

Solution structures for the regulatory SCR-1/5 and cell-surface-binding SCR-16/20 fragments of Factor H reveal different self-associative properties

Azubuike I. Okemefuna¹, Hannah E. Gilbert¹, Kim Griggs², Rebecca Ormsby², David L. Gordon² and Stephen J. Perkins¹

¹ *Department of Biochemistry and Molecular Biology, Darwin Building, University College London, Gower Street, London WC1E 6BT, U. K.*

² *Department of Microbiology and Infectious Diseases, Flinders Medical Centre, Bedford Park SA 5042, Australia.*

Factor H (FH) plays a central role in the regulation of complement activation via the alternative pathway. It is composed of 20 short complement regulator (SCR) domains. The SCR-1/5 region is required for decay acceleration and cofactor activity while the SCR-16/20 region possesses C3b/C3d and heparin binding sites. X-ray scattering and analytical ultracentrifugation showed that SCR-1/5 is monomeric while SCR-16/20 is monomeric and dimeric. The Guinier radius of gyration R_G of 4.4 nm for SCR-1/5 and those of 4.7 nm and 7.8 nm for monomeric and dimeric SCR-16/20 respectively showed that their structures are not extended. SCR-1/5 has a maximum dimension of 15 nm, while those for monomeric and dimeric SCR-16/20 are 17 nm and 27 nm respectively. The sedimentation coefficient of 2.4 S for SCR-1/5 showed no concentration dependence, while that for SCR-16/20 is 2.8 S for the monomer and 3.9 S for the dimer. Sedimentation equilibrium data showed a single species for SCR-1/5 and a monomer-dimer equilibrium for SCR-16/20. The concentration dependences of the Guinier parameters and equilibrium data resulted in a monomer-dimer dissociation constant of 16 μM . The constrained scattering modelling of SCR-1/5 and SCR-16/20 showed that partially bent flexible SCR arrangements fit the data better than linear arrangements, and that the dimer can be modelled by the end-to-end association of two SCR-20 domains. It is concluded that the N-terminal and C-terminal regions of FH showed different self-associative properties. The models for SCR-1/5 and SCR-16/20 are consistent with the partially folded back structure for intact wild-type FH.