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Platelet activation is a key event in the pathogenesis of streptococcal infections

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1. ABSTRACT

Diverse *Streptococcus* species including *Streptococcus Pneumoniae*, *Sanguis*, *Gordonii*, *Mitis* and *Mutans* cause life-threatening conditions including pneumonia, bacteremia and meningitis. These diseases bear a high morbidity and mortality and for this reason, understanding the key events in the pathogenesis of these infections have a great significance in their prevention and/or treatment. Here, we describe as how the activation of the platelets and their affinity to bind to bacterial proteins act as early key events in the pathogenesis of *Streptococcal* infections.

2. INTRODUCTION

Streptococcus is a genus of spherical Gram-positive bacteria belonging to the phylum Firmicutes (1) and the lactic-acid bacteria group, which is classified into alpha- and beta-hemolytic streptococci based on their hemolytic properties (2). The genus *Streptococcus* causes a multitude of diseases, including pink eye, meningitis, bacterial pneumonia, endocarditis, erysipelas and necrotizing fasciitis. The most important pathogens are the alpha-hemolytic streptococci *Streptococcus pneumoniae* and *Streptococcus viridans*-group and the beta-hemolytic streptococci of Group A and B. Many streptococcal species are nonpathogenic and are part of the commensal human microbiome of the mouth, skin, intestine, and upper respiratory tract.

Platelets are small, clear, disk-shaped cytoplasmic fragments which are released from bone marrow megakaryocytes (3). Platelets are maintained in a resting state by a continuous endothelial lining of the circulatory system. When the integrity of vessels is interrupted and the endothelial layer is injured, platelets are activated, change shape, aggregate and secrete contents of their granules, and lead to clotting to prevent blood loss. However, in certain *Streptococcal* infections, platelets bind to bacteria and such interaction leads to subsequent tissue injury and inflammation (4-5). In this review, we will focus and address the interactions that take place between platelets and *Streptococci*, which are the key events in the pathogenesis of *Streptococcus* infection.

3. GROUP B STREPTOCOCCUS

Group B *Streptococcus* (GBS), also known as *Streptococcus agalactiae*, can cause pneumonia, meningitis and endocarditis in neonates and the elderly. The binding of GBS to platelets plays a role in endocarditis, in which GBS produces platelet-binding proteins and thereby promotes *S. agalactiae*-induced endocarditis. One example is FbsA, a fibrinogen-binding protein that induces platelet aggregation via the integrin glycoprotein (GP) IIb/IIIa (6). Another example is Srr1, a serine repeat-rich glycoprotein from GBS that binds directly to the Aα chain of human fibrinogen (7). In a study on the intracellular signaling of GBS-induced platelet activation, GBS isolates from septic patients induced platelet thromboxane synthesis, platelet aggregation, and P-selectin (CD62P) expression via the FcγRIIA

receptor signaling pathways and pathways distinct from IgG-mediated signaling, including the protein kinase C, p38 mitogen-activated protein kinase, stress-signaling kinase SEK1/MKK4 and focal-adhesion kinase (FAK) pathways (8). Because interactions between GBS and platelets induce inflammation during GBS-induced infection, pretreated platelets may disturb this link. Drago and colleagues (9) reported that platelet-rich plasma (P-PRP) inhibits GBS growth in patients, suggesting an interaction between GBS and platelets in infection.

4. GROUP A STREPTOCOCCUS

In a manner similar to the inhibition of GBS growth in patients, Group A *Streptococcus* (GAS) and platelets are also known to interact in GAS infection. PRP inhibits the growth of methicillin-sensitive and -resistant GAS *in vitro* (10,11), suggesting a role for platelets in GAS infection. By contrast, Liu and colleagues (4) observed that GAS reduces neutrophil recruitment to localized infections and facilitates innate immune evasion by secreting an esterase, which is produced by serotype M1 GAS (SsE (M1)) and hydrolyzes platelet-activating factor (PAF). This group further demonstrated that SsE proteins are more potent hydrolases of, and have a high affinity for, PAF. SsE (M28) has potency similar to SsE (M1) for PAF hydrolysis, resulting in enhanced innate immune and skin invasion (12), and null mutations of the *covS* gene of *Streptococcus pyogenes* demonstrated that the protein product of this gene is an upstream factor that regulates SsE. CovS inhibits neutrophil recruitment by up-regulating SsE expression (13), suggesting that this pathogen gene mutation is involved in platelet interaction during infection.

Streptococcus pyogenes is a spherical, Gram-positive bacterium that causes many Group A streptococcal infections (1), and this species displays Group A antigens on the cell wall. Platelets promote infection by binding to *S. pyogenes*, thereby promoting platelet-neutrophil complex formation, neutrophil activation in response to infection and bacterial dissemination (14). In *S. pyogenes* infection, the toxin streptolysin O induces the coaggregation of platelets and neutrophils in a process mediated by platelet P-selectin (CD62P), which leads to vascular dysfunction and ischemic destruction (15). GAS also secretes streptococcal pyrogenic exotoxin B (SpeB) to render endothelial cells unresponsive to thrombin, prevents human platelets from thrombin-induced aggregation by cleaving human PAR-1 at the N-terminal amino acid residue leucine 44, and helps GAS escape from innate host responses (16).

5. STREPTOCOCCUS PNEUMONIAE

S. pneumoniae is an opportunistic human pathogen that causes life-threatening, invasive pneumococcal diseases, including pneumonia, meningitis, bacteremia, sepsis, osteomyelitis, septic arthritis, endocarditis, peritonitis, pericarditis, and brain abscesses (17). Invasive *S. pneumoniae* can induce platelet activation via Toll-like receptor 2, resulting in thrombotic complications of sepsis (18). In recent years, the PAF receptor has been a focus of the study of *S. pneumoniae* infection. PAF, which can be produced by platelets, is a potent phospholipid activator and mediator of many leukocyte functions, including platelet aggregation and degranulation and inflammation. The PAF receptor works by binding PAF, and both *in vitro* and *in vivo* studies have shown that *S. pneumoniae* attaches to the PAF receptor, which enhances bacterial adherence in a process that is coupled to the invasion of endothelial, epithelial and PAF-receptor-transfected cells (19). By enhancing pneumococcal adhesion to lower airway cells via PAF receptor upregulation, *S. pneumoniae* can induce severe bacteremic pneumococcal pneumonia (20). The adherence of *S. pneumoniae* to cultured human airway epithelial cells is enhanced by acid exposure (21) and cigarette-smoke extract (22). Moreover, influenza virus up-regulated the PAF receptor, potentiating pneumococcal adherence and invasion in the lung of a mouse model (23). In turn, pneumococci can cause severe pneumonia via the PAF receptor in a host previously exposed to influenza A (24). Thus, by suppressing the PAF receptor, fosfomycin, an antimicrobial agent, suppresses human respiratory syncytial virus-induced *S. pneumoniae* and *Haemophilus influenzae* adhesion to respiratory epithelial cells (25).

By orchestrating the interactions between coagulation and inflammation, protease-activated receptor-1, a member of the G protein-coupled receptor family, plays a role in *S. pneumoniae*-induced sepsis through crosstalk between PAR1 and the PAF receptor (26). Furthermore, beta-arrestin 1 contributes to the successful translocation of pneumococci by PAF receptor-mediated endocytosis in *Streptococcus pneumoniae* infection (27). In contrast, interferon-beta downregulates the PAF receptor and upregulates tight-junction proteins, resulting in a reduction in the development of bacteremia following intranasal infection with *Streptococcus pneumoniae* (28).

6. STREPTOCOCCUS SANGUIS

Streptococcus sanguis, also known as *Streptococcus sanguinis,* is a member of the *S. viridans* group, and is a normal inhabitant of the healthy human mouth that sometimes causes opportunistic bacterial endocarditis. Platelet-interacting *S. sanguis* expresses a 65-kDa platelet-aggregation-associated protein antigen on cell-wall fibrils that serves as a polyvalent agonist (29). The platelet-interaction domains of *S. sanguis* was shown to a structural motif with the consensus sequence X-P-G-E-P/Q-G-P-X (30). Subsequently, this sequence was determined to be P-G-G-G-G-P-L, which conforms

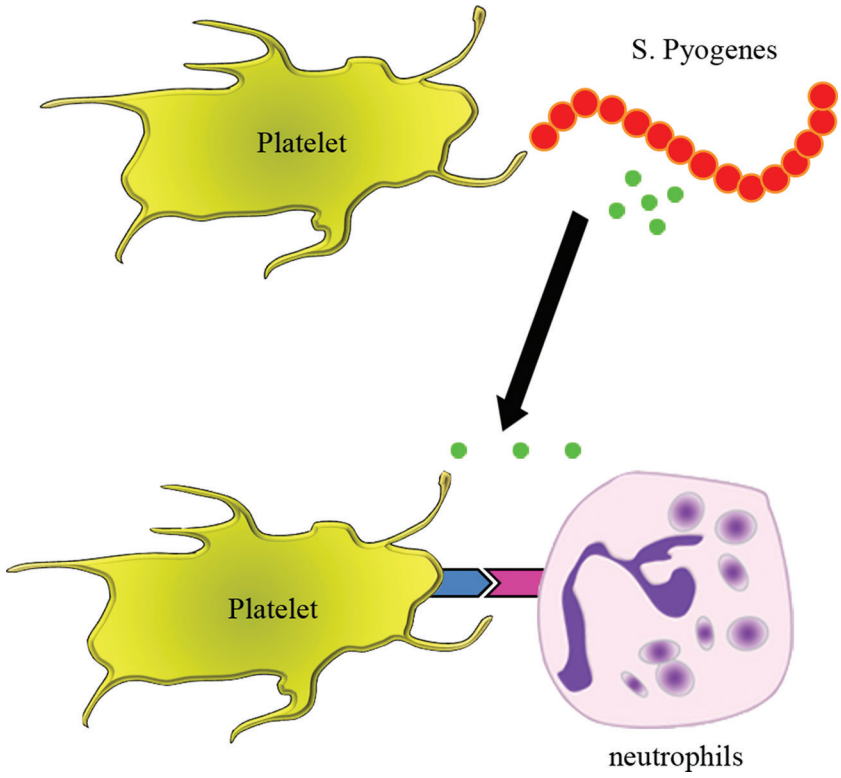

Figure 1. *Streptococcus pyogenes* induces the coaggregation of platelets and neutrophils. This bacterium binds to platelets, which then promotes platelet-neutrophil complex formation, neutrophil activation in response to infection and bacterial dissemination. In this process, the toxin streptolysin O induces the coaggregation of platelets and neutrophils, which is mediated by platelet P-selectin (CD62P).

to the predicted structural motif for the platelet-interactive domains of types I and III collagen (31). In the presence of type I collagen, collagens II through VI regulate the expression and conformation of platelet aggregation-associated protein from strain 133-79 (Adh+, Agg+) of *S. sanguis* (32). The platelet aggregation-associated protein gene was confirmed to *agg4*, a gene encoding a putative collagen-binding protein (CbpA) that contributes to platelet aggregation in response to *S. sanguis* (33). Another factor from *S. sanguis* that influences platelet activation and platelet aggregation-associated protein in infection is the identity of the strain itself. Agg+ strains have been shown to induce platelet aggregation *in vitro* (34). Additionally, the platelet aggregation-associated protein expressed by Agg+ *S. sanguis* makes this strain a more virulent pathogen in experimental endocarditis than an Agg- strain (35).

When *S. sanguis* invades the body, the secretory response of platelets is modulated by alpha 2-adrenoreceptors and G proteins (36), whereas the aggregation of platelets depends on multiple stimuli/agonists, including interactions involving immunoglobulin G (IgG)-Fc receptors, complement and fibrinogen (37). Thus, IgG is required for platelet activation induced by *S. sanguis*, and platelet activation by *S. sanguis* depends on a common IgG (38). *S. sanguis* binds to IgG, crosslinks FcγRIIA and initiates a signaling pathway that is down-regulated by PECAM-1-bound SHP-1. $\alpha_{IIb}\beta_3$ is then engaged, resulting in SHP-1 dephosphorylation, TxA2 release and subsequent platelet aggregation (39). In addition, complement proteins are involved in the platelet aggregation induced by *Streptococcus sanguis* NCTC 7863 (40). Thus, the immune system contributes to *Streptococcus sanguis*-induced platelet aggregation.

In *S. sanguis*-induced endocarditis, the platelet aggregation response to *S. sanguis* involves the cyclooxygenase (COX) pathway, GPIIb/IIIa and GPIb (41). GPIb directly interacts with *S. sanguis* and contributes to the pathogenesis of infectious endocarditis, even without binding to its normal ligand (42). In addition to the cyclooxygenase pathway, platelet activation is involved in the signaling in response to *S. sanguis* in a process involving the platelet MAP kinases Erk2 and p38 in addition to cPLA2 phosphorylation (43).

7. STREPTOCOCCUS GORDONII

Streptococcus gordonii typically colonizes the periodontal environment. The development of an infected platelet thrombus induced by *S. gordonii* on a heart valve is crucial for infectious endocarditis (44). The binding of platelets to *S. gordonii* is mediated by the 286-kDa,

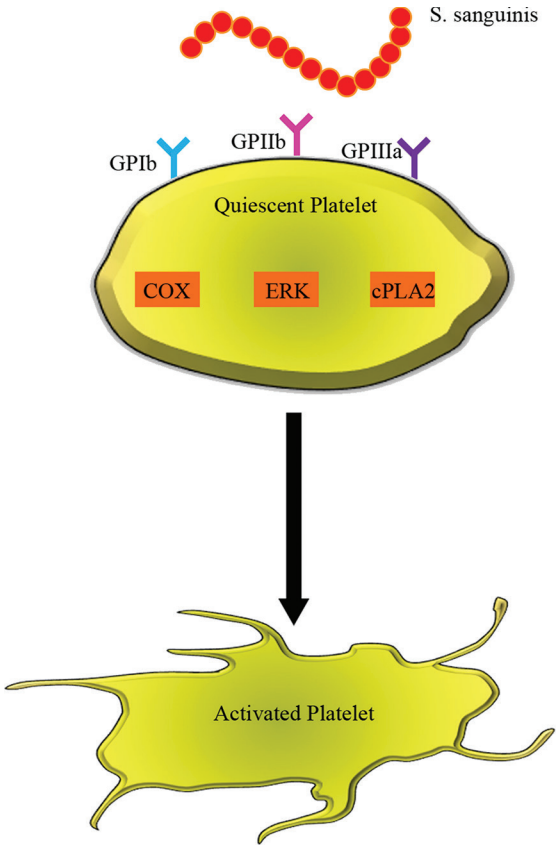

Figure 2. Platelets are activated by *Streptococcus sanguinis*. In infection by *Streptococcus sanguinis*, the pathogen interacts with GPIb and GPIIb/IIIa in platelets. In response to this pathogen, the cyclooxygenase pathway, MAP kinases, Erk2, p38 and cPLA2 are phosphorylated, and platelets are then activated.

cell wall-anchored protein GspB (45), a protein that is glycosylated prior to export (46). In platelet activation, GspB mediates binding of *S. gordonii* to sialylated carbohydrate epitopes on GPIb alpha from the platelet membrane (47). The BRs of GspB, a putative, N-terminal signal peptide and a short serine-rich region, are the binding domains of these adhesins (48). GPIb alpha and GPIIb are platelet receptors for the DL1 sialic acid-binding adhesin from *S. gordonii* (49). Moreover, GPIIb/GPIIIa-dependent platelet adhesion and aggregation can be induced by the *S. gordonii* surface proteins SspA/SspB (50). The binding sites for platelet GPIIb/IIIa on the *S. gordonii* surface protein PadA, including 454AGD and 383RGT, not only contribute to fibrinogen binding to GPIIb/IIIa to generate outside-in signaling but also play a role in dense granule secretion and platelet spreading (51).

8. STREPTOCOCCUS MITIS

Streptococcus mitis is similar to *S. gordonii* in that it inhabits the human mouth and can cause endocarditis (52). Human blood platelet aggregation factor has been identified in the extracellular products of *S. mitis* (53,54), suggesting that there is an interaction between platelets and *S. gordonii*. *Streptococcus mitis* also expresses the platelet-binding proteins PblA and PblB on its cell surface (55). Through the interaction of PblA and PblB with α2-8-linked sialic acids on ganglioside GD3, *S. mitis* binds to platelets and contributes to the pathogenesis of infectious endocarditis (56). In recent years, a recombinant *S. mitis*-derived human platelet aggregation factor has been found that has 36-56% identity with a family of cholesterol-dependent cytolysins and the ability to induce platelet aggregation (57). Moreover, *Streptococcus oralis*, which has been classified as a member of the *S. mitis* group, has been found to induce platelet aggregation via GPIb alpha and platelet FcγRIIa (58). These findings suggest that platelet-binding proteins from *S. mitis* play a crucial role in the pathogenicity of this pathogen.

Streptococcus tigurinus is a novel member of the *S. mitis* group that can cause invasive infections, including infectious endocarditis (59). Although *S. tigurinus* is highly virulent in endocarditis, its ability to induce aortic infection may not be associated with platelet aggregation (60). Therefore, the platelet-related pathogenicity of *S. mitis* differs between strains.

9. STREPTOCOCCUS MUTANS

Streptococcus mutans is commonly found in the human oral cavity, where it is implicated in the pathogenesis of certain cardiovascular diseases (61). *S. mutans* induces platelet activation by secreting serotype polysaccharides (62) and cell surface protein antigen c (63). The cell-surface glucosyltransferases (GTFB, GTFC, and GTFD) of *S. mutans* are associated with platelet aggregation (64). These findings suggest a possible interaction between platelets and *S. mutans* in infectious diseases caused by this pathogen. Further investigation on this subject is needed in the future.

10. CONCLUSIONS

In conclusion, the activation of platelets by the various *Streptococcus* species is crucial for the pathogenesis of certain infectious diseases, and streptococcal-binding proteins play a key role. Understanding the interaction between platelets and *Streptococcus* species in the pathogenesis of *Streptococcus* infection may provide novel insight into the diagnosis of and therapy for these diseases.

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Abbreviations: GBS, Group B *Streptococcus*; PAF, platelet-activating factor; GP, glycoprotein; FAK, focal-adhesion kinase; SpeB, streptococcal pyrogenic exotoxin B; CbpA, collagen-binding protein; IgG, immunoglobulin; COX, cyclooxygenase

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