

Session: Complement and infection

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Introduction

Pathogenic microorganisms employ a broad range of strategies to survive in and to persistently infect the human host. Far from being completely understood by which highly sophisticated means invading pathogens overcome the host's destructive immune defence, there is a growing body of evidence on complement-evading mechanisms which play a pivotal role for immune evasion. From the pathogen view it is important to immediately avoid recognition by the innate immune system after entering the host.

In this particular session I will focus on the interaction of fluid phase complement regulators with bacterial proteins and will discuss the nature of the molecular binding mechanism. Expression of microbial surface molecules that capture human complement regulators from the fluid phase and fixing them in a functionally active state allows pathogens to control, inhibit and finely regulate complement activation directly on their surface. Fluid phase complement regulators such as Factor H, Factor H-like protein 1, C4-binding protein, and vitronectin are employed for complement subversion by a number of diverse pathogens, not only by bacteria, but also by viruses, fungi, and parasites (as recently reviewed in Blom et al., 2009; Lambris et al., 2008, Rooijackers & van Strijp, 2007).

There are a range of bacterial molecules that differentially interact with complement regulators such as factor H, FHL-1, factor H-related protein 1 (FHR-1), C4Bp or vitronectin. Examples of factor H-binding proteins include the streptococcal M proteins, FbA, Scl1, and the β protein, the pneumococcal PspC and Hic proteins, the gonococcal Por1A protein, the borrelial CRASP proteins, FhbA and HcpA, the YadA and Ail proteins of *Yersinia enterocolitica*, the LfhA protein of *Leptospira interrogans*, and two unidentified proteins of *Haemophilus influenzae*. Examples of C4Bp-binding proteins include the streptococcal M proteins, the gonococcal Por1A and Por1B proteins and type IV pili, UspA1 and UspA2 from *Moraxella catarrhalis*, and OmpA of *Escherichia coli*. The molecules interacting with vitronectin are the meningococcal OpaA protein, the Hsf fibrin of *Haemophilus influenzae*, and the UspA2 protein of *Moraxella catarrhalis*.

The nature of the molecular interaction is mostly dictated by different kind of driving forces, covalent and non-covalent interaction which includes electrostatic forces, van der Waals contacts and hydrogen bonds. For some bacterial proteins, the basis of the molecular interaction has been described in detail, i.e. the interaction of C4Bp with M proteins.

Beside acquisition of complement regulators additional strategies have been attracted particular interest to enzymatic attenuate complement: capture and inactivation of the central complement component C3 and secretion of proteases that specifically target complement proteins which also be discuss in this session.

Educational objectives

- To get an overview about the immune evasion strategies used by human pathogenic microorganisms to evade complement-mediated killing
- To get an insight into the complex molecular mechanisms of host-pathogen interaction
- To learn how laboratory methods are common and useful to analyse the molecular interaction between complement regulators and a pathogen-derived molecule

Topic questions

- Which mode of action are known to be common or distinct by human pathogens to evade complement-mediated killing?
- What is known about the molecular nature of the interaction between the bacterial and the host protein(s)? Could differences/similarities be specified?
- Could a structure (linear, conformational, coiled-coil) be defined which is common among the bacterial binding proteins that interacts with the same complement regulator?

Practical questions

- How bacterial proteins that interact with complement regulators could be identified?
- Which are the pro and con of the methods commonly used?

Critical thinking

- Would binding of complement regulatory proteins or an other strategy be sufficient to fully protect pathogens from the destructive attack by complement?

Literature

Blom et al., 2009, Complement evasion strategies of pathogens-Acquisition of inhibitors and beyond. *Mol. Immunol.* doi:10.1016/j.molimm.2009.04.025.

Lambris et al., 2008, Complement evasion by human pathogens, *Nat. Rev. Microbiol.* 6 :132-142.

Rooijackers & Strijp, 2007, Bacterial complement evasion, *Mol. Immunol.* 44:23-32.