



# Crosstalk Between Platelets and Microbial Pathogens

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Platelets, small anucleate cells circulating in the blood, are critical mediators in haemostasis and thrombosis. Interestingly, recent studies demonstrated that platelets contain both pro-inflammatory and anti-inflammatory molecules, equipping platelets with immunoregulatory function in both innate and adaptive immunity. In the context of infectious diseases, platelets are involved in early detection of invading microorganisms and are actively recruited to sites of infection. Platelets exert their effects on microbial pathogens either by direct binding to eliminate or restrict dissemination, or by shaping the subsequent host immune response. Reciprocally, many invading microbial pathogens can directly or indirectly target host platelets, altering platelet count or/and function. In addition, microbial pathogens can impact the host auto- and alloimmune responses to platelet antigens in several immune-mediated diseases, such as immune thrombocytopenia, and fetal and neonatal alloimmune thrombocytopenia. In this review, we discuss the mechanisms that contribute to the bidirectional interactions between platelets and various microbial pathogens, and how these interactions hold relevant implications in the pathogenesis of many infectious diseases. The knowledge obtained from “well-studied” microbes may also help us understand the pathogenesis of emerging microbes, such as SARS-CoV-2 coronavirus.

**Keywords:** platelets, microbial pathogens, host immune responses, COVID-19, thrombosis

## INTRODUCTION

Platelets are the second most abundant cells in human blood circulation (1, 2). Anucleate platelets are found only in mammals; in lower vertebrates, cells involved in hemostasis and blood coagulation are nucleated and termed thrombocytes (3, 4). Under physiological conditions, thrombopoietin (TPO) predominantly produced by the liver, via binding to the TPO receptor c-Mpl on megakaryocytes, is the major regulator of megakaryocyte differentiation and megakaryopoiesis (5–7). Historically it is known that platelets are produced from their precursor megakaryocytes in the bone marrow of mammals (3, 8, 9). However, recent research surprisingly uncovered that platelets could also be generated by megakaryocytes in the lung of mice (10), although further validation is required in both murine and human studies. Additionally, the relative contribution of lung-generated platelets to total circulating platelets and whether they possess different function is still unclear (11). In extension to their traditional roles in haemostasis and thrombosis (12–15), recent studies suggest that platelets are also involved in

many other physiological and pathophysiological processes, such as innate and adaptive immunity, angiogenesis, atherosclerosis, and tumor progression (2, 3, 16–22). We have previously compiled a comprehensive overview of the importance of platelets in modulating immune responses (23). In this review article, we mainly focus on the bidirectional interplay between platelets and microbial pathogens and the significant impact it has on the host responses.

Infectious diseases are unresolved challenges to human health, and remain as one of leading causes of morbidity and mortality worldwide, especially in resources-limited countries (<https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>). Microorganisms encounter platelets when they enter the mammalian blood circulation. Platelets can directly bind to many pathogens (e.g., bacteria, viruses, and parasites), or pathogen-IgG immune complexes via Fc receptors expressed on platelets (24–26). This platelet-pathogen interaction has functional consequences on both platelets and pathogens (Figure 1). Reduced levels of circulating platelets are commonly observed in patients with infectious diseases, and the underlying mechanisms vary depending on specific pathogens (18, 19, 25, 26). In addition, it has been demonstrated that reduced platelet counts in patients or mice are associated with increased susceptibility of the host to infections (27–30). Sepsis is a life-threatening inflammatory syndrome caused by a dysregulated host response to infection (31), and it has been demonstrated that sepsis altered the transcriptional and translational profiles of platelets in both humans and mice (32). Although the evolutionary pressure to drive the pathogens to develop various strategies to target platelets is not well-understood, one possibility is that platelets may protect the host from certain invading pathogens.

## VERSATILE ROLES OF PLATELETS IN PHYSIOLOGY AND PATHOBIOLOGY

### Role of Platelets in Haemostasis and Thrombosis

Platelet adhesion, activation and aggregation at the damaged vessel endothelium are critical for bleeding arrest (12–15). Platelet surface glycoprotein receptor, GPIIb/IIIa, via interacting with von Willebrand factor (VWF; anchored on collagen in the injured vessel wall), initiates platelet adhesion, particularly under the high shear conditions (14, 15, 33, 34). The GPIIb/IIIa-VWF interaction is also critical for endovascular growth of occlusive thrombi at sites of arterial stenosis where blood flows with wall shear rates that may exceed  $40,000\text{ s}^{-1}$ , corresponding to shear stresses exceeding  $1,600\text{ Pa}$  (35). The glycoprotein GPIIb/IIIa ( $\alpha\text{IIb}\beta\text{3}$  integrin), can also contribute to platelet adhesion under the lower shear conditions. This abundant platelet integrin is essential for both fibrinogen-dependent and fibrinogen-independent platelet aggregation (34, 36–39). Interestingly, in addition to the platelet accumulation (platelet adhesion and aggregation, the first wave of haemostasis), we recently found that the plasma fibronectin can rapidly deposit onto the injured vessel wall and mediate a “protein wave of hemostasis,” which occurs

even earlier than the first wave of haemostasis (40, 41). Platelets may release their plasma fibronectin content from  $\alpha$  granules and contribute to this protein wave of hemostasis, which is likely a compensatory mechanism for hemostasis in fibrinogen-deficient mice and humans since their platelet fibronectin levels increase 3–5-fold (34, 42, 43). Notably, activated platelets can promote the cell-based generation of thrombin that markedly enhances the blood coagulation (the second wave of haemostasis) leading to the generation of polymerized fibrin (2, 14, 44). Thus, platelets contribute to all three waves of haemostasis, which may directly or indirectly affect the dissemination of micropathogens *in vivo*.

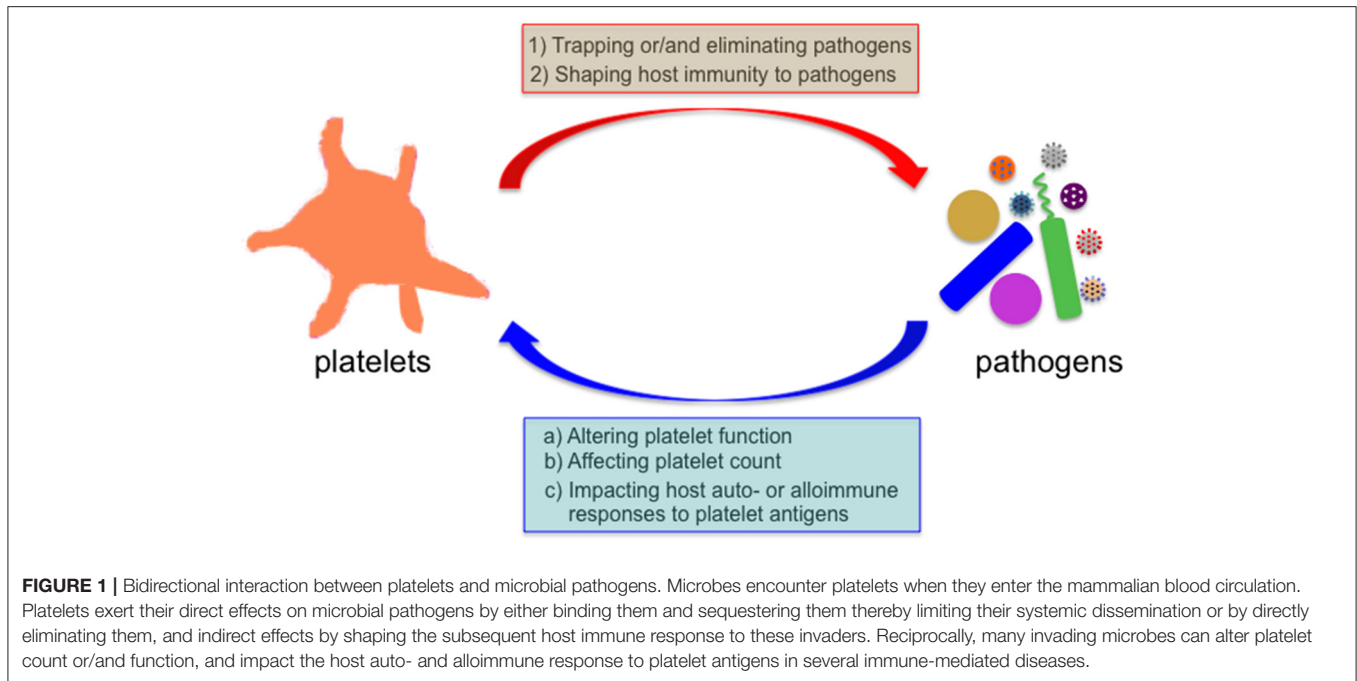
It has been well-understood that deficiencies in platelet adhesion/aggregation or the coagulation system are linked with various bleeding disorders (2, 36, 45). However, inappropriate formation of platelet plug may lead to thrombosis, and thrombosis in the cerebral or coronary arteries is the major cause of morbidity and mortality worldwide (46–48). Moreover, it has been recognized that thrombus formation in the placenta can lead to fetal loss during pregnancy in several disease conditions (49), such as antiphospholipid syndrome (50, 51).

### Role of Platelets in Innate and Adaptive Immunity

As platelets contain both pro-inflammatory and anti-inflammatory molecules, platelets can interact with many immune cells (e.g., dendritic cells, neutrophils, and lymphocytes), which can shape both innate and adaptive immunity (3, 16, 17, 21, 23). In addition, platelets are involved in the development of lymphatic vessels, the critical network facilitating immune cell trafficking and surveillance (52, 53). Platelets achieve this via the binding of platelet C-type lectin-like receptor 2 to podoplanin on lymphatic endothelial cells, leading to the separation of lymphatic vessels from blood vessels during embryonic development (54–56).

Platelets contribute to the host innate immunity in various ways. Platelets express the functional pathogen recognition receptors, such as Toll-like receptors (TLRs) (TLRs 1–10 in human platelets and TLRs 1–8 in murine platelets), and Nod-like receptor 2 (19, 25, 57, 58). Platelets contain many pro-inflammatory molecules (e.g., CD40 and serotonin), cytokines (e.g., IL-1) and chemokines (e.g., CCL3, CXCL4, and CCL5), and antimicrobial factors (e.g., kinocidins and defensins) in their granules (3, 19). In addition, platelets express several functional chemokine receptors, such as CCR3, CCR4, and CXCR4 (59). Platelets can also shed microparticles that are capable of transporting inflammatory molecules (e.g., CD40L and IL-1) to inflammatory cells (16, 60). Interestingly, platelets also contain multiple anti-inflammatory molecules and cytokines, such as transforming growth factor- $\beta$  (TGF- $\beta$ ) (3). It has been shown that platelet-derived TGF- $\beta$  diminishes the anti-tumor activity of natural killer (NK) cells (20, 61).

Platelets also modulate adaptive immune response of the host. Activated platelets express CD40L on their surface, which plays a key role in supporting antibody isotype switching (e.g., from IgM to IgG) and enhancing CD8<sup>+</sup> T cell function (62, 63).



Upon platelet activation, P-selectin is translocated from the  $\alpha$ -granule to the platelet surface (64). P-selectin, via interacting with peripheral node addressin on high endothelial venules and P-selectin glycoprotein ligand-1 on lymphocytes, mediates the rolling and recruitment of lymphocytes to peripheral lymph nodes (65). And platelet-derived TGF- $\beta$  was shown to inhibit the cytotoxic T cell response in the tumor microenvironment (66), and might improve function of regulatory T cells (67).

TGF- $\beta$  is a key factor in IgA isotype switching (68). Since IgA plays an important role in controlling the homeostasis of gut microbiota (68), and preventing pathogen invasion at mucosal sites (69), it remains to be investigated whether platelet TGF- $\beta$  contributes to the production of intestinal IgA. In addition, TGF- $\beta$  is critical for the differentiation of regulatory T cells under non-inflammatory conditions, in both mice and humans (70–72).

## EFFECTS OF PLATELETS ON MICROBIAL PATHOGENS

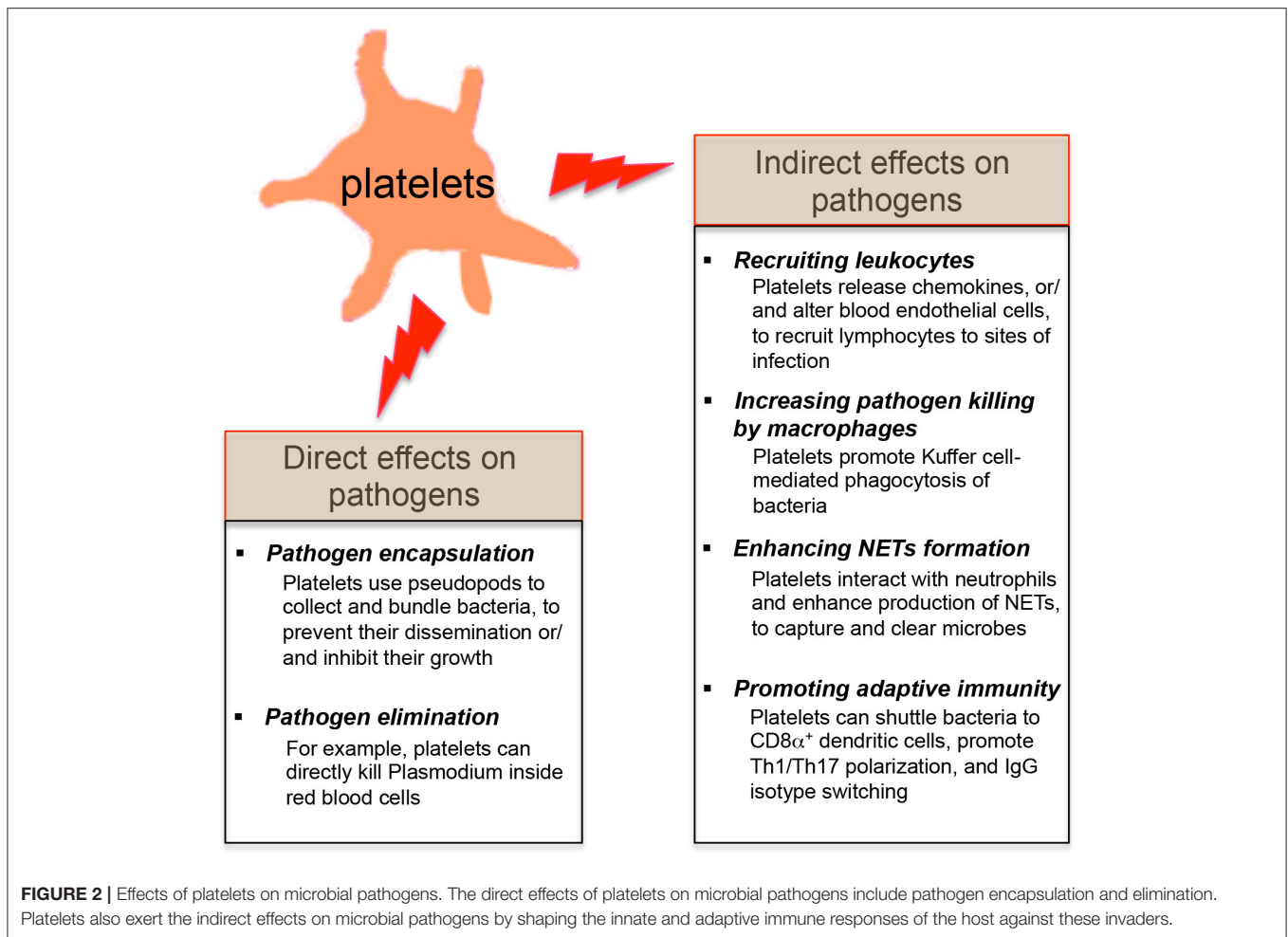
Since platelets contain many pro-inflammatory molecules, and reduced platelet counts in patients or mice are linked with the host's susceptibility to infections (3, 23, 27, 28, 30), it suggests that platelets may protect the host from certain microbial infections. Platelets are involved in the early detection of invading microorganisms and are actively recruited to sites of infection (18, 19, 25). Review of recent literatures shows that platelets exert their direct effects on microbial pathogens by either binding them and sequestering them thereby limiting their systemic dissemination or by directly eliminating them

(Figure 2). Platelets also have indirect effects on microbial pathogens by shaping the subsequent innate and adaptive immunity of the host to these invaders (Figure 2).

## Direct Effects of Platelets on Pathogens

In the context of *Staphylococcus aureus* (*S. aureus*) infection, platelets bind *S. aureus* and use the pseudopods to encapsulate the bacteria (73). This ability of platelets to collect and bundle bacteria [e.g., *S. aureus*, *Escherichia coli* (*E. coli*) and *Listeria monocytogenes* (*L. monocytogenes*)] may trap these bacteria, limit their dissemination within the bloodstream and present them to phagocytes (74, 75). Moreover,  $\alpha$ -toxin derived from *S. aureus* stimulated human platelets to release  $\beta$ -defensins, which significantly retarded the growth of two strains of *S. aureus* isolated from patients with sepsis (73).

In addition to pathogen trapping, platelets can kill certain pathogens. *Plasmodium falciparum* is the most common species that cause malaria in humans. In the infected host, *Plasmodium* invades red blood cells in the bloodstream and replicate until erythrocytes burst. It has been demonstrated platelets can bind *Plasmodium*-infected erythrocytes and directly kill *Plasmodium* inside red blood cells both *in vitro* and *in vivo* (28, 76). Subsequent studies revealed that the chemokine platelet factor 4 (also known as CXCL4) released from platelets plays a key role in this platelet-mediated parasite destruction (77, 78). In addition, platelets can secrete many antimicrobial factors including defensins to inhibit the growth of bacteria and viruses (19). Notably, human platelets and megakaryocytes express the antiviral immune effector molecule: interferon-induced transmembrane 3 (IFITM3) (79). It has been recently demonstrated that viral infections (e.g., influenza and dengue viruses) upregulated the expression of IFITM3 on platelets and



megakaryocytes, eliciting rapid antiviral immunity, and that megakaryocytes were capable of limiting viral infections in both megakaryocytes and hematopoietic stem cells via secretion of type I interferons (79).

However, it is important to note that some viruses [e.g., Dengue virus, human immunodeficiency virus (HIV), and hepatitis C virus (HCV)], which can be actively engulfed by platelets and induce platelet activation through TLR signaling, may also utilize platelets to disseminate through the entire body of host (80–83). Therefore, the protective role of platelets against viruses may be context-dependent.

### Indirect Effects of Platelets on Pathogens

In addition to the direct effects on pathogens, platelets can shape the host immune responses to invading pathogens and the involved mechanisms are summarized as follows (Figure 2):

#### Recruiting Leukocyte to Sites of Vascular Invasion

Platelets can utilize the functional pattern recognition receptors expressed on their surface to sense the intravascular pathogens, and release various chemokines (e.g., CCL3, CXCL4, and CCL5)

to recruit leukocytes to sites of vascular invasion (18). In addition, activated platelets use CD40L to trigger the inflammatory reaction on CD40-expressing vascular endothelial cells, leading to increased expression of the adhesion molecules (e.g., vascular cell adhesion molecule 1 and intercellular adhesion molecule 1) and secretion of proinflammatory cytokines (e.g., CCL2) by endothelial cells (84). This phenotypic alteration of vascular endothelial cells may further promote the recruitment of leukocytes at sites of infection (85, 86).

Activated platelets can also directly interact with leukocytes, forming platelet-leukocyte conjugates, and this interaction is largely mediated by P-selectin on activated platelets and P-selectin glycoprotein ligand 1 on leukocytes (47). The platelet-leukocyte triggers the activation of leukocytes and their increased expression of  $\beta 1$  and  $\beta 2$  integrin, leading to enhanced adhesion of leukocytes to vascular endothelial cells (87). In addition, activated platelets already deposited at sites of infection can act as docking platforms for leukocyte recruitment (47). More importantly, activated platelets deposit chemokines CXCL4 and CCL5 on the surface of vascular endothelial cells, instructing the extravasation of leukocytes at sites of infection (88, 89).



### Increasing Pathogen Elimination by Macrophages

In the liver, the tissue-resident macrophages, Kupffer cells, play a key role in the innate defense against blood-borne pathogens. Wong et al. showed that Kupffer cells act as docking platforms for both bacteria and platelets. Platelets formed aggregates around the bacteria that are bound to Kupffer cells, and promoted Kupffer cell-mediated phagocytosis of these bacteria (90).

### Enhancing Formation of Neutrophil Extracellular Traps (NETs)

During Gram-negative bacterial infections, platelets actively contribute to NETs formation (29, 91). Platelet TLR4 is capable of detecting intravascular TLR4 ligands [e.g., lipopolysaccharide (LPS)], inducing platelet binding to neutrophils. This TLR4-dependent platelet-neutrophil interaction results in robust neutrophil activation and production of NETs, which are DNA-based structures capable of capturing and eliminating microbes from the bloodstream (29, 77). Platelet depletion *in vivo* significantly impairs NETs formation and bacterial clearance (29, 92).

### Promoting Adaptive Immune Response to Pathogens

Antigen acquisition by dendritic cells is critical for generation of the cytotoxic CD8<sup>+</sup> T cell response against intracellular pathogens (93). Verschoor et al. found that platelets could actively bind *L. monocytogenes* in the circulation and shuttle this subset of gram-positive bacteria to splenic CD8 $\alpha$ <sup>+</sup> dendritic cells, enhancing anti-bacterial CD8<sup>+</sup> T cell expansion (94). In addition to affecting antigen presentation, platelets have been shown to promote the polarization of Th1 and Th17 cells, and modulate the balance of regulatory and non-regulatory T cells (95, 96). Furthermore, platelet-derived CD40L alone is sufficient to induce IgG isotype switching against adenovirus (62), but it remains to be investigated whether platelet CD40L also promotes antibody class switching to other immunoglobulin isotypes (e.g., IgA), since antibody class switching to different isotypes involves distinct DNA repair pathways (97).

Conversely, platelet antimicrobial responses may be detrimental to the host if they are dysregulated. For example, it has been reported that NETs formation contributed by platelets that were activated by microbial derived products could cause the injury to blood endothelial cells due to the many proteases contained within NETs (29), which can directly act as a scaffold and stimulus for thrombus formation (98).

## EFFECTS OF MICROBIAL PATHOGENS ON PLATELETS

As mentioned above, reduced platelet count is a common feature with some infectious diseases, and the underlying mechanisms vary depending on specific pathogens (18, 25, 26). Considering the important role of platelets in the regulation of host immunity, it is not surprising that various pathogens target platelets in the course of infections. Many invading pathogens can directly or indirectly target platelets

in the host, altering platelet function or/and count (Figure 3); in addition to these alterations, it has been shown that viral infections (e.g., dengue and influenza viruses) and sepsis can markedly alter the platelet transcriptome (32, 79). Furthermore, microbial pathogens impact the host autoimmune and alloimmune response to platelet antigens in several immune-mediated diseases, such as immune thrombocytopenia, and fetal and neonatal alloimmune thrombocytopenia (99–101) (Figure 3).

### Impact of Microbial Pathogens on Platelet Function

The interaction between microbial pathogens and platelets can lead to alteration of platelet function (i.e., platelet activation and apoptosis) (Figure 3). Activated platelets can trigger the coagulation system, leading to excessive clotting (102, 103), which may exacerbate the symptoms caused by microbial infections and thus may be detrimental to the host.

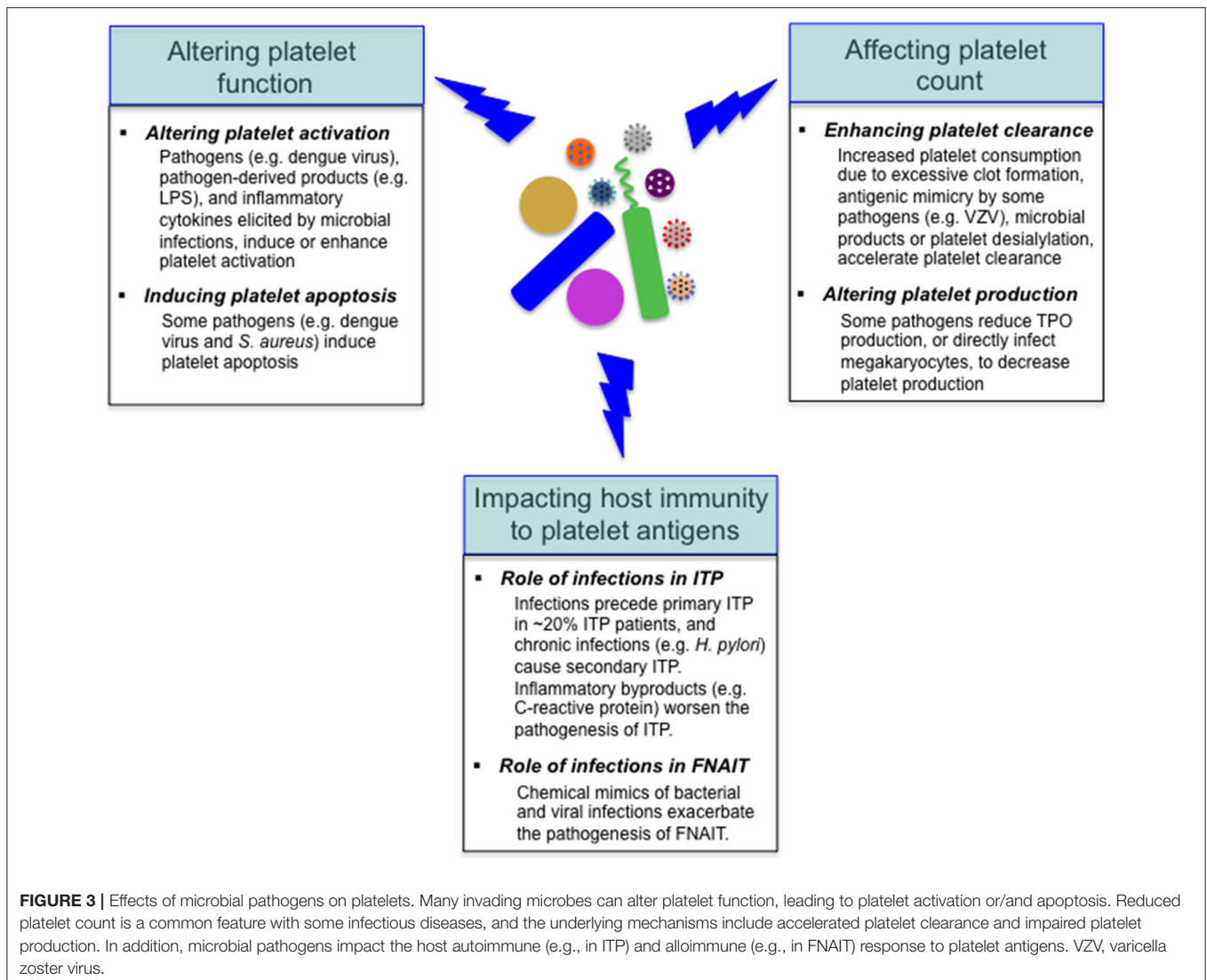
### Altering Platelet Activation

The capacity to trigger platelet activation is a well-known feature for many pathogens. For example, LPS purified from Gram-negative bacterium *E. coli*, via interacting with TLR4, induces platelet activation both *in vitro* and *in vivo* (58, 104), and direct interaction between *E. coli* and platelets has also been observed *in vivo* (75). Dengue virus, which causes hemorrhagic fever in around 10% infected patients, directly bind platelets via multiple receptors (e.g., DC-SIGN, heparin sulfate proteoglycan receptors and TLR-4), and activate platelets, triggering the conformational activation of platelet  $\alpha$ Ib $\beta$ 3 integrin, the translocation of P-selectin to platelet surface and the release of pro-inflammatory molecules (e.g., IL-1 $\beta$ ) (25, 105, 106). In addition, microbial infections cause the release of inflammatory cytokines in the host (31, 107), and these cytokines (e.g., TNF- $\alpha$ ) were shown to enhance platelet activation *in vivo* (108). And for some pathogens (e.g., influenza virus), anti-microbial antibodies form the immune complexes with pathogens and activate platelets via Fc receptors (18, 109).

It has been shown that the secreted products by *S. aureus*, such as  $\alpha$ -toxin and Staphylococcal superantigen-like 5, can directly activate platelets (110, 111). Interestingly, the lipoteichoic acid secreted by *S. aureus* can inhibit platelet activation and aggregation (112). Thus, the effects of microbial pathogens on platelet function is dependent on microbial strain or/and the microbial products.

### Inducing Platelet Apoptosis

Once activated, platelets undergo apoptosis (25). In addition, some pathogens (e.g., pathogenic *E. coli* and *S. aureus*) are found to directly induce platelet apoptosis through degradation of anti-apoptotic Bcl-xL protein (113). Platelet apoptosis induced by microbial pathogens (e.g., dengue virus) not only reduces mitochondrial potential, but also increases the surface exposure of phosphatidylserine that potentially triggers the activation of coagulation system (106, 114).



## Impact of Microbial Pathogens on Platelet Count

Reduced platelets in the context of infectious diseases can be due to enhanced platelet clearance or/and altered platelet production (Figure 3).

### Enhancing Platelet Clearance

As mentioned above, some microbial pathogens can activate the platelet and coagulation system, leading to thrombosis (18). Exaggerated thrombus formation, especially within the setting of sepsis-associated disseminated intravascular coagulation, may excessively consume platelets, resulting in reduced circulating levels (31, 115, 116). Secondly, platelet clearance may be enhanced through collateral stimulation of the immune system by some microbial pathogens [e.g., varicella zoster virus, HIV, HCV, and *Helicobacter pylori* (*H. pylori*)] (117–121). For example, thrombocytopenia in children following varicella zoster virus infection first described antigenic mimicry for some

microbial pathogens that encompass host generation of cross-reactive antibodies to certain glycoproteins (e.g., GPIIIa) on the platelet surface, resulting in accelerated platelet clearance (117). Third, direct platelet-bound microbial products (e.g., LPS) or inflammatory byproducts (e.g., C-reactive protein) could enhance antibody mediated phagocytic responses (122–124).

Microbial induced platelet clearance can also occur via removal of terminal sialic residues of the abundantly expressed platelet surface glycans. Scavenging of host sialic residues by microbial pathogens increases immune evasion and assists in survival and dissemination (125, 126). Direct cleavage of platelet sialic residues by pathogen-derived neuraminidase has been reported in bacterial, and parasitic infections (127). Indirectly, pathogens could induce platelet desialylation mediated by platelet-derived neuraminidase, as was reported with dengue virus infection (128). By either mechanism, loss of terminal sialic residues not only leads to rapid platelet clearance via lectin receptors predominantly in the liver (129),

but also potentiates platelets to hyperactivity contributing to pathological disseminated intravascular coagulopathy and thrombotic complications of sepsis (130–132). Although, animal models and preliminary human studies demonstrate sialidase inhibitors or hepatic lectin receptor Ashwell-Morell inhibitors can ameliorate coagulopathies and thrombocytopenia in microbial infections (133, 134), other lectin receptors such as the recently identified Kupffer macrophage galactose lectin receptor may also contribute (135). Likely there are multiple and redundant receptor/ligand interactions that mediate clearance of desialylated or desialylation activated platelets.

### Altering Platelet Production

Depending on the specific pathogens, there are several means by which invading microbes can negatively impact the platelet production by megakaryocytes in the bone marrow. For example, HCV can interfere with TPO production by damaging the liver tissue (136). Some pathogens (e.g., dengue virus and HIV) can directly infect megakaryocytes or their precursors, or alter the bone marrow microenvironment, leading to the defective platelet production in bone marrow (137–140).

However, it is important to note that inflammatory cytokines (e.g., TNF- $\alpha$  and IL-6) induced by certain microbial infections are capable of enhancing platelet production by triggering acute emergency megakaryopoiesis (18, 141). Thus, the impact of microbial infections on platelet production is context-dependent.

In addition to the effects on platelet count and function, microbial pathogens impact the host auto- and alloimmune response to platelet antigens in several immune-mediated diseases, such as immune thrombocytopenia (ITP), and fetal and neonatal alloimmune thrombocytopenia (FNAIT) (99–101) (Figure 3).

### Role of Infections in ITP

ITP is an autoimmune disorder in which an abnormal immune response develops against one's own platelets, leading to autoantibody-induced platelet/megakaryocyte destruction and suppressed platelet production, and an increased risk of bleeding (3, 99, 142–145). In adult ITP patients, detectable antibody reactivity against GPIIb/IIIa and GPIb/IX predominate (60–70%) (99, 142, 146). However, it is uncommon for patients to possess single antibody specificities, other glycoprotein targets including GPV, GPIV, and GPIa/IIa are often detected (147–149). Moreover, extensiveness of anti-glycoprotein antibody repertoire has been correlated with more severe disease (147). The anti-platelet antibodies not only accelerate platelet clearance mediated by splenic macrophages and hepatic Kupffer cells (135, 150, 151), but also inhibit the development of bone marrow megakaryocytes and promote their apoptosis, thus inhibiting platelet production (3, 99, 129, 142, 152). In addition to anti-platelet autoantibodies, cytotoxic CD8<sup>+</sup> T cells, and regulatory CD8<sup>+</sup> T cells might also contribute to the pathogenesis of ITP (99, 142, 153–158). Cytotoxic CD8<sup>+</sup> T cells were shown to directly lyse platelets, induce the apoptosis of platelets, and inhibit platelet production by megakaryocytes (153, 159, 160). It has been reported that the frequency or/and function of regulatory CD4<sup>+</sup> T cells were defective in the circulation of ITP patients (161–169), and interestingly, the TGF- $\beta$  level was also reduced in these patients

(161, 170, 171). It has been reported that peripheral deficiency of regulatory CD4<sup>+</sup> T cells might be caused by their retention in the thymus in murine model of ITP (172), although it remains to be investigated whether this mechanism is also present in ITP patients. The therapies (e.g., steroids and B cell depletion) that improve platelet counts also restored the frequency or/and function of regulatory CD4<sup>+</sup> T cells in the periphery (67, 163, 166, 169, 173), and the level of circulating TGF- $\beta$  in ITP patients (170, 171), although it remains to be investigated whether the improvement of regulatory T cells is due to changes in circulating TGF- $\beta$  (3).

Chronic infections (e.g., HIV, HCV, and *H. pylori*) can cause secondary ITP, in which antimicrobial antibodies cross-react with platelets, leading to platelet destruction (174). Acute infections have long been suspected as triggers that initiate the pathogenesis of primary ITP, but in most acute ITP cases, the specific pathogen could not be identified (175). Retrospective studies suggested that infectious events (e.g., viral and fungal infections) precede the development of primary ITP in around 20% ITP patients (176), but future definitive studies are required to confirm the causal relationship between the specific pathogen(s) and initiation of primary ITP, and to identify the underlying mechanisms (151, 152). Furthermore, it has been demonstrated that infections during ITP worsened the pathogenesis of primary ITP and the therapeutic response to platelet transfusions, but the underlying reasons were unclear (30).

Since inflammation induced hemorrhage in thrombocytopenic mice (177), it is possible that inflammation associated with microbial infections may aggravate the bleeding risk in thrombocytopenic patients (e.g., ITP). C-reactive protein is markedly upregulated during acute infections and inflammation (178), and it has been shown that C-reactive protein, via binding to platelet phosphorylcholine residues, enhanced the IgG-mediated phagocytic responses against platelets and thereby thrombocytopenia, which has implications in the pathogenesis of both ITP and FNAIT (123, 124). In addition to ITP, infections also play an important role in the pathogenesis of heparin-induced thrombocytopenia, in which pathogenic antibodies to the complexes of platelet factor 4 (PF4) and heparin develop post-heparin exposure, leading to life-threatening complications of thrombocytopenia and thrombosis (179, 180). It has been demonstrated that PF4 bound to various bacteria, induces the generation of antibodies that could cross-react with the major antigen in PF4/heparin complex, resulting in heparin-induced thrombocytopenia (181, 182).

### Role of Infections in Alloimmune Thrombocytopenia

FNAIT results from the development of maternal alloantibodies targeting paternally derived antigens on fetal platelets during pregnancy, and these maternal antibodies cross the placenta and destroy fetal or neonatal platelets, leading to bleeding disorders (183–189). Similar to ITP, most of the reported FNAIT cases are characterized by maternal alloantibodies to platelet GPIIb/IIIa (183–185, 190). In contrast, there are very few reported cases of FNAIT with anti-GPIb $\alpha$  complex antibodies (191–195), which is different from the 20 to 40% prevalence of anti-GPIb $\alpha$  antibodies in ITP patients (99, 142). To gain new insights into the pathogenesis of FNAIT, our laboratory established animal

models of FNAIT using  $\beta 3^{-/-}$  and  $\text{GPIIb}\alpha^{-/-}$  mice, respectively (187, 188, 196, 197). We observed neonatal thrombocytopenia and severe bleeding disorders (e.g., intracranial hemorrhage) in the heterozygous pups from wild-type (WT) platelet immunized  $\beta 3^{-/-}$  dams, which recapitulated FNAIT in humans (187, 196). In contrast, miscarriage unexpectedly occurred in most of the anti-GPIIb $\alpha$ -mediated FNAIT, which is far more frequent than that mediated by anti- $\beta 3$  antibodies (49). Besides miscarriage, maternal immune response against fetal platelet antigens caused intrauterine growth restriction to fetuses due to placental abnormalities in animal models of FNAIT (197).

The roles of bacterial/viral infections in the pathogenesis of FNAIT were unclear. To test whether bacterial infection contributed to FNAIT, we utilized LPS to mimic Gram-negative bacterial infection, and co-administered it with low-dose WT platelet antigens to  $\text{GPIIb}\alpha^{-/-}$  and  $\beta 3^{-/-}$  mice (100). We found that LPS co-administration significantly boosted the production of anti-GPIIb $\alpha$  and anti- $\beta 3$  antibodies, and miscarriage occurred in most of these co-stimulated  $\text{GPIIb}\alpha^{-/-}$  and  $\beta 3^{-/-}$  mice, while miscarriage infrequently occurred in the dams immunized with low-dose WT platelets alone. Furthermore, we utilized Poly I:C to mimic viral infections, and observed that co-injection of Poly I:C and WT platelets also enhanced production of anti-GPIIb $\alpha$  antibodies in  $\text{GPIIb}\alpha^{-/-}$  mice and the severity of FNAIT (100). However, it remains to be investigated whether live bacterial or viral infections indeed exacerbate the pathogenesis of FNAIT. Overall, our data suggested that both bacterial and viral infections were likely to be involved in the pathogenesis of FNAIT in animal models, but it warrants further studies to test whether this is also the case for human FNAIT patients.

The effects of microbial infections in the pathogenesis of FNAIT may be also translatable to another alloimmune thrombocytopenia: post-transfusion purpura, in which anti-platelet alloantibodies develop against transfused platelets from genetically distinct donors (3).

## FUTURE PERSPECTIVES

Our understanding of platelet functions beyond haemostasis and thrombosis has dramatically expanded in the past years. Accumulating evidence indicates that platelets play an important role in the host immunity against microbial infections, and future discoveries will undoubtedly uncover more versatile features of platelets. The interaction between platelets and microbial pathogens are bidirectional, as this interaction causes the biological consequences on both platelets and microbes (Figure 1). The knowledge we obtained from these “well-studied” microbes may also help us understand the pathogenesis of emerging microbes, such as severe acute

respiratory syndrome coronavirus (SARS-CoV-2). The SARS-CoV-2 infection causes the pandemic coronavirus disease 2019 (COVID-19) in humans, but the pathogenesis of COVID-19 is still largely unclear (198, 199). Thrombocytopenia has been observed in around 5–36% of COVID-19 patients (198, 200), and two recent meta-analysis studies with COVID-19 patients revealed that severe reduction in platelet counts might be a poor prognostic marker for this life-threatening disease (201, 202). Importantly severely ill COVID-19 patients exhibit profound hypercoagulable states (203, 204), and excessive clotting has been observed in severely ill COVID-19 patients (205–207). Is the thrombocytopenia in severe COVID-19 cases caused by the platelet hyperactivities and consumption during micro-thrombi formation? Do the hypercoagulable states synergize with platelet activation, which provide phosphatidylserine, propel the cell-based thrombin generation (44), and lead to thrombosis? Do platelets release/synthesize their cytokines and contribute to the cytokine storm in COVID-19 patients? Do platelets contribute to the immune response against SARS-CoV-2? Finally, are platelets friends or foes or able to switch their roles during SARS-CoV-2 infection? All these questions are important and warrant further investigations.

Overall, we believe that understanding the interactions between platelets and microbial pathogens will shed light on the pathogenesis of infectious diseases and that modulation of platelet-pathogen interactions could provide new therapeutic avenues.

## AUTHOR CONTRIBUTIONS

CL designed and wrote most of the paper. JL wrote and edited the manuscript. HN was the principal investigator who designed and wrote the paper. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer RK declared a past co-authorship with one of the authors HN to the handling editor.

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