MS10-1-1 Extensive substrate recognition by the streptococcal antibody-degrading enzymes IdeS and EndoS #MS10-1-1

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Abstract
The cleavage of human IgG antibodies is a potent immune evasion mechanism utilised by some pathogenic bacteria. The Streptococcus pyogenes bacterium, which has the capacity to cause necrotising fasciitis, employs multiple enzymes to deactivate the human adaptive immune system. Two such proteins, IdeS and EndoS, prevent immune detection by ablating the immune effector functions of IgG, by cleavage and deglycosylation of its Fc region, respectively. Their fine specificity for IgG has led to a wide range of clinical and biotechnology applications, with IdeS having received clinical approval facilitating organ transplantation in hypersensitised individuals, while EndoS has found application in engineering antibody glycosylation. Here, we present crystal structures of IdeS and EndoS in complex with their IgG1 Fc substrate, with both enzymes exhibiting exquisite target specificity. The IdeS protease is shown encasing the antibody hinge target, but also recognises the Fc globular domains. In contrast, the glycan hydrolase domain in EndoS traps the Fc glycan in a flipped-out conformation, while additional antibody specificity is driven by protein recognition by the so-called carbohydrate binding module. Understanding the molecular basis of antibody recognition by bacterial enzymes will facilitate the development of next-generation enzymes.