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Mini Review

Staphylococcus aureus: The multi headed hydra resists and controls human complement response in multiple ways

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ABSTRACT

The Gram positive human pathogen *Staphylococcus aureus* causes a spectrum of human diseases including pneumonia, tissue and skin infections, endocarditis, pneumonia and sepsis. The increasing number of resistant bacteria and the threat of methicillin resistant *S. aureus* (MRSA) urge for the need to develop new antibacterial compounds. A prerequisite for development of such anti microbial compounds is a better understanding of the complex immune crosstalk between the pathogenic bacterium and its human host. To this end proteins staphylococcal proteins that contribute to innate immune evasion especially to complement control need to be identified and their mode of action needs to be analyzed in order to provide new targets for immune interference.

Introduction

The Gram positive human pathogen *Staphylococcus aureus* causes a spectrum of human diseases including pneumonia, tissue and skin infections, endocarditis, pneumonia and sepsis (Rooijakkers et al., 2005a,b; Foster, 2005). The increasing number of resistant bacteria and the thread by MRSA, methicillin resistant *S. aureus*, show the need to develop new antibacterial or antimicrobial compounds (Kraus and Peschel, 2008; Gould et al., 2012). A prerequisite for development of such new anti microbial compounds is a better understanding of the intense complement and immune crosstalk between the pathogenic bacterium and the human immune system. To this end the staphylococcal proteins that mediate this interaction need to be identified and their mode of action needs to be analyzed in detail. Such immune evasion proteins can provide new targets for immune interference.

The pathogen: *Staphylococcus aureus*

Staphylococcus aureus has the ability to survive in an immune competent human host and can cause different symptoms and a spectrum of diseases. To survive in the human host this pathogen controls many steps of the host defense, including complement attack, as well as innate and adaptive immune reactions (Foster, 2005; Zecconi and Scali, 2013). *S. aureus* is considered the master of immune evasion, and at present a large arsenal of immune evasion proteins and virulence factors have been identified from this pathogen. Single immune evasion proteins interfere and control specific levels of host innate-, as well as adaptive immune reactions. Several of the identified staphylococcal evasion proteins have multiple roles, they bind several human ligands and plasma proteins, including complement and immune regulators. These staphylococcal evasion proteins control and modulate complement and also coagulation, and promote adhesion, colonization and dissemination into deeper tissue layers. The concerted action of this arsenal of multifunctional staphylococcal evasion proteins ultimately allows the pathogenic bacterium to survive in an immunocompetent human host. Several complement evasion proteins of this Gram-positive bacterium *S. aureus* have been identified and the exact mechanism how these bacterial proteins influence human complement response is well described. Recent progress in this research field underlines the complexity of complement as well as the effort of *S. aureus* to escape these damaging complement and innate immune reactions (Grumann et al., 2008). The better understanding of staphylococcal complement escape reveals conserved and common complement escape patterns among microbial pathogens, including Gram negative, Gram positive bacteria, as well as pathogenic fungi and multicellular parasites (Zipfel et al., 2013).

In this review we summarize the known complement evasion strategies of the pathogenic bacterium *S. aureus*, outline the complexity of the crosstalk between the pathogen and the human host

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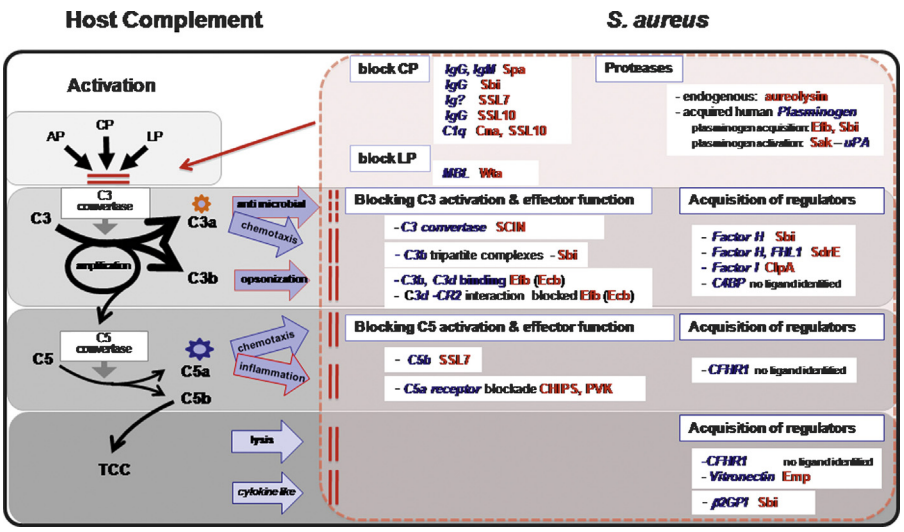

Fig. 1. *Staphyloccocus aureus* controls human complement response on all four levels. The pathogen uses surface exposed proteins and also secretes proteins into the surrounding medium that control, block, modulate or exploit host complement response. *Panel on the left*: the four major levels of the human complement response are indicated (from top to bottom: I, Activation level; II, C3 convertase level; III, C5 convertase level; IV, Terminal pathway level). The thick arrows in level II "C3 convertase" shows that the plasma concentration of C3 is about 10 times higher compared to C5. In consequence about 10 times as many effector proteins C3a and C3b can be formed on this level. The amplification loop of the C3 convertase is indicated. *Panel on the right*: *Staphylococcus aureus*, the Gram positive pathogen responds to host complement attack in many ways and uses an arsenal of complement- and immune evasion proteins. Staphylococcal immune evasion proteins interfere at each complement level. The staphylococcal immune evasion proteins are either encoded in the bacterial genome, or the bacterium expresses surface moieties that mimic surface features of their host and bind host immune regulators. Human host proteins are indicated in black color and staphylococcal interacting or modulating proteins in red color. *Abbreviations*: Sbi, second staphylococcal binding of IgG; Efb, extracellular fibrinogen binding protein (member of the family Ecb); cflA, clumping factor A binds factor I and fibrinogen; SCIN, Staphylococcal complement inhibitor (Family members: SCIN-A, SCIN-B; SCIN-C) SSC; SSL7, staphylococcal superantigen like protein #7; CHIPS, blocks C5a R signaling; cna, collagen-binding microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) from *S. aureus* binds C1q and blocks the classical pathway of complement. Staphylokinase cleaves Plasminogen; Aurelysin cleaves C3; Eap, extracellular adherence protein; Emp, extracellular matrix binding protein; Eap, extracellular adherence protein; PVL, panton-valentine leukocidin.

and focus on the armory of staphylococcal evasion proteins that act on the complement and innate immune system of the human host. This provides insights into the current understandings how *S. aureus* controls, blocks, directs, modulates, targets and also fine tunes host complement and innate immunity (Figs. 1 and 2).

Host complement- and immune defense

Overview on the human complement response to infectious agents

The human organism has a highly efficient complement system that controls homeostasis and that in general terms is responsible for recognition and elimination of invading infectious agents (Zipfel and Skerka, 2009; Zipfel, 2009). However, infectious microbes that survive and propagate in an immunocompetent host represent pathogens that express an armory of evasion proteins targeting the host complement- and or coagulation cascade, as well as innate and adaptive immune responses (Zipfel et al., 2013).

Any infectious agent that enters an immune-competent human host faces the adverse reactions of the immune systems including complement (Zipfel et al., 2013; Garcia et al., 2012). Upon infection with a microbe the immune system of the host reacts immediately and in sequential layers (Zipfel and Skerka, 2012). The complement system is activated immediately upon recognition and initiates a direct response that integrates and sets in motion additional cellular innate immune responses, e.g. by recruiting and activating neutrophils, macrophages and NK cells (Zipfel and Skerka, 2009; Song, 2012; Walport, 2001). The innate immune response can also direct the adaptive immune response. Upon first encounter of a pathogenic microbe the adaptive immune response needs time to select and propagate AG-specific T- and B cells and to allow subsequent selection, proliferation, affinity maturation, somatic hypermutation and differentiation to specific effector cells (Köhl, 2006; Song, 2012).

Complement is a major part of the immune system of the human organism. This network system is protective and regulates central homeotic and inflammatory reactions in the human organism. Complement becomes activated on the surface of modified self as well as foreign infectious microbes and generates toxic activation products that recognize and remove modified self particles and destroy the invading infectious microbe. Thus pathogenic microbes, which during evolution learned to survive in an immune-competent host have found means to control activation of the host defense system. Thereby pathogenic microbes have a chance to survive when they efficiently and specifically control early acting immune responses, like the complement system.

Complement activation is determined by the type and nature of a surface. Activation and amplification are actively blocked and prevented on the surface of intact self cell and tissues. However activation is desired and beneficial on modified self surfaces, e.g. apoptotic or necrotic cells and also on non self surfaces, such as infectious microbes. Apoptotic and modified self-cells activate complement moderately and in consequence are removed from the circulation in a silent, non-inflammatory manner. In contrast pathogenic microbes as foreign cells actively block complement and thus induce pathology (Zipfel and Skerka, 2009; Köhl, 2006). Similar to apoptotic cells infectious, innocuous microbes likely are eliminated in a non-inflammatory manner. In contrast, pathogenic microbes survive by immune disguise. These pathogens mimic host surface structures or components, camouflage their surface as host like, and hence appear to the host complement and innate immune system as a 'wolf in sheep's clothing'.

Complement activation

The human complement system comprises a set of 30–50 germ line genes, and the encoded proteins either circulate in plasma and body fluids or are expressed on the surface of cells and biological