ANTIBODIES

Getting the trigger the right way round

Numerous bacterial species express surface proteins that bind to IgG antibodies via the Fc domain (IgGFc-binding proteins), and this is thought to protect the bacteria from opsonization and subsequent killing. Nordenfelt *et al.* now report that in humans the presence and orientation of IgG antibodies on the surface of bacteria differ at different anatomical sites and determine bacterial killing.

This study started with the analysis of a diabetic patient who presented with an asymptomatic throat infection, toxic shock and necrotizing fasciitis. *Streptococcus pyogenes* — which expresses the IgGFc-binding proteins M1 protein and protein H and in most individuals causes superficial throat and skin infections — was identified in samples from the throat, necrotic tissue and blood of this patient. Using negative-staining electron microscopy, the authors found that IgG bound to *S. pyogenes* in the throat via the Fc region, whereas it bound via the fragment of antigen binding (Fab) region in the blood. In the necrotic tissue, complexes of M1 protein, fibrinogen and IgG had been released from the bacterial surface, and these complexes have previously been shown to induce a cardinal feature of toxic shock and necrotizing fasciitis.

> “the binding orientation of IgG on *S. pyogenes* is directly linked to antibody concentrations”

Using an *in vitro* system, the authors next found that IgG bound via its Fc region only at low IgG concentrations, and reverted to the normal Fab-binding orientation at higher concentrations. The concentration of IgG is much lower in saliva than in blood (~10,000-fold lower), which may explain the difference in binding orientation in the throat and blood samples. Indeed, following the incubation of *S. pyogenes* with plasma, IgG was found to bind all over the surface of the bacteria (including to IgGFc-binding proteins) mainly via the Fab region. By contrast, in saliva, IgG binding was highly localized to the central regions of the IgGFc-binding proteins and was mediated by the Fc domain. These data confirmed that the binding orientation of IgG on *S. pyogenes* is directly linked to antibody concentrations, which vary at different tissue sites.

But what is the functional relevance of these different binding orientations? In plasma, bacteria were mainly bound by IgG1, IgG3 and high levels of the complement components C3 and C4b-binding protein, as well as by components of the membrane attack complex. By contrast, bacteria in saliva were bound by IgG1, IgG2 and complement factor H, which is a negative regulator of the alternative complement pathway. Correspondingly, neutrophil-mediated uptake and killing of *S. pyogenes* was greatly reduced in saliva compared with plasma. Interestingly, although fewer bacteria were taken up by neutrophils in saliva, intracellular bacterial survival was greater than in plasma.

So, these data suggest that the IgGFc-binding proteins of bacteria that reside in IgG-low environments, such as *S. pyogenes*, may have evolved not only to allow the bacteria to avoid opsonization and killing but also to enhance their survival in neutrophils. However, if the pathogen moves into the circulation, the protection offered by these proteins is overcome by high IgG levels and the bacteria are killed. This may explain why severe invasive infections with *S. pyogenes* are rare. But, if the bacteria reach a damaged tissue site, this could provide a protective microenvironment for the pathogen to colonize and grow.

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