Factor H ligand complexes - Structural studies on complement regulation and disease

Kajander, T\textsuperscript{1}, Lehtinen, M\textsuperscript{*}, Hyvärinen, S\textsuperscript{*}, Bhattacharjee, A\textsuperscript{2}, Meri, T\textsuperscript{3}, Kolodziejczyk, R\textsuperscript{3}, Meri, S\textsuperscript{*}, Jokiranta, S\textsuperscript{*} and Goldman, A\textsuperscript{3}.

University of Helsinki, §Institute of Biotechnology and *Department of Bacteriology and Immunology.

Email: tommi.kajander@helsinki.fi

Factor H (FH), a plasma glycoprotein composed of twenty globular domains, is essential component of alternative pathway of complement in protecting host cells and extracellular matrix from activation of the alternative pathway, as indicated by severe diseases caused by mutations in FH. While the regulatory activity resides in FH domains 1-4, discrimination of host and nonhost is due to joint binding of domain 20 to glycosaminoglycans and domain 19 to the main complement opsonin C3b. Furthermore several pathogens have acquired FH from host plasma onto their surface for immune evasion but how this occurs has been unclear.

We have recently determined the crystal structures of FH19-20 domains in complex with C3d which explain the host recognition by FH, with a surprising two-site binding mechanism. Further, recently we have determined the structure of Borrelia OspE in complex with FH19-20 giving further insight into how pathogens use FH to evade the immune response. These structures give new insights into the multifunctional nature of FH.

Keywords: Factor H, complement, complex structures.

Fucose binding lectins from opportunistic pathogens and blood group antigens

Annabelle Varrot\textsuperscript{a}, Aymeric Audfray\textsuperscript{a}, Josef Houser\textsuperscript{b}, Ondrej Sulak\textsuperscript{b}, Gianluca Cioci\textsuperscript{c}, Martina Lahmann\textsuperscript{d}, Anne Imberty\textsuperscript{a}, Michaela Wimmerova\textsuperscript{b}.

\textsuperscript{a}CERMAV-CNRS, BP53, 38041 Grenoble cedex 9, France, \textsuperscript{b}NCBR, Faculty of Science, Masaryk University, Kotlarska 2, 611 37 Brno, Czech Republic, \textsuperscript{c}ESRF, 6 rue Jules Horowitz, 38043 Grenoble, France, \textsuperscript{d}School of Chemistry, University of Bangor, Deiniol Road, Bangor, Gwynedd, LL57 2UW, UK.

Email: varrot@cermav.cnrs.fr

Oligosaccharide-mediated recognition and adhesion to the host are key steps in microbial infections. They are mediated through the interactions of the host glycoconjugates with specific proteins called lectins which recognise sugars in a reversible and specific manner without modifying them. Lectins are therefore interesting targets for the development of new anti-infectious compounds such as glycomimetics for anti-adhesive therapy since blocking the adhesion will be a way to fight against infection.

Pathogenic microorganisms produce an arsenal of lectins (glycostategy) which encompass soluble lectins, fimbrial and flagellar lectins (adhesins). We try to dissect the glycostrategy of several opportunistic pathogens such as \textit{Pseudomonas aeruginosa}, \textit{Burkholderia cenocepacia}, \textit{B. ambifaria} and \textit{Aspergillus fumigatus}. They are responsible for bronchopulmonary infections and have a high incidence in nosocomial infections. Those infections are associated with substantial morbidity and mortality in immunocompromised patients and are the first cause of death in cystic fibrosis patients. All those organisms present at least one fucose binding lectin.

In the recent years, we have characterised several fucose binding lectins and determined their structure, with the help of methylselenofucoside for some. They present different fold and oligomerisation state [1,2,3]. Glycan arrays experiments have shown that blood group antigens are often natural ligands of those lectins [2,3]. The specificity can be broad but usually one blood group antigen is favoured. Structures of the different lectins in complex with several oligosaccharides have given clues on the molecular basis of the interaction. The lectins are multivalent and present from two to six sugar binding sites. The fucose binding can be done in two different ways.

Is there then a predisposition for infections by some microorganism according to the host blood group?


Keywords: lectins, adhesion, blood group antigens.