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Role of platelets in detection and regulation of infection

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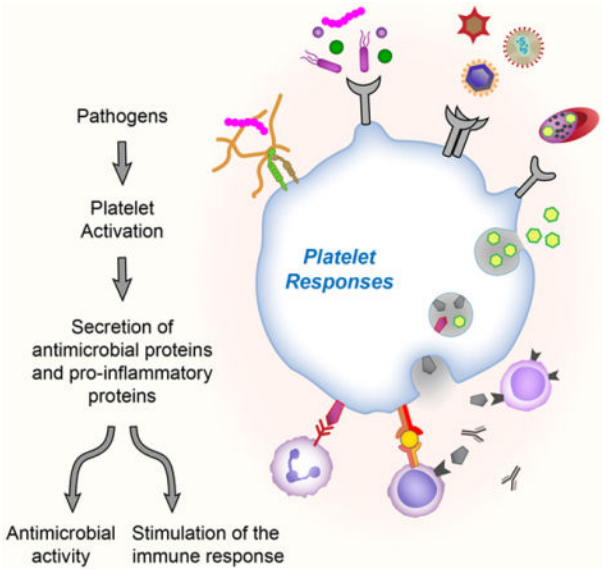
Abstract

Platelets are classically known as essential mediators of hemostasis and thrombosis. However, in recent years, platelets have gained recognition for their inflammatory functions which modulate the immune response during infectious diseases. Platelets contain various immunoreceptors that enable them to act as sentinels to recognize intravascular pathogens. Upon activation, platelets directly limit pathogen growth through the release of antimicrobial peptides and ensure pathogen clearance through activation of immune cells. However, aberrant platelet activation can lead to inflammation and thrombotic events.

Graphical Abstract



Introduction

Infectious diseases have a significant impact globally with high mortality and morbidity rates reported each year by the World Health Organization. Over the past few decades, new

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challenges associated with infectious diseases have placed additional burdens on health care due to the emergence of antimicrobial resistance, malaria, HIV/AIDS and the recent COVID-19 pandemic. As research continues to elucidate the pathogenesis of acute infections, one striking conclusion observed by many studies is the extensive contribution of platelets to host defense against pathogens. Platelets are small, anucleate cells derived from their mother cell the megakaryocyte, and considered critical in hemostasis and thrombosis. However, as platelets constantly scan the endothelium for vessel damage, they are well-positioned to act as first responders to detect invading pathogens resulting in their activation which triggers and contributes to the host immune response to fight the infection.[1]

On the other hand, pathological activation of platelets due to overwhelming pathogen invasion, damage to blood vessel walls or non-infectious inflammatory triggers can often lead to thromboinflammation, a process that intimately links inflammation and thrombosis, which can be detrimental to the host and can contribute to the pathophysiology of the disease.[1] Thrombocytopenia, or low platelet counts, is common in acute infections and can correlate with disease severity.[2] Increased vascular permeability is also common during thromboinflammation and infection. Both processes closely involve platelets and can lead to inflammatory vasculopathy and thrombosis.[3]

In this review, we discuss how platelets recognize and respond to a variety of pathogens beginning with an overview of platelet receptors involved in sensing invading pathogens. In addition, we examine how platelet activation contributes to host-defense through secretion of antimicrobial proteins and chemokines, which can directly interact with the pathogen, but also trigger the innate and adaptive immune system to combat against infections.

Platelets sense pathogens

Similar to innate immune cells, platelets contain pattern recognition receptors (PRRs) which recognize different components that increase during infection. These can be generically expressed microbial structures called pathogen-associated molecular patterns (PAMPs) or host-derived components known as damage-associated molecular patterns (DAMPs). Different families of PRRs are expressed on platelets, such as Toll-like receptors (TLRs), C-type lectin receptors (CLRs), and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs)[3], and are depicted in Figure 1. Engagement of these receptors by pathogens or antigens generally lead to platelet activation, differential granule release, and interaction with leukocytes, allowing platelets to act as both thrombotic and immune cells.[1,3,4]

Toll-like receptors –

Although all 10 human TLRs are detected at a transcriptional level in human platelets, only TLR1,−2,−3,−4,−6,−7 and −9 have reported functionality in platelets (Figure 1A).[5–10] TLR4 and TLR2 are the best characterized platelet PRRs and both recognize structural components of pathogens, especially bacteria. TLR4 is specific for the Gram-negative bacterial cell wall component lipopolysaccharide (LPS) and activation of platelet TLR4 is linked to different aspects of the pathogenesis of sepsis.[5,11–13] Many studies have attempted to examine the role of TLR4 agonists, including LPS, on platelet activation with conflicting results. In

general studies have shown LPS directly induces cytokine release, including sCD40L and platelet activation factor.[14] In addition, LPS has been shown to increase splicing of IL-1ß and tissue factor mRNA, which may contribute to both thrombosis and inflammation during sepsis.[12,13] Others have reported LPS potentiates platelet activation when platelets are stimulated with low levels of platelet agonists, resulting in increased dense granule release, P-selectin expression, and platelet aggregation.[15]

TLR2 has a broader specificity, binding peptides from Gram-negative or Gram-positive bacteria, in conjunction with TLR1 or TLR6, respectively.[6] Activation of TLR2 on platelets was first described through the use of a synthetic triacylated lipopeptide, that mimics the N-terminus of bacterial lipopeptides, called Pam3CSK4.[7] Activation of TLR2 was also demonstrated by Gram-negative *Porphyromonas gingivalis,* which increased CD40L surface expression on platelets and induced platelet-neutrophil aggregate (PNA) formation.[7,16] In addition, sepsis-inducing Gram-positive *Streptococci* strains through lipoteichoic acid and peptidoglycan interact with TLR2, resulting in platelet aggregation and $\alpha_{IIb}ß_3$ activation via phosphoinositide 3-kinase signaling.[17,18]

Interestingly, recent studies have demonstrated that platelet TLR engagement is not exclusive to bacteria. For example, platelet activation is induced by Dengue virus (DENV) nonstructural protein 1 (NS1) through TLR4[19] and the viral envelope glycoproteins from cytomegalovirus (CMV) via TLR2[20]. Stimulation of platelet TLR2 and −4 by DAMPs, including histones in neutrophil extracellular traps (NETs), also result in platelet activation.[21]

Unlike TLR2 and −4, platelet TLR3, −7 and −9 are located intracellularly in endosomal compartments and recognize nucleotide derivatives.[8] TLR3 traditionally recognizes dsRNA and is the least characterized of the three endosomal platelet TLRs. *In vitro* stimulation of platelets with TLR3 agonists have resulted in contradictory observations regarding platelet activation and further studies are necessary to elucidate the role of platelet TLR3.[9,22] In contrast, platelet TLR7 plays an important role in the detection of ssRNA viruses including, influenza[23], human immunodeficiency virus type-1 (HIV-1)[24], hepatitis C virus[25] and DENV[26], as these viruses are known to be internalized by platelets. Previous studies have demonstrated activation of TLR7 by encephalomyocarditis virus (ECMV) resulting in mild thrombocytopenia and increased PNA formation, notably, without any pro-thrombotic effect.[10] Activation of platelet TLR7 by influenza resulted in release of complement C3, triggers neutrophil-DNA release. This may enhance vascular occlusions and partially explain the increased risk of myocardial infarction observed in influenza patients.[23] While TLR7 recognizes, ssRNA, platelet TLR9 typically recognizes dsDNA containing unmethylated CpG oligodeoxynucleotides from bacteria or viruses. TLR9 can also recognizes carboxy(alkylpyrrole) protein adducts, a class of DAMPs linked to oxidative stress that induce platelet activation and aggregation, enhancing *in vivo* thrombosis.[27] Recently, activation of the TLR7 and −9 signaling pathways in platelets were further characterized. In these studies, both HIV-1 pseudovirions and synthetic TLR7 and −9 agonists induced platelet activation, including granule secretion and platelet leukocyte aggregate (PLA) formation, albeit to a lesser extent in comparison to thrombin stimulation. Importantly activation of the both TLR signaling pathways was dependent on endocytosis of the virion

particles in a dynasore-sensitive, VAMP (vesicle-associated membrane protein)-3-and Arf6 (ADP-ribosylation factor 6)-dependent manner followed by endosomal acidification.[8]

C-type lectin receptors –

CLRs are a large family of surface receptors specialized in the recognition of glycans through their conserved carbohydrate-binding domains. Two platelet CLRs, involved in various infectious diseases, are dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) and C-type lectin-like receptor 2 (CLEC-2) (Figure 1B). As a PRR, DC-SIGN recognizes N-linked high mannose glycans on viral envelope proteins, which enables viruses such as HIV-1[28] and DENV[26] to bind platelets. Additionally, extracellular mitochondrial DNA (Mt-DNA), a DAMP released during inflammation, has been shown to induce platelet activation through DC-SIGN based on antibody blocking studies.[29]

Another platelet CLR with an important role during inflammation and infection is CLEC-2.[28] Similar to DC-SIGN, HIV-1 and DENV bind CLEC-2 on platelets, which contributes to disease severity and the overall inflammatory response, especially during dengue infection.[28,30] CLEC-2 is one of three platelet receptors, which contain immunoreceptor tyrosine-based activation motif (ITAM sequence) along with FcγR and FcγRIIa (see below). Besides viral binding to CLEC-2, podoplanin, the endogenous CLEC-2 ligand, plays an important role in bacterial infections. While the CLEC-2-podoplanin axis was shown to mediate inflammation-triggered thrombosis in the liver after *Salmonella* infection[31], another study reported a thrombosis-independent inhibitory role towards systemic inflammation in sepsis[32]. In addition, to the role of CLEC-2 in thrombosis, the receptor is critical in regulating vascular integrity during inflammation. Loss of platelet CLEC-2 or podoplanin disrupts high endothelial venules, which are responsible for mediating lymphocyte trafficking to lymph nodes.[33] Furthermore, loss of platelet CLEC-2 signaling leads to diminished immune response function of lymph nodes.[34] Recently, hemin, a synthetic form of free heme, was also shown to activate platelets in a CLEC-2 dependent manner.[35] Considering free heme is released during hemolysis, this interaction might be important in hemolytic infectious diseases including malaria and hemolytic-uremic syndrome.

NOD-like receptors –

NLRs are cytoplasmic PRRs that regulate inflammatory and apoptotic responses. The best characterized platelet NLR is nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing protein 3 (NLRP3), a sensor for inflammasome activation (Figure 1A). Platelet NLRP3 function was first described during DENV infection as DENV induces the assembly of the NLRP3 inflammasome, resulting in IL-1ß secretion through platelet-derived microparticles (MPs).[36] Later, it was determined that NLRP3 activation was dependent on DENV NS1 binding to platelet TLR4. Activation of TLR4 induces splicing and synthesis of pro-IL-1ß, while cleavage of pro-IL-1ß to mature IL-1ß occurs in a caspase-1-dependent, which is activated by a secondary signal through ATP or other DAMPs.[19] The increased synthesis of IL-1ß during Dengue infection is thought to enhance inflammation and endothelial cell permeability.

Platelet Fc receptor –

Besides PRRs human platelets also express Fcγ Receptor IIa (FcγRIIa), which is the only receptor on platelets to recognize the constant fragment (Fc) of immunoglobulin (Ig)G, which enables binding of IgG-immune complexes.[37] IgG bound bacteria, including *Escherichia coli* and *Streptococcus oralis,* are recognized by FcγRIIa and trigger platelet activation and aggregation.[38,39] In addition, FcγRIIa engagement renders platelets hypersensitive to other thrombotic stimuli as bacteria-induced platelet activation often occurs after simultaneous stimulation of FcγRIIa and additional platelet receptors.[40–43] Similar to the role of FcγRIIa in bacterial infections, immunocomplexes of influenza A/H1N1 virus[44] and fungal spores from *Mucor circinelloides*[45] are also known to activate platelets through FcγRIIa and $\alpha_{IIb}ß_3$. Importantly, FcγRIIa is not expressed on mouse platelets, limiting relevant *in vivo* models.

Major Histocompatibility Complex (MHC) class I –

Platelets are also capable of processing pathogenic antigens through an MHC class I-dependent manner to activate the adaptive immune system. In an experimental cerebral malaria model (ECM), platelets were capable of directly presenting antigens to $CD8^+$ T-cells (Figure 1C). Importantly, robust early antigen presentation by platelets resulted in activation of $CD8^+$ T-cells and protected in ECM.[46]

Hemostatic platelet receptors –

Finally, platelets also express a wide range of receptors that are specific for platelets and megakaryocytes. In addition to their well-established roles in hemostasis and thrombosis, these receptors detect and interact with pathogens to regulate infection (Figure 1C).

Platelet activation through glycoprotein VI (GPVI), the major collagen receptor on platelets, was reported with recombinant staphylococcal superantigen-like protein 5 (SSL5).[47] Furthermore, soluble GPVI was recently shown to predict the development of sepsis in ICU patients.[48] Interestingly, platelet GPVI contributes to local host defense in a *Klebsiella pneumonia*e-induced mouse model of pneumonia-derived sepsis by regulating bacterial growth in the lungs.[49] The involvement of GPVI in viral infections has been less studied with only hepatitis C virus reported to bind GPVI.[50] However, the clinical significance of this interaction remains unclear.

Glycoprotein Ib (GPIb) is classically known to regulate platelet adhesion under high shear conditions by binding von Willebrand factor (VWF). However, several *in vitro* studies reported that GPIb also interacts directly with several bacterial proteins such as streptococcal protein B and streptococcal hemagglutinin[51] of *Streptococcus gordonii*, SSL5 of *Staphylococcus aureus*[47] and serine-rich protein A of *S. sanguis*[52], inducing platelet activation. Several bacterial proteins also indirectly interact with GPIb through VWF.[40] Importantly, platelet GPIb is also a key receptor in the surveillance mechanism consisting of platelets and Kupffer cells, the liver-resident macrophages, which detects and clears blood-borne bacterial infections. Upon infection the transient interactions of platelet GPIb with constitutively expressed VWF on the surface of Kupffer cells switches into a firm adhesion, followed by platelet aggregate formation around the bacterium.[53] The role of GPIb during

viral infections is less clear. A recent report suggests that DENV has a selective tropism for GPIb[54], but further research is needed to investigate the clinical significance of this finding.

The most abundant glycoprotein on platelets is $\alpha_{IIb}ß_3$ integrin, which recognizes different ligands including fibrinogen. Direct interactions of bacterial proteins with $\alpha_{IIb}ß_3$ resulting in platelet adhesion have been previously described.[42,55–57] In addition, bacteria can bind fibrinogen via bacterial surface proteins, including *S. aureus* clumping factor A[41], the serine-aspartate repeat protein G of *S. epidermidis*[42], and the M1 protein of *S. pyogenes*[43] to interact with $\alpha_{IIb}ß_3$. This interaction, in combination with simultaneous stimulation of FcγRIIa, leads to platelet activation and aggregation.[41–43] Integrin $\alpha_{IIb}ß_3$ is also critically involved in platelet migration. A recent study demonstrated platelets recruited to sites of injury become motile, enabling them to act as mechano-scavengers to collect bacteria-fibrin bundles within invaginations of the open canicular system. While these migrating platelets were unable to kill the engulfed bacteria (*E. coli* and *S. aureus*) directly, they facilitated bacterial removal by neutrophils.[58]

Activated platelets release α-granule content

Platelets act as specialized sentinels for pathogens invading the bloodstream. Recognition of PAMPs or DAMPs by different platelet receptors results in platelet activation and the release of platelet α-granules. One class of α-granule-stored proteins, particularly relevant to infectious diseases, are antimicrobial proteins (AMPs), subdivided in kinocidins, platelet microbicidal proteins (PMPs), and defensins.[59] The most abundant kinocidin in platelets is platelet factor 4 (PF4; CXCL4) and is often used as the prototype to describe this family of AMPs. Its dual function is a direct consequence of its multidomain structure that consists of an anionic N-terminal chemokine domain with CXC-motif and a C-terminal AMP-like domain. The latter contains the typical amphipathic α-helix, in which cationic and hydrophilic side chains segregate on opposite sides of the molecule, allowing disruption of anionic microbial cell membranes.[60] The antimicrobial activity of PF4 is particularly well-characterized for malaria parasites. Intraerythrocytic parasite killing by PF4 has been observed *in vitro* after binding to the erythrocytic Duffy-antigen receptor for chemokines.[61] This interaction facilitates endocytosis and accumulation of PF4 into the infected erythrocyte resulting in lysis of the *Plasmodium* digestive vacuole (Figure 1C).[62] This antiparasitic activity may be solely ascribed to its C-terminal region as a cyclic PF4 peptide dimer, containing only the last 14 amino acids, had a similar potency as full-size PF4.[60] Importantly, the clinical relevance was recently demonstrated as PF4-mediated parasite killing occurred in samples of patients infected with all major human *Plasmodium* species.[63] In addition, PF4 also works as an antimicrobial agent against bacteria and viruses. For example, platelets are able to kill bacteria in a PF4 and FcγRIIa-dependent manner. Secreted PF4 binds to bacterial polyanions on *E. coli* leading to the formation of anti-PF4/polyanion IgGs. These IgGs opsonize circulating *E. coli* leading to platelet FcγRIIa-mediated release of antimicrobial factors to destroy the opsonized bacteria (Figure 1C).[64] PF4 can also inhibit HIV-1 entry into cells by blocking viral attachment.[65]

While PF4 has beneficial antimicrobial properties, the kinocidin is not completely protective during infection as PF4 also acts as a chemokine to recruit and activate leukocytes.

Interestingly, elevated plasma levels of PF4 were observed in patients that died from severe cerebral malaria[66] and PF4 deficiency improved outcomes after ECM[67], demonstrating a detrimental role for PF4 besides its antimicrobial activity. Presumably, the immunomodulatory activity of the PF4 chemokine domain contributes to immune activation and T-cell recruitment to the brain, which aggravates ECM pathology.[67] Interestingly, this role is consistent with other findings demonstrating that PF4 promotes leukocyte recruitment to the lungs of influenza infected mice to help in viral clearance.[68]

Other kinocidins include platelet basic protein (CXCL7) and RANTES (CCL5). The latter has proven anti-viral activity as it blocks HIV-1 entry to T-cells via CCR5[69] and assists PF4 in the recruitment of monocytes[70]. CXCL7 generates upon proteolytic cleavage neutrophil-activating peptide 2 (NAP-2), ß-thromboglobulin and connective tissue-activating peptide III (CTAP-III). Interestingly, C-terminal truncation of NAP-2 and CTAP-III results in PMPs called thrombocidins, which are bactericidal and fungicidal.[71] Proteolytic cleavage of different PMPs is very common as PMPs are exposed to several proteases after secretion resulting in the formation of bactericidal, anti-viral and fugicidal peptides.[72,73] Finally, defensins are a group of AMPs subdivided into α- and ß-defensins. While platelet ß-defensin 1 impairs the growth of *S. aureus*[74], platelet α-defensin 1 has antibacterial activity against *E. coli*[75]. Interestingly, α-defensins are known to regulate human papillomaviruses infection.[76] However, if platelet α-defensins have these anti-viral properties is unknown.

While many of the AMP and chemokines directly influence viral and bacterial pathogens, platelets also contain molecules, which help activate and regulate the innate and adaptive immune systems. P-selectin, an adhesion molecule exposed on the surface of activated platelets (Figure 1C), binds to endothelial cells and leukocytes through P-selectin glycoprotein ligand-1 (PSGL-1) and assists in the recruitment of circulating monocytes, neutrophils and lymphocytes to the inflamed endothelium.[70] While, P-selectin and PSGL-1 initiate PLA formation, the interaction is further strengthened by leukocyte ß2-integrins interacting directly with GPIb and indirectly through fibrinogen binding to $\alpha_{IIb}ß_3$. PLA formation is a common feature in HIV[77], influenza[78], DENV[79], severe sepsis[80] and COVID-19[81] and promotes thromboinflammation during infection. The recruitment and activation of innate immune cells (neutrophils and monocytes/macrophages) by activated platelets leading to thromboinflammation was just recently reviewed in[70].

Platelets also play a major role in adaptive immunity, mainly through the release of CD40 ligand (CD40L) and tumor growth factor (TGF)-β, which are both located in α-granules. Both soluble and membrane-bound CD40L have immunomodulatory activities through binding to CD40 on immune cells. Activated platelets stimulate dendritic cells through soluble CD40L, resulting in increased phagocytosis and intracellular killing of bacteria.[82] Platelet CD40L also regulates B-cell isotype switching and enhanced CD8 T-cell responses in mice infected with adenoviral vectors after prior immunization (Figure 1C).[83]

Platelet-derived TGF-β regulates differentiation of $CD4^+$ T-cells into regulatory T-cells (T_{reg}), which are immunosuppressive and help maintain tolerance towards self-antigens. Platelets contribute significantly to circulating levels of TGF-β which is required for the

differentiation of T_{regs}. Interestingly, the importance of platelet TGF-β is underscored by the observation that T_{reg} numbers and function are impaired in thrombocytopenic disorders.[84,85]

Conclusion

As part of the innate immune system, platelets recognize pathogens from all major classes of microorganisms. These interactions result in platelet activation and secretion of a broad range peptides to form a first-line defense against infection. Activated platelets also release chemokines and express ligands to activate leukocytes in order to trigger both the innate and adaptive immune response.

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Abbreviations

AMP	Antimicrobial protein
CD40L	CD40 ligand
CLEC-2	C-type lectin-like receptor 2
CLR	C-type lectin receptor
CMV	Cytomegalovirus
CTAP-III	Connective tissue-activating peptide III
DAMP	Damage-associated molecular pattern
DC-SIGN	Dendritic cell-specific intercellular adhesion Molecule-3-grabbing non-integrin
DENV	Dengue virus
ECM	Experimental cerebral malaria
ECMV	Encephalomyocarditis virus
E. coli	Escherichia coli
FcγRIIa	Fcγ Receptor IIa
GP	Glycoprotein
HIV-1	Human immunodeficiency virus type-1
Ig	Immunoglobulin

LPS	Lipopolysaccharide
MHC	Major histocompatibility complex
Mt-DNA	Mitochondrial DNA
MP	Platelet-derived microparticle
NAP-2	Neutrophil-activating peptide 2
NET	Neutrophil extracellular trap
NLR	Nucleotide-binding oligomerization domain (NOD)-like receptor
NLRP3	Nucleotide-binding oligomerization domain, Leucine-rich repeat and pyrin domain-containing protein 3
NS1	Nonstructural protein 1 of Dengue virus
PAMP	Pathogen-associated molecular pattern
PF4	Platelet factor 4
PLA	Platelet-leukocyte aggregate
PMP	Platelet microbicidal protein
PNA	Platelet-neutrophil aggregate
PRR	Pattern recognition receptor
PSGL-1	P-selectin glycoprotein ligand-1
S. aureus	Staphylococcus aureus
SSL5	Staphylococcal superantigen-like protein 5
TGF-ß	Tumor growth factor-ß
TLR	Toll-like receptors
T_{reg}	Regulatory T-cells
VWF	von Willebrand factor

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Highlights

- Platelets sense invading pathogens through their receptors, which results in platelet activation
- Activated platelets release antimicrobial proteins and molecules that regulate the host response against infection
- Antimicrobial proteins directly target the pathogen to limit the spread of the infection
- Soluble and surface exposed molecules on activated platelets trigger both the innate and adaptive immune response

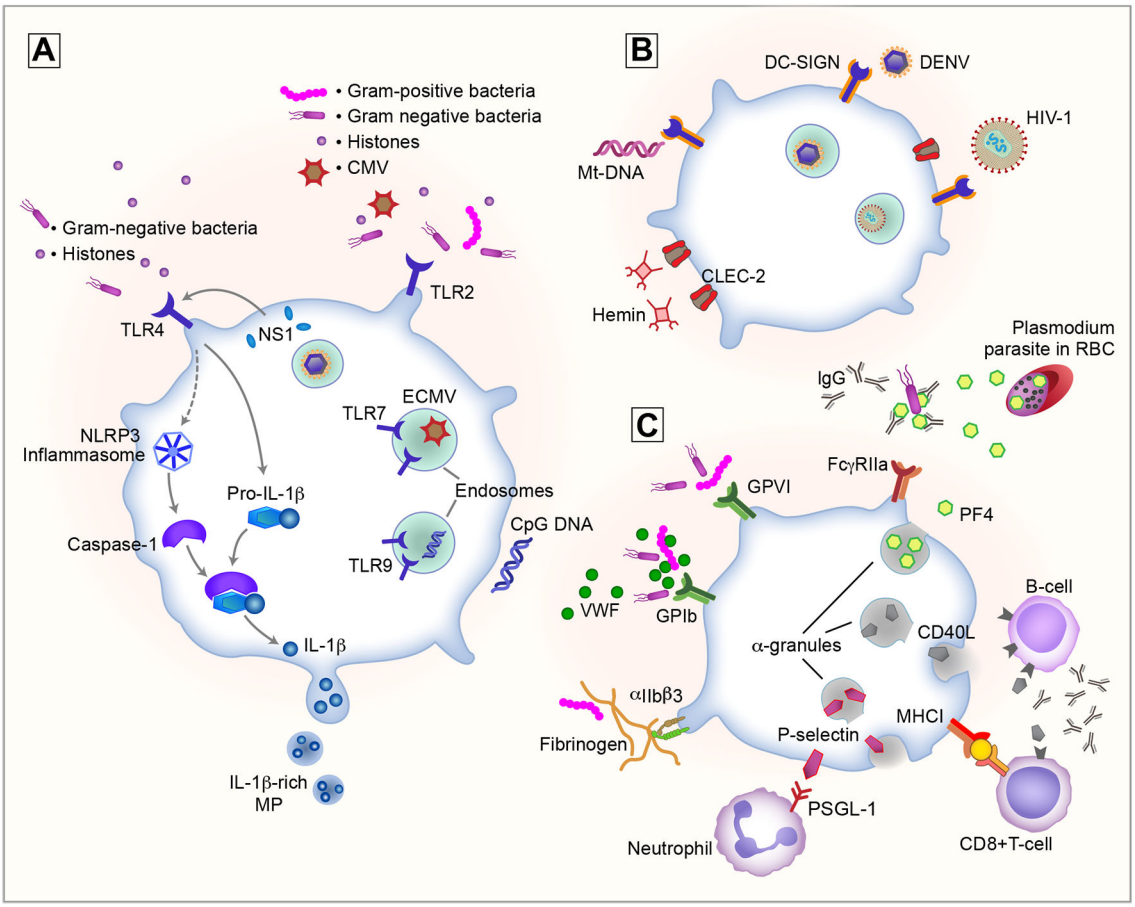

Figure 1: During infectious diseases, platelets sense pathogens via receptors and respond through secretion and expression of antimicrobial proteins, cytokines and adhesion molecules.

Platelets sense pathogens and host damage through recognition of pathogen- or damage-associated molecular patterns (PAMPs or DAMPs) using receptors. A) Toll-like receptors (TLRs) include surface receptors TLR2 and −4 with a broad tropism for bacterial pathogens as well as cytomegalovirus (CMV) and histones. Endosomal TLR7 and −9 recognize ssRNA viruses and unmethylated CpG DNA, respectively. TLR4 activation by NS1 or other TLR4 agonist induces splicing and synthesis of pro-IL-1ß, while caspase-1-mediated cleavage of pro-IL-1ß is activated by secondary signals. NLRP3 inflammasome activation results in the production IL-1ß-rich microparticles (MP). B) C-type lectin receptors DC-SIGN and CLEC-2 are involved in the binding of different viruses as well as the recognition of DAMPs such as hemin and mitochondrial DNA (Mt-DNA). C) Hemostatic platelet receptors GPIb, GPVI and $\alpha_{IIb}ß_3$ also interact with gram-positive and -negative bacteria either directly or indirectly using von Willebrand factor (VWF) or fibrinogen as bridging proteins. Engagement of the discussed receptors with their ligand results in the recognition of invading pathogens and triggers platelet activation and the release of α-granules. Released antimicrobial proteins such as platelet factor 4 (PF4) act as a first-line defense against the invading pathogens, killing *Plasmodium* parasites in infected red blood cells (RBCs) or coating gram-negative bacteria resulting in recognition of the opsonized bacterium with IgGs through FcγRIIa. Finally, surface receptors such as major histocompatibility complex

class I (MHC-I) along with α-granules releasing proteins such as P-selectin and CD40L, result in recruitment and activation of both innate and adaptive immune responses.