogen and thus aids in destruction of extracellular matrix of the host.

3.8. A single pathogen expresses multiple surface proteins to evade complement

Diversity of immune escape comes from the multiple ligands and multiple functions of each of the immune escape proteins or CRASP expressed at the surface of pathogens. However, the number of surface expressed proteins varies between different isolates. *S. pyogenes* can express up to three different M-like proteins and also the Fba protein. Similarly *Borrelia* express several CRASP and simultaneous expression of up to five CRASP proteins by one single isolate has been shown. This diverse expression of multiple immune escape proteins demonstrates that a single pathogen utilizes a repertoire of escape proteins at its surface to interfere with host immune attack. The diverse binding profile of individual immune escape proteins and the multiplicity of simultaneously expressed surface proteins shows how well pathogens are adapted to survive immune attack during the infection phase.

4. Other complement inactivation proteins

Surface molecules mediating complement disguise represent one pattern of complement evasion used by pathogens. Interestingly, pathogens utilize additional complement inhibitors that have been identified and characterized only during the last few months.

4.1. Staphylococcus aureus

S. aureus secretes a staphylococcal complement inhibitor (SCIN) which is a 10 kDa protein that blocks the alternative, the lectin and the classical pathways of complement activation. SCIN binds specifically to activator bound convertases, but not to free components. Following binding, surface bound C3 convertases are stabilized and enzymatic activity is inhibited (Rooijakkers and van Strijp, 2007). In addition to this potent complement inhibitor, *S. aureus* expresses a 15.6 kDa extracellular fibrinogen binding protein (Efb) which binds fibrinogen and also the thioester containing C3d domain of C3b. By binding the C3d domain, Efb inhibits the deposition of C3b on to sensitized surfaces. Efb binds fibrinogen and C3b simultaneously as the fibrinogen binding site is contained in the N-terminus and the C3d binding site in the C-terminus of the protein (Lee et al., 2004a). The crystal structure for the C3 binding domain of Efb in complex with the C3b domain was recently solved (Lee et al., 2004b). Structure-based functional studies show that binding of Efb to native C3 alters the conformation of the central complement component and thus prevents subsequent C3 activation (Hammel et al., 2007).

5. Complement inhibitors derived from ticks

In addition to human pathogenic microbes, human parasites such as soft ticks, which transmit bacteria of the *Borrelia* species, represent an additional source for complement inhibitors, anticoagulant and anti-inflammatory proteins. The saliva of ticks is proving a rich source for complement inhibitors, and several such inhibitors have been identified and characterized. Upon blood feeding, ticks actively control complement activation, coagulation and inflammation at the site of entry, and during the blood meal a non-inflammatory state is maintained. Several complement inhibitors were identified in saliva of blood feeding ticks, including *Ixodes* sp. and *Ornithodores moubata.* Two related complement inhibitors were isolated from the saliva of Ixodes ticks and, dependent on the strain used, termed ISAC or IRAC (*Ixodes scapularis*/*ricinus* anti complement inhibitor protein). Based on the feeding habits of different tick strains these complement inhibitors would be expected to act in a wide range of host species ranging from human to sheep and rodents. For example, the tick-derived C5 inhibitor OmCI has inhibitory activity in humans, mice, rats and guinea pigs, but the exact mode of action is not understood at present.

5.1. Ixodes scapularis and Ixodes ricinus: ticks which transmit borreliae

Ticks are ectoparasites that feed for several days with their mouth-parts embedded into the skin of their vertebrate hosts. When ticks feed in their natural host a minimal inflammatory reaction is observed. Therefore it was reasoned that tick saliva must contain anti-complement, anti-coagulant and anti-inflammatory components. Several anti-complement proteins,

as well as anti-inflammatory proteins, were identified in *Ixodes scapularis* and *I. ricinus*, the complement inhibitors were termed ISAC and IRAC (Daix et al., 2007; Schroeder et al., 2007). Apparently, the tick saliva contains multiple proteins which interfere with the host reactions, as complement inhibitors, anti-coagulants, anti-inflammatory agents, etc. have all been identified (Valenzuela et al., 2000; Ribeiro, 2004).

5.2. *Ornithodoros moubata*

The tick *Ornithodoros moubata* expresses a complement inhibitor termed OmCI, a 17 kDa nonglycosylated protein that inhibits the classical and alternative complement pathways in humans, mice, rats and guinea pigs. The protein is 150 aa long in its mature form. Both recombinant and native OmCI abolish production of C5a by human classical (C4bC3bC2a) and alternative (C3bC3bBb) C5 convertases. OmCI binds C5 in plasma with a high binding affinity and has been proposed as an ideal target for the development of therapies for complement mediated diseases (Nunn et al., 2006; Hepburn et al., 2007).

6. Summary and outlook

The studies described above reveal that single pathogenic microbes utilize diverse mechanisms to escape complement and immune recognition. The multiplicity of anti-complement proteins and complement evasion strategies that are used by one single microbe are a strong indication for the powerful and devastating effects of the activated host complement system. The multiplicity of evasion strategies used by a microbial pathogen demonstrates that multiple levels of attack and counter defense are needed to overcome this early layer of immune defense. However, while the host has developed this complement system to fight infectious agents, at the same time the host developed strategies and uses protective molecules to control the damaging effects at the surface of its own cells. During evolution, pathogens have exploited the protective host system for their own benefit in order to survive and damage the host with its own weapons.

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