

S004 Protein: protein interactions of complement factor H using a multidisciplinary strategy

Stephen J. Perkins, Ruodan Nan and

Azubuike I. Okemefuna

Department of Structural and Molecular Biology, University College London

Experimental studies of protein-protein interactions are very much affected by whether the complexes are fully formed (strong, with nM dissociation constants) or partially dissociated (weak, with μ M dissociation constants). Interactions between the complement proteins of innate immunity are governed by the weak interplay between activated proteins and their regulators. Complement is effective in attacking pathogens, but not the human host, and imbalances in this process can lead to disease conditions. Complexity is augmented by the multivalency of the main complement regulator factor H. The unravelling of these weak protein-protein interactions requires a multi-disciplinary approach. Synchrotron X-ray scattering and constrained modelling resulted in the determination of the solution structure of the factor H and its self-associative properties, while analytical ultracentrifugation identified multimers of factor H and the formation of even larger multimers through the addition of metals such as zinc or copper. The protein ligands of factor H themselves undergo self-association as well. The combination of X-rays and ultracentrifugation with surface plasmon resonance proved to be essential to identify the multimers formed with the C3d fragment of the main complement protein C3. Studies of C3d-factor H complexes provided novel insight on how factor H controls C3 activation on host cell surfaces. Likewise, the three methods together clarified how factor H interacted with C-reactive protein, where we showed unexpectedly that C-reactive protein binds to two non-contiguous sites on factor H.