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Development of a surface-bound peptide conjguate to prevent complement attack: structure-activity relationship and first translational steps

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Although important progress has been made to protect biomaterials such as transplants, implants or liposomes from undesired host immune attack, several problems remain unsolved. Among those is the involvement of the complement system, the major humoral part of innate immunity. It broadly and swiftly recognises non-self surfaces, leading to direct cell damage and induction of adaptive and cellular innate immune responses. During the clinical use of biomaterials, complement activation may contribute to adverse reactions including inflammation, rejection or loss of function. Under physiological conditions, complement gains selectivity by tightly controlling activation on host cells through regulators in solution and on cell surfaces. One promising approach to protect biomaterials from complement attack, which is inspired by microbial immune evasion, is to coat material/cell surfaces with capturing entities that specifically recruit circulating complement regulators and thereby prevent complement attack in situ. Pursuing this idea, a disulphide-bridged cyclic peptide (5C6) was previously discovered by our group through phage display screening. 5C6 showed nanomolar binding affinity to the plasma-borne, major complement regulator Factor H (FH). Therapeutically, FH presents an attractive target as it inhibits complement's central self-amplification loop where all three activation pathways converge. In proof-of-concept studies, 5C6 was shown reduce complement activation when combined with appropriate tethering motifs by acting as a bridge between FH and model surfaces.[1,2] However, little was known about the target-binding, selectivity and specificity profiles of 5C6 or about optimal tethering strategies. In the study presented here, we employed peptide and medicinal chemistry to conduct comprehensive structure-activity relationship studies, focusing on individual residues and on macrocycle conformation, allowing us to determine critical structural features. We further demonstrated that the spacing and orientation of the peptide on surfaces largely determines the recruiting efficacy. Importantly for translational aspects, we could demonstrate that 5C6 shows strong selectivity for FH, with no notable recognition of the structurally homologous yet functionally antagonistic protein FHR5. Our finding that 5C6 not only binds human FH but also mouse FH suggest that the peptide coating can be translationally assessed in animal studies. Finally, we could determine the peptide's activity in a nanoparticle-type model system as a validation for the clinical relevance of this approach.

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