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Platelets interact with bacterial pathogens

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The predominant role of platelets is in haemostasis. Resting platelets patrol the vasculature and become activated in response to endothelial damage and exposure to sub-endothelial matrix components, such as collagen or vonWillebrand factor. Adhesion and activation results in the release of the contents of platelet granulae, and in the upregulation of surface receptors for fibrinogen/fibrin and other plasma proteins. This allows firm binding between platelets to occur, resulting in aggregation and formation of platelet thrombi. Platelets may also contribute to the immune response to endovascular bacterial pathogens, by releasing pro-inflammatory factors including cytokines, chemokines, and antimicrobial peptides (1). Conflicting reports exist on the role of platelets during bacterial infection. On the one hand the production of antimicrobial peptides will kill bacteria, and the release of pro-inflammatory substances and the formation platelet-leukocyte aggregates may prime the immune response. On the other hand the ability to bind platelets may facilitate bacterial adherence to the endothelium and bacteria contained within a platelet aggregate may be protected from immune defences.

In order to initiate an infection, bacteria must adhere and multiply at normally sterile sites within the host. Many bacterial pathogens bind to host matrix proteins such as fibrinogen/fibrin, collagen, or vonWillebrand factor and since many of these host proteins are also associated with activated platelets, abundant platelets may represent an adhesive focus for bacteria. Furthermore, a number of significant Gram-positive endovascular pathogens been shown to directly stimulate platelet activation *in vitro* in the absence of other agonists

(for a review see (2)). The most well characterised interactions occur between platelets and the bacteria that cause endocarditis: *Staphylococcus aureus*, *Streptococcus sanguis* and other streptococcal species. During endocarditis, bacteria adhere to the heart valves and a vegetation of bacteria, fibrin and platelets is formed, therefore the ability of the bacteria to activate or adhere to platelets is considered to contribute to the formation of vegetations. A number of endocarditis pathogens have been reported to bind either directly to the platelet surface or indirectly via a plasma protein bridge. Binding in itself does not mediate activation, and plasma immunoglobulin G specific for the bacterium is also required to mediate platelet activation through the Fc receptors on the platelet surface (2). As previously mentioned, activated platelets release antibacterial peptides, which could kill the bacteria. Interestingly, it has been shown that many of the *S. aureus* strains isolated from endocarditis are resistant to these antibacterial peptides (3) (4).

To date, platelet interactions have been mainly studied for the causative agents of endocarditis and the results obtained may be specific for this infection. In order to elucidate the role of platelets during infection, it is important that platelet interactions are investigated for other bacterial pathogens. In a study published in this edition of Thrombosis & Haemostasis, Niemann et al have investigated the interaction between platelets and the significant human pathogen, *Streptococcus pneumoniae* (5). *S. pneumoniae* is not a significant cause of endocarditis but is a leading cause of respiratory tract infections and may cause invasive infection and septicaemia. Niemann et al report that *S. pneumoniae* can bind to activated platelets and this binding is mediated by platelet bound fibrin and further stimulated by thrombospondin released from activated platelets. Platelet activation in the absence of fibrin generation, for example collagen stimulation, does not stimulate bacteria-platelet associations. Niemann et al have previously described a similar interaction of *S. aureus* with activated platelets and this implies that the mechanism may be conserved for significant Gram-positive

pathogens (6). As previously mentioned, *S. aureus* can also mediate platelet activation in the absence of other agonists. The authors do not investigate the ability of *S. pneumoniae* to stimulate platelet activation in the absence of other agonists, and it will be interesting to determine if this significant human pathogen has, like *S. aureus*, multiple mechanisms to interact with platelets. The ability to adhere to activated platelets on the damaged endothelium may provide an advantage for the bacteria by protecting them from killing by immune cells, which may not recognise bacterial pathogens coated in host proteins. Alternatively, bacteria attached to a platelet aggregate may also be able to disseminate via the bloodstream to other foci. Indeed, bacteria-platelet aggregates can become sequestered in the microvasculature, contributing to the organ damage observed in septicaemia and sepsis.

The contribution of thrombospondin to these bacteria-platelet associations is interesting since thrombospondin has previously been reported to bind to bacterial peptidoglycan (7). Peptidoglycan is an essential component of the Gram-positive cell wall and therefore the ability to bind thrombospondin may be conserved for all Gram-positive bacteria. However, while many Gram-positive pathogens have been reported to bind fibrinogen/fibrin (8), the bacterial ligand differs between species and the ability to bind fibrin may not be conserved for all Gram-positive bacteria. This is conceptually important for our understanding of whether the activated platelet can recognise all Gram-positive bacteria or whether the most adept Gram-positive pathogens have acquired the ability to bind platelets in order to facilitate pathogenesis. The associations did not occur when the bacteria were encapsulated, indicating that the capsule masks the ligand for fibrin as well as thrombospondin. It is well appreciated that the capsule is one of the most significant virulence factors produced by *S. pneumoniae*, therefore the ability of the capsule to downregulate the formation of platelet associations implies that platelet binding is not advantageous for the bacteria and they want to counteract this, perhaps in order to avoid the antibacterial peptides released by activated platelets. This is

one of the first studies to address the role of capsule formation for platelet interactions and it will be interesting to determine if the findings can also be applied to other important capsulated pathogens, such as *S. pyogenes, S. agalactiae,* or *Neisseria spp*. The study provides important information on the role of platelets during bacterial infection. As the authors themselves point out, it may well be that platelet activation during infection is a "double edged sword", on one hand contributing to the innate defence against bacteria, while at the same time contributing to the pathogenesis of infection with specific pathogens.

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