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Platelets in sepsis — are there any new aspects?

Małgorzata Lipińska-Gediga

Department of Anaesthesiology and Intensive Care, 4th Military Hospital of Wroclaw, Poland
Faculty of Health Science, Wrocław Medical University, Poland

Abstract

Platelets display a number of properties besides the crucial function of repairing a damaged vascular endothelium and stopping bleeding. Platelets constitutively express molecules that are classically acknowledged to function in primary haemostasis. Platelets specialize in pro-inflammatory activities, and can secrete a large number of molecules, many of which display biological response modifier functions. Recently, platelets expressing receptors for infectious and possibly non-infectious danger signals were shown to be involved in pathophysiological reactions including an immune-inflammatory response. In sepsis, platelets play a key role in immunothrombosis, participate in the formation of NETs (neutrophil extracellular trap) resulting in the trapping and killing of pathogens and are one of the main factors influencing mortality.

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Key words: sepsis, pathogens; sepsis, thrombocytes; NETs; receptors

Platelets constitutively express molecules that are acknowledged to function in primary haemostasis. Platelets are highly active in shedding their surface molecules and play a central role in driving and modulating host inflammatory and immune responses, influencing directly the function of endothelium cells, neutrophils, and lymphocytes. Platelets are the most numerous circulating cells revealing an immune function.

Platelets express:

1) ligands that bind pathogens or pathogen-derived structures,
2) receptors that enable the ingestion of pathogens to destroy them or inhibit pathogenicity,
3) secrete many molecules to communicate with other cells in the microenvironment, or at distance, to mediate reaction such as inflammation,
4) respond to signalling molecules activating mechanisms which, either locally or at a distance, fight danger or repair tissue damage [1].

PLATELET IMMUNO-INFLAMMATORY ACTIVITY — SOME FACTS

Human platelets and megakaryocytes express mRNA for the TLRs (toll-like receptors) 1, 2, 4–7, and 9, which bind diverse ligands from bacteria, viruses, parasites and protozoa [2]. Platelets having different functional programs and secreting specific cytokines are able to adapt their response to the type and extent of the danger [3]. Platelets influence innate and adaptive immune responses participating in:

1) antimicrobial activity,
2) the induction of innate effector cells function,
3) the modulation of antigen presentation,
4) the enhancement of adaptive immune response [3] (Fig. 1).

Platelets are small in size (~4 μm) and are present in large numbers (~200,000 per μL blood in humans). There are 3 types of platelet granules: α-, dense and lysosomal granules. The α-granules are the most numerous (50–60 per platelet) and largest (200–400 nm) and contain about 284 proteins. Less numerous (3–8 per platelet) and smaller (~150 nm) are dense granules which contain small molecules. Lysosomal granules containing degradative enzymes and glycohydrolases are sparse. After platelet stimulation, granules undergo exocytosis releasing their contents into the extracellular environment [4].

Platelet α-granules contain growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and metalloproteinases (MMPs) and proteins. Platelets also con-

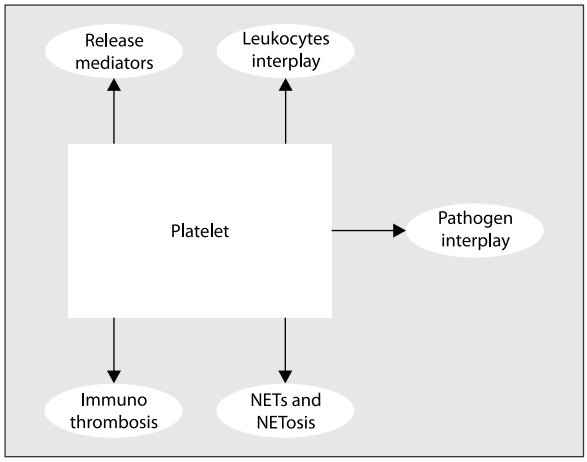

Figure 1. Global inflammatory/septic platelet activity

tain angiostatin and endostatin (both potent inhibitors of angiogenesis), thrombospondin-1 (TSP1) which is an inhibitor of endothelial cell proliferation and capillary tube formation, as well as tissue inhibitors of metalloproteinases [5]. Platelets express several immune related receptors: TLR, receptors for the Fc domain of IgG FcγRII and FcεRI, complement receptors, and cyto- and chemokine receptors [6]. Platelets express CC and CXC chemokine receptors such as CCR1, CCR3, CCR4 and CXCR4-detecting signals for all four classes of chemokines (C, CC, CXC and CX3C) generated at sites of infection and resulting in rapid accumulation of platelets to the site of infection [3]. Additionally expressed by platelets, platelet protease activated receptor PAR1, PAR4, glycoprotein (GP)IV, GPIIb-IIIa and GPIbα can play a role in a platelet's inflammatory activity. GPIbα is a member of the leucine-rich repeat family of proteins, which is exclusively expressed on platelets and megakaryocytes. Although it can bind several different ligands, its crucial role in primary haemostasis relies on its ability to interact with von Willebrand factor (VWF). GPIbα exists in a complex with GPIbβ,GPIX and GPV in a ratio of 2:2:2:1 [7].

Activated GPIIb-IIIa mediates platelet activation by its ability to bind soluble fibrinogen, which bridges other platelets. Activated platelets enhance further platelet activation via catalysation of the coagulation cascade, TXA2 and ADP release [8].

Circulating platelets have on their surface scavenger receptors including CD36 scanning the surrounding area for the presence of DAMPs (damage-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns) [9]. Many of these receptors have been called "immunoreceptors" because of their molecular structure and the ligands they recognize. Platelet Fc receptors bind immunoglobulins of the IgE, IgG, and IgA class and immune complexes, directly inducing immune signalling pathways. Glycoprotein VI (GPVI), which is only found on platelets, triggers platelet microvesicle release and subsequent inflammatory signals through interleukin IL-1 [10]. During infection platelets might be a source of IL-1β though they possess IL-1β pre-mRNA and no mature IL-1β mRNA/IL-1β protein. After activation by agonists like LPS or thrombin platelets synthesize pro-IL-1β protein. Components of inflammasome within platelets cause conversion of pro-IL-1β to the mature IL-1β cytokine being released into the systemic circulation or packaged within microparticles [2]. Surface membrane glycoproteins, such as integrin αIIbβ3 (GPIIb/IIIa), GP Ib-IX, and FcγRIIa, all have been implicated in forming an interface with bacterial cells. The exact mechanism of binding to platelets are pathogen-dependent and the engagement of platelet GPIIb-IIIa or GPIb by pathogens is the most common mechanism with using a plasma protein bridge such as fibrinogen or VWF. Bacterial adhesion via these platelet receptors and simultaneous binding of opsonising IgG to FcγRIIa triggers platelet activation, leading to fibrinogen-dependent aggregation [11, 12]. Fibrinogen is involved in platelet-leucocyte interactions, is an adhesive substrate for neutrophil and monocyte recruitment, activates macrophages (TLR4) and neutrophils (Mac-1). Platelets interact with granulocytes, vessel walls, and pathogens, enabling them to modulate the inflammatory response via both anti-inflammatory and pro-inflammatory mechanisms [11].

PLATELET ACTIVATION AND RESPONSE IN SEPSIS

Platelets play an active role in pathogen capture and sequestration through the induction of neutrophil extracellular traps (NETs), encasing pathogens within platelet aggregates, and direct internalization of pathogens. Inflammation-induced activation of the coagulation cascade results in platelet activation via PARs (protease-activated receptors). Binding to platelets agonists like thrombin, collagen, ADP, thromboxane A_2, LPS triggers platelet activation, aggregation, adhesion and secretion. The activation process results in the following:

- platelet surface ligand expression such as P-selectin, integrin $\alpha IIb\beta_3$ (GPIIb-IIIa),
- binding to other platelets and to leucocytes,
- new protein synthesis,
- inducing the expression of prothrombotic and proinflammatory genes by leucocytes,
- the release of thrombo-inflammatory factors: PF4, fibrinogen, vWF, CD40L, IL-1β,
- catecholamine uptake and release,
- interaction with endothelium and induction of endothelial signalling [2].

Endothelial cell damage leads to subendothelial collagen exposure and VWF and TF expression on endothelial cells which bind to a platelet's GPVI and GPIbα-GPIX-GPV respectively. Platelets roll on P-selectin presented on an acti-

vated endothelium through P-selectin GP ligand-1 (PSGL)-1 and GP1b and are arrested via GPIIb-IIIa and fibronectin on endothelial $\alpha_v\beta_3$ and ICAM-1. Platelets connected with the endothelium are a source of P-selectin for incoming leucocytes. Platelet P-selectin is also the primary ligand for leukocyte PSGL-1 in platelet–leukocyte interactions. PSGL-1 engagement upregulates leukocyte tissue factor, and triggers the synthesis and release of cytokines and other inflammatory molecules, in order to locally amplify both neutrophil and platelet activation [13]. After adhesion to neutrophils, platelets enhance phagocytosis and promote neutrophil degranulation. GPIba enables a second, fibrinogen-dependent mode of contact via leukocyte Mac-1 [12].

Using an animal model, Asaduzzaman *et al.* revealed that platelets play a key role in regulating the infiltration of neutrophils and edema formation in the lung via upregulation of Mac-1 in abdominal sepsis [14].

The $P2Y_{12}$ receptor mediates ADP-induced aggregation and secretion in platelets. Liverani *et al.* using a mouse model of intra-abdominal sepsis and acute lung injury, investigated the role of the P2Y12 receptor in neutrophil migration and lung inflammation in P2Y12 null mice and in mice pretreated with the P2Y12 antagonist clopidogrel. The author revealed a decrease in circulating white blood cells and a decrease in platelet activation and platelet–leukocyte interactions in treated mice compared with untreated mice. Lung injury and platelet sequestration were diminished in clopidogrel-treated mice compared with untreated mice. Similar results were observed in $P2Y_{12}$ null mice: platelet activation and platelet–leukocyte aggregates were decreased in septic $P2Y_{12}$ null mice compared with wild-type mice. $P2Y_{12}$ null mice were refractory to lung injury compared with wild-type mice. The authors concluded that $P2Y_{12}$ null mice are refractory to sepsis-induced lung injury, suggesting a key role for activated platelets and the $P2Y_{12}$ receptor during sepsis [15].

Complement C1q activates platelets via C1qR (a complement receptor). Complement factors are involved in bacterial binding to platelets. Bacteria coated with C1q factor are recognized by the gC1q receptor (gC1qR) overexpressed after platelet activation on the platelet membrane [16]. Activation via FcγRIIa is dependent on IgG and GPIIb-IIIa. PF4 binds to bacteria and reduces the lag time for aggregation. Other platelet receptors that mediate platelet-bacterial interactions are GPIbα, PAR1, and TLRs [8]. It has been suggested that platelets, through the expression of TLR4, act as a barometer for systemic infection [17] and function as sensors of pathogens. During sepsis, circulating pathogens, released PAMPs and DAMPs (such as histones) are involved in platelet activation through TLR signalling. When platelet TLRs detect microbial species, platelet activation is started, causing cells degranulation and release of proinflammatory mediators. Protein products released by platelets coordinate the intercellular signalling for the immune-inflammatory response. The release of chemotactic agents by platelets recruits the following inflammatory inflammatory cells: platelet-derived growth factor (PDGF) and 12-hydroxyeicosatetraenoic acid (12-HETE) recruit neutrophils; platelet factor 4 (PF4- CXCL4) and platelet-derived histamine releasing factor (PDHRF) recruit eosinophils in airway disease; PDGF and transforming growth factor β (TGF-β) recruit monocytes and macrophages and TGF-β recruits fibroblasts [18]. In addition, alpha granules release many antimicrobial peptides such as beta-lysin, platelet microbicidal protein (PMP), neutrophil activating peptide (NAP-2), Released upon Activation Normal T-cell Expressed and Secreted (RANTES) and fibrinopeptides A and B. Activated platelets can promote the activation of monocytes and dendritic cells particularly through CD40-CD40L interactions. This results in increased antigen presentation to T cells and enhances adaptive immune responses [12]. Platelets reveal direct microbicidal activity and secrete microbicidal peptides/proteins-thrombocidin-1 and 2, platelet microbicidal protein-1 (PMP-1), β-defensin 1. Platelets cause indirect microbe destruction by transporting surface-bound immune complexes, complement fractions or Igs with antibody activity. They enlarge antimicrobial activity of neutrophils macrophages [19].

The precise mechanism(s) of pathogen disintegration within platelets is not a classical phagocytosis as platelets do not contain a complete phagosome ultrastructure. Platelets have extracellular FcγRIIa, with an intracellular immunoreceptor tyrosine-based activation motif (ITAM) that is important for immune complex clearance [1]. FcγRIIa also plays a critical role in the pathogenesis of heparin-induced thrombocytopenia (HIT) where platelets are bound by antigenic complexes of heparin and PF4. After the antibody-bound

complex is bound to the platelet surface, the Fc portion induces FcγRIIa-dependent platelet activation and aggregation, thrombocytopenia and the onset of thrombosis. Recent studies have demonstrated that bacterial DNA may substitute for heparin to form similar antigenic complexes with similar degrees of platelet aggregation and thrombosis [19].

Rondina *et al.* [20] proved that bacterial and host factors induce splicing of TF pre-mRNA, expression of TF mRNA and tissue factor-dependent clotting activity in human platelets. According to the authors, platelets from septic patients express mature, spliced TF mRNA revealing that sepsis may alter the platelet transcriptome. Many of these changed transcripts increase host defences to pathogens [20]. In sepsis, alterations in platelet number and function are correlated with a high risk of morbidity and mortality. Sepsis is a syndrome of systemic infection-related endothelial activation and dysfunction that leads to systemic microvascular leak and multiple-organ failure. Ang-1 (angiopoietin-1) stabilizes the endothelium and prevents microvascular leak,

while platelets are one of its major sources. In septic shock the decline of serum levels of Ang-1 has been described and it is possible that this is one of the mechanisms in which thrombocytopenia contributes to adverse outcomes [21].

Septic patients with thrombocytopenia had whole-blood leukocyte transcriptome patterns that revealed the under-expression of genes encoding proteins involved in leukocyte adhesion, diapedesis, and extravasation signalling. These findings demonstrate the significance of thrombocytopenia as a risk factor for both dysregulated host response and adverse clinical outcomes [22, 23]. In a study by Venkata *et al.*, a group of 304 patients was included. The majority (93.7%) had septic shock while pneumonia was the most common infection (38.8%). Thrombocytopenia developed in 145 patients (47.6%): 77 (25.3%) at ICU admission and 68 (22.3%) during their ICU stay. The median (IQR) duration of thrombocytopenia was 4.4 (1.9–6.9) days. Patients with thrombocytopenia had a higher incidence of acute kidney injury (44.1% vs. 29.5%, $P < 0.01$), prolonged vasopressor support (median (IQR): 37 (17–76) vs. 23 (13–46) h, $P < 0.01$), and a longer ICU stay (median (IQR): 3.1 (1.6–7.8) vs. 2.1 (1.2–4.4) days, $P < 0.01$). The 28-day mortality was similar between patients with and without thrombocytopenia (32.4% vs. 24.5%, $P = 0.12$). In addition, 15 of 86 patients (17.4%) who resolved their thrombocytopenia died, while 32 of 59 patients (54.2%) whose thrombocytopenia did not resolve died ($P < 0.01$). Patients with thrombocytopenia had more episodes of major bleeding, increased incidence of acute kidney injury, and prolonged ICU stay. The authors concluded that the non-resolution of thrombocytopenia, but not thrombocytopenia itself, was associated with increased 28-day mortality [24].

PLATELET MICROPARTICLES

Microparticles (MPs) are small plasma membrane vesicles (50–1000 nm) shed from different cells upon activation or apoptosis. A main part of this fact is the detachment of the actin cytoskeleton from the plasma membrane which occurs primarily through the increase in intracellular calcium concentration [25]. The calcium then interacts directly with the proteins involved in proteolysis of the cytoskeleton, such as calpain. Platelet-derived microparticles (PMPs) create the majority of the pool of MPs circulating in the blood . PMPs contain a subset of proteins derived from the parent cell and reveal important biological functions. One of these functions is their participation in blood coagulation by providing a source of tissue factor (TF) and negatively-charged surfaces where clotting factor complexes can assemble [5]. PMPs promote the expression of adhesion molecules on a variety of cells, stimulate the release of cytokines, alter vascular reactivity, induce inflammation and angiogenesis [5]. PMPs can express and transfer functional receptors from platelet membranes, such as glycoprotein IIb-IIIa (GPIIb-IIIa) and P-selectin, to different cell types [5].

PLATELETS AND NETS

Platelets are part of the innate immune system through activation of and close interaction with leucocytes, secretion of chemokines and cytokines that attract immune cells. As bacteria can bind to platelets via receptors involved in haemostasis, they may induce aggregation, which has been described for *Streptococcus sanguinis*, *S. epidermidis*, or *S. pneumoniae* infections [16]. The platelets are activated by an LPS concentration 100 times greater than that inducing neutrophil activation. Platelets may therefore be helpers of the neutrophils by enabling them to form NETs when the bacterial load is too high and their normal functions are insufficient for correctly eliminating bacteria [26]. Platelet involvement in DNA extracellular trap formation was first described in 2007, when Clark *et al.* [27] showed in a mouse model of sepsis that lipopolysaccharide (LPS) binds to TLR4 present in the platelet membrane, allowing the binding of platelets to neutrophils and leading to rapid neutrophil activation. Although CD14 is a coreceptor for LPS signalling through TLR4, CD14 itself is not expressed by platelets, causing platelets needing other sources of soluble CD14 in order to be able to respond to LPS. Platelet TLR4 signalling leads to their activation with shedding of IL-1β-rich microparticles. This process promotes platelet adhesion with the endothelium, other platelets and leucocytes, leading to the formation and release of inflammatory and thrombotic agents, further leucocyte recruitment, oedema formation [28]. It has been shown that, LPS leads to enhanced formation of neutrophil–platelet complexes, resulting in the formation of neutrophil extracellular traps (NETs), a key mechanism used by innate immune cells in immunothrombosis [4, 7] (Fig. 2). NETs occur as a result of a special cell death program named NETosis involving the release of DNA webs with all five types of histones and with neutrophil-derived granular proteins revealing antimicrobial activity, such as elastase, myeloperoxidase (MPO), and the bactericidal/permeability-increasing protein [17]. NETs are able to entrap and kill microbes [28], and reveal proinflammatory and prothrombotic properties [29]. The negatively-charged nucleobases of the NETs are capable of initiating the contact pathway of coagulation. The contact -dependent pathway increases circulating thrombin concentration, which, in turn, increase platelet activation. NETs activate factor XII, inactivate TFPI [30] while serving as a platform for the docking and activation of platelets. Direct engagement of microbes by platelets also contributes to platelet stimulation and thrombosis [31].

Platelet TLR4 appears to be a major target involved in platelet-mediated NETosis. Cooperation between neutrophil

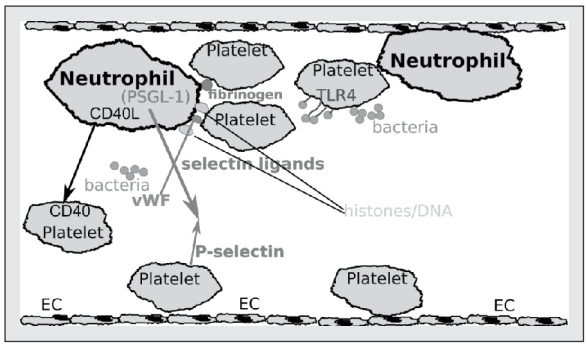

Figure 2. NETs and platelet-neutrophil cooperation in bacteria "trapping". Capillary lumen: Activated platelets can induce NET formation, form neutrophil-platelet and platelet-platelet aggregates. Platelet toll-like receptor (TLR) expression enables activated platelets to bind bacteria. TLR4-toll-like receptor4; PSGL-1 P-selectin glycoprotein ligand-1; VWF-von Willebrand factor; EC-endothelial cell

β2 integrin (CD18) and platelet glycoprotein (GP)Ib has been considered as another major event involved in platelet–neutrophil adhesion and its specific inhibition by gene deletion, while using blocking antibodies in human platelets [32] also affected the formation of NETs, demonstrating its participation in this process. The ability of platelets to promote NET formation has been observed in human cells, not only with Gram-negative bacterial components but also with Gram-positive bacteria [31] and it has been shown that platelets are also required for NETosis-mediated virus clearance [17]. During sepsis, an increase in circulating platelet-neutrophil complexes is observed. These complexes initially rise in the beginning of sepsis and decrease when MODS (multiple organ dysfunction syndrome) occurs indicating peripheral sequestration [8].

CONCLUSIONS

As platelets have been attributed many functions, they may be recognized as cells though their lack of a nucleus. Recent findings indicate that they are active not only in haemostasis, but are part of the innate immune defence system. Participating in the recognition of pathogens, signal transduction, or the release of cytokines/chemokines, they reveal a functional similarity with leucocytes in sepsis and septic shock. Although preclinical evidence indicating that platelets can influence key host responses to sepsis is abundant, clinical studies addressing this pathophysiological link are limited. The question whether platelets may become a therapeutic target in septic conditions is still open for discussion and further study.

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Corresponding author:
Małgorzata Lipińska-Gediga, MD
4th Military Hospital of Wroclaw
Department of Anaesthesiology and Intensive Care
Weigla 5, 50–981 Wrocław, Poland
e-mail: starling@poczta.onet.pl

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