Abstract

Structural insights into innate immune evasion mechanisms of African trypanosomes and type C adenoviruses

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The human body has evolved a plethora of intricate defence mechanisms to fend off any potentially pathogenic microorganisms, in turn prompting the latter to develop countermeasures. Obtaining a detailed understanding of the structural foundation underlying the immune evasion mechanisms employed by human-infective pathogens is crucial for development of effective drugs and therapeutics. In this work, a protocol for improvement of recombinant expression of proteins with complex fold and generation of a minimal construct amendable to structural characterisation is presented by example of invariant surface glycoprotein 65 (ISG65) from the blood-stream form of the human infective parasite *Trypanosoma brucei gambiense (Tbg)*. In addition, the findings shown here reveal the biological function of ISG65 as a receptor for human complement C3b, describe its role as a selective inhibitor of the alternative pathway of the complement system and present the first structures of *Tbg*ISG65 in complex with human C3 and C3b. To elucidate how other invariant surface receptors of the parasite may exert their function within the protective shield formed by the surrounding variant surface glycoproteins (VSGs), the conformational flexibility of the parasites blood-stream surface coat was assessed. While infection with African trypanosomes has severe consequences for patient health, infections with the widespread human adenovirus C5 on the contrary are usually mild and self-limiting. Despite its high prevalence around the world and great potential in gene therapy and vaccination applications, the molecular mechanisms governing the infection are still poorly understood. Results presented here provide structural insights into how species C adenoviruses may exploit human lactoferrin, an antimicrobial component of the human innate immune defence, to facilitate infection of the respiratory epithelium. This discovery holds promise for the development of novel antivirals or adjuvants for improved transduction efficacy in gene therapy applications.