Meeting in the Danish Society of Immunology

In association with graduate programme of Immunology and Infectious Diseases

Title: Understanding complement dysregulation in AMD pathogenesis: implications for new therapeutic avenues

Time: Thursday May 31, 2018 at 4 pm
Place: Room 07-13-143A Mærsk Tower, The Panum Institute, University of Copenhagen, Blegdamsvej 3C, 2200 Copenhagen N

Short biography Simon J Clark

Simon works in the Faculty of Biology, Medicine and Health, University of Manchester, where he holds an MRC Career Development Fellowship and studies ocular immunity, with a particular speciality in the complement system. Indeed, Simon's primary research focuses on the regulation of the complement system in the human eye and how this links with an increased risk of developing age-related macular degeneration (AMD), the leading cause of blindness in the developed world. In 2015 Simon co-founded the Manchester Eye Tissue Repository, where genotyped and phenotyped human eye tissue is collected and stored to act as an international resource for academic research into eye diseases. Simon also has translational interests and has recently developed novel complement inhibitors that can be used as therapeutics against complement-mediated diseases, such as AMD.

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Understanding complement dysregulation in AMD pathogenesis: implications for new therapeutic avenues

The recent revolution in age-related macular degeneration (AMD) genetics has demonstrated that genetic alterations affecting the alternative pathway of the complement cascade have a major influence on AMD risk. One of the two most important genetic loci is on chromosome 1 and contains genes encoding complement factor H (FH) and the factor H related proteins (FHR proteins). In macular tissue, especially Bruch's membrane, relatively high levels of a truncated splice variant of FH called factor H-like protein 1 (FHL-1) are present. Genetic variations in the *CFH* gene that encodes both the negative complement regulators FH and FHL-1 alter the amounts, or by altering their protein sequences, the functions of these proteins. In particular, a very common Y402H polymorphism affects the ability of FHL-1 to localize to Bruch's membrane and the inner choroid because it alters the proteins ability to bind heparan sulphate in these structures. Furthermore, genetic variations in the genes of the FHR proteins, including whole deletions of individual genes, also moderate levels of disease risk given their role as positive regulators of complement activation. The presence and/or absence of the FHR proteins alter the fine balance of complement homeostasis that exists in the back of the eye. Finally, the lack of permeability of Bruch's membrane to soluble complement proteins essentially creates two semi-independent compartments with respect to complement activation and regulation. Complement proteins synthesized locally on either side of Bruch's membrane (or on the choroidal side perhaps derived from the circulation) predominantly remain on their side of origin. This has implications for targeting specific complement components as a strategy for treating AMD.