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

Ming Jia¹, Yuling Xiong², Hua Lu¹, Ruqing Li¹, Tiantian Wang¹, Yanyao Ye¹, Min Song¹, Bing Li¹, Tianlun Jiang¹, Shuming Zhao¹

¹Department of Blood Transfusion, Southwest Hospital, The Third Military Medical University; ²Institute of Infectious Diseases of Chinese PLA, Southwest Hospital, Third Military Medical University

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/IIa (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, meningitis, 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-P-L, which conforms
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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).

S. Pyogenes

Platelet

neutrophils

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 FcyRIIA and initiates a signaling pathway that is down-regulated by PECAM-1-bound SHP-1. α_{IIb}β_{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,
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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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Send correspondence to: Shuming Zhao, Department of Blood Transfusion, Southwest Hospital, The Third Military Medical University, No. 30 Street Gaotanyan, Chongqing 400038, China, Tel: 86-15923929156, Fax: 86-23-68765475, E-mail: shumingzhao2014@163.com