Nouvelle Cuisine: Platelets Served with Inflammation

Rick Kapur, Anne Zufferey, Eric Boilard and John W. Semple

*J Immunol* 2015; 194:5579-5587; doi: 10.4049/jimmunol.1500259
http://www.jimmunol.org/content/194/12/5579

References

This article cites 139 articles, 67 of which you can access for free at:
http://www.jimmunol.org/content/194/12/5579.full#ref-list-1

Why The JI? Submit online.

• Rapid Reviews! 30 days* from submission to initial decision
• No Triage! Every submission reviewed by practicing scientists
• Fast Publication! 4 weeks from acceptance to publication

Subscription

Information about subscribing to *The Journal of Immunology* is online at:
http://jimmunol.org/subscription

Permissions

Submit copyright permission requests at:
http://www.aai.org/About/Publications/JI/copyright.html

Email Alerts

Receive free email-alerts when new articles cite this article. Sign up at:
http://jimmunol.org/alerts
Nouvelle Cuisine: Platelets Served with Inflammation

Rick Kapur,*† Anne Zufferey,* Eric Boilard,‡ and John W. Semple*,†,§,‖

Platelets are small cellular fragments with the primary physiological role of maintaining hemostasis. In addition to this well-described classical function, it is becoming increasingly clear that platelets have an intimate connection with infection and inflammation. This stems from several platelet characteristics, including their ability to bind infectious agents and secrete many immunomodulatory cytokines and chemokines, as well as their expression of receptors for various immune effector and regulatory functions, such as TLRs, which allow them to sense pathogen-associated molecular patterns. Furthermore, platelets contain RNA that can be nascently translated under different environmental stresses, and they are able to release membrane microparticles that can transport inflammatory cargo to inflammatory cells. Interestingly, acute infections can also result in platelet breakdown and thrombocytopenia. This report highlights these relatively new aspects of platelets and, thus, their nonhemostatic nature in an inflammatory setting. The Journal of Immunology, 2015, 194: 5579–5587.

Platelets are traditionally described as cellular fragments derived from megakaryocytes in the bone marrow that circulate and continually assess the vessel endothelium for damage (1). A single megakaryocyte can give rise to ∼1000 platelets that are released into the circulation by a process called proplatelet formation (1). Platelet generation is a highly regulated and organized process, and platelets are key cellular players from a functional perspective. Circulating human platelets are anucleate and have a diameter ∼3–4 μm and a lifespan of 8–10 d before they are primarily destroyed by macrophages within the spleen. There, circulating numbers range from 150 to 400 × 10^9/l in humans, whereas rodents have approximately three times as many circulating platelets. Although anucleate, platelets have several specialized organelles within their cytoplasm, including α granules, dense granules, endosomes, lysosomes, and mitochondria. The α and dense granules contain different cargos that are responsible for the platelet’s ability to aggregate and activate the coagulation cascade at the site of vessel injury. Platelets also have a series of invaginated folded membranes that form the inner canalicular system, and this allows the platelet to significantly increase surface area upon activation. What has become clear over the last 50 years is that, in addition to their primary role in hemostasis, platelets are multifunctional and are key players in many other physiological and pathological processes (e.g., wound repair, inflammatory processes, and the immune response) (2–8).

Interestingly, in many invertebrate life forms, a single cell type is responsible for multiple innate defense functions, including hemostasis (9, 10). Further specialization into various blood cell types occurred by the vertebrate stage, and this eventually evolved into mammalian anucleate platelets, with both hemostatic and inflammatory properties (9, 10). The relationship between platelets and inflammation has been suspected for decades because of observations made from the atherosclerosis literature (11). Atherosclerosis is a chronic inflammatory process and platelet interactions with, for example, leukocytes and endothelium represent an important association between inflammation and atherogenesis. This includes platelet activation, adhesion of platelets to endothelium, and the platelet’s ability to secrete inflammatory molecules that can alter the chemotactic, adhesive, and proteolytic properties of endothelial cells. This can ultimately support the migration and adhesion of monocytes to the site and facilitate the formation of atherosclerotic plaque. This review briefly outlines some of the nonhemostatic roles that platelets can play, particularly with respect to inflammation and immunity. Although it is beyond the scope of this article to comprehensively discuss all of the literature, several excellent and comprehensive reviews are cited to direct the reader to more details on the respective subjects.

Platelets and pathogens

It is well known that platelets can harbor pathogens, including viruses (12, 13), bacteria (14–16), and parasites (4), on their...
plasma membrane and internally (3, 13). Platelets are also known to be involved in acute and chronic liver disease related to hepatitis B virus infection via upregulation of virus-specific CD8+ T cells and nonspecific inflammatory cells into the liver (17). Furthermore, platelets were implicated in the clearance of bacterial infections: thrombin-stimulated platelets facilitated clearance of streptococci in infective endocarditis (18). In addition, activated platelets were shown to surround *Staphylococcus aureus*, thereby inhibiting their bacterial growth rate via secretion of the antimicrobial peptide β-defensin and the induction of neutrophil extracellular trap (NET) formation (13, 19), a process that also was described to occur in other settings, including thrombosis, transfusion-related acute lung injury, storage of RBCs, and sickle cell disease (20–25). Interestingly, platelets also were shown to be involved in the trapping of bacteria (methicillin-resistant *S. aureus* and *Bacillus cereus*) on the surface of Kupffer cells in the liver (5). In this study, GPIbα-deficient mice were more prone to endothelial and Kupffer cell damage, with increased vascular leakage and rapid mortality, than were wild-type mice. McMorrane et al. (4) elegantly showed that activated platelets can limit the growth of the malarial parasite *Plasmodium falciparum* by entering the infected RBC via a platelet factor (PF)-4– and Duffy Ag-dependent manner. How the platelets actually kill the internalized parasite is still unknown. Therefore, it is possible that patients with platelet disorders, in which the aforementioned pathogen-reducing mechanisms would be compromised, are more susceptible to infections.

Alternatively, the binding of infectious agents to platelets could contribute to spread of the infection. During sepsis, activation of platelets can contribute to the development of disseminated intravascular coagulation, which can subsequently occlude blood vessels, leading to increased ischemia and multiple organ failure. Additionally, septic platelet activation can facilitate the production of both pro- and anti-inflammatory cytokine networks (26). The nature of this platelet activation is characterized by increased surface P-selectin expression (27, 28); increased levels of α granule-released factors in plasma, such as soluble P-selectin (29); and increased levels of triggering receptor expressed on myeloid cells-like transcript-1 (30) or PF-4 in mice (31). Clark et al. (6) also showed a novel mechanism of platelet–neutrophil interaction that leads to enhanced bacterial trapping during sepsis. Platelet binding stimulated neutrophils to release NETs, and the extended DNA contributed significantly to trapping bacteria. Elegant in vivo imaging demonstrated that the liver sinusoids and lung capillaries where platelets and neutrophils bound during sepsis were the primary sites of NET formation (6). Platelet-induced NET formation, although beneficial in trapping bacteria, may also be of detriment because it may occur at the expense of injury to the host. It appears that when LPS-activated neutrophils bind endothelium, little damage occurs; however, if the bound neutrophils encounter LPS-bearing platelets, they become significantly activated and release their NETs together with reactive oxygen species that cause damage to the underlying endothelium (6). Moreover, Sreeramkumar et al. (7) showed that neutrophils were able to scan platelets for activation in the bloodstream through the P-selectin ligand signaling pathway, leading to inflammation. Currently, there is a wealth of evidence to suggest that platelets can act as pathogen sensors within the blood as a result of their expression of several receptors that have no obvious function in hemostasis.

**Platelet TLRs**

Platelets express functional immune receptors called pattern recognition receptors, which include complement receptors and TLRs (2). These platelet-associated structures allow them to bind foreign microbial invaders and products derived from microbes. Thus, infectious binding allows platelets to participate in “danger sensing” (pathogen, or damage in the case of sterile inflammation) that is typically described for cells of the innate immune system. Pathogens are thought to be first encountered by TLRs on professional phagocytes, such as neutrophils, macrophages, and dendritic cells (DCs) (2, 32, 33). TLRs are germline-encoded proteins that bind a variety of infectious molecular structures and are critical for stimulating innate immune mechanisms (2, 32, 33). The ligands of TLRs have been studied extensively, and they range from secretory components of pathogens to nucleic acids. Many articles reported that TLRs 1–9 are expressed on both human and murine platelets, and some of these are functional, such as TLR4 in the mediation of LPS-induced thrombocytopenia and TNF-α production in vivo (34–40). Likewise, the previously mentioned platelet–neutrophil interaction leading to NET formation and subsequent trapping of bacteria during sepsis is triggered via platelet TLR4 (6). It was suggested that platelets might be primarily responsible for reactivity against bacterial products, and it was speculated that platelets act as circulating sentinels that bind infectious agents and present them to neutrophils and/or cells of the reticuloendothelial system (36–40).

Relatively few studies have examined the expression and function of TLRs on megakaryocytes; however, it was demonstrated that endotoxemia can increase in vivo thrombopoietin (TPO) levels, which was associated with an increase in circulating young reticulated platelets and enhanced platelet–neutrophil aggregates (41). Furthermore, bone marrow treated with LPS showed increased levels of TPO, suggesting that inflammation and infection may have roles to play in platelet production (42). Related to this, compared with control mice, TLR4-knockout mice have decreases in circulating platelet counts and reticulated platelets, suggesting that TLR4 may have a role in thrombopoiesis (34, 43).

**Platelet CD40L (CD154)**

In addition to their critical role in costimulation, CD40L (CD40L/CD154) and CD40 were proposed to play a central role in thrombotic diseases (44). Platelets contain a significant amount of CD40L that is expressed and released upon platelet activation. Once expressed, platelet CD40L can interact with membrane-bound CD40 on endothelial cells, triggering several inflammatory reactions leading to local release of adhesion molecules including, for example, ICAM1, VCAM1, and CCL2 (45). Upon activation, platelets release most of their expressed CD40L, producing its soluble form (sCD40L); the vast majority of sCD40L circulating in the plasma is derived from activated platelets (46). Upon exposure to CD40-expressing vascular cells (including endothelial cells), platelet-derived sCD40L can induce the expression of adhesion molecules, such as E-selectin and P-selectin, and initiate the release of tissue factor and IL-6 (47, 48). Thus, it
is becoming increasingly clear that the platelet CD40L–CD40 axis may play a central link between the endothelium/coagulation and inflammation.

Platelet-derived CD40L also was shown to enhance CD8+ T cell responses and to promote T cell responses postinfection with *Listeria monocytogenes* (49, 50), thereby bridging the gap between innate and adaptive immunity. Such studies extend platelet function to modulation of innate and adaptive immunity through, for example, release of chemokines, cytokines, and immunomodulatory ligands, including CD40L, and showed that platelets, via CD40L, can induce DC maturation (51). With respect to the latter, it appears that platelets can bind DCs in a CD40L-dependent manner and significantly affect their differentiation and activation. For example, Kissel et al. (51) showed that activated platelets could impair DC differentiation, suppress proinflammatory cytokines IL-12p70 and TNF by DCs, and increase the production of IL-10 by DCs. These types of platelet–DC interactions could potentially affect adaptive immune responses. In addition, activated platelets can augment lymphocyte adhesion to the endothelium (52) and facilitate lymphocyte homing in high endothelial venules (53) and migration into inflammatory regions. Furthermore, platelets can facilitate B cell differentiation and Ab class switching because of their large content of CD40L (54, 55). A nongenomic role for NF-κB was shown to be important as well, because the CD40L–CD40 axis was demonstrated to trigger NF-κB activation in platelets (56). Also, there have been several reports supporting both positive and negative pathways of platelet activation involving NF-κB signaling cascades (57–61), as well as platelet pathways involving other nuclear receptors, such as peroxisome proliferator-activated receptors (PPARs) (62–64) and retinoid X receptors (65). Thus, there are several possible avenues by which platelets can modulate adaptive immune mechanisms through interactions with their CD40L and/or sCD40L derived from platelets.

**Platelet MHC class I**

Platelets also harbor MHC class I molecules both on their plasma membrane and intracellularly (66). On the platelet plasma membrane, MHC class I molecules are primarily adsorbed from plasma and generally consist of denatured H chains. The membrane-bound MHC also appears unstable because the molecules can passively dissociate from the platelet upon blood bank storage or can be eluted from the surface by chloroquine diphosphate or acid washing, without affecting platelet membrane integrity (67–73). At the allogeneic level, through transfusions, the denatured platelet MHC class I can evoke faulty interactions with CD8+ T cells, which appear to anergize CTLs. For example, allogeneic platelet MHC class I molecules cannot stimulate CTL-mediated cytotoxicity on their own (73) but can mediate the so-called “transfusion effect,” an immunosuppressive-like response to transfused blood products. CBA mice transfused with allogeneic BALB/c platelets readily accepted donor-specific skin grafts compared with nontransfused recipients (74). This observation supports the concept that allogeneic platelets may interfere with T cell–mediated cytotoxicity reactions, such as skin graft rejection. In contrast, more recent data suggest that, intracellularly, platelet MHC class I molecules are associated with α granules and are mostly intact integral membrane proteins associated with β2-microglobulin (75). Moreover, molecular analysis of platelet proteins revealed that platelets contain the entire proteasome system, together with TAP molecules; however, they lack endoplasmic reticulum. It now appears that, in syngeneic systems, activated platelets can express nascent MHC class I molecules, and these have the ability to present Ags to CD8+ T cells. Chapman et al. (76) elegantly demonstrated that activated platelets can present malarial peptides to malaria-specific T cells, and this leads to an enhanced immunity against the parasite. Thus, depending on the source of MHC (surface bound or internalized), platelets can mediate either T cell suppression or activation.

**Platelet cytokines/chemokines**

Platelets carry a plethora of chemokine and cytokine cargo that can play roles in diverse processes associated with hemostatic functions and wound repair (77), as well as with proinflammatory and anti-inflammatory processes, such as TGF-β, a potent immunosuppressive factor (78). Although the physiological role of large amounts of TGF-β in platelets (78) is unclear, platelets appear to regulate blood levels of TGF-β. For example, in patients with immune thrombocytopenia (ITP), low levels of TGF-β were observed in active disease but these levels normalized concomitantly with increasing platelet counts upon treatment (79, 80). Most of the chemokines and cytokines are found within the various platelet granules. For example, the α granules contain several immunomodulatory soluble factors, such as chemokines, including PF (CXCL4), β-thromboglobulin (β-TG; an isoform of CXCL7), RANTES (CCL5), and MIP-1α (CCL3) (81). When released upon platelet activation, these chemokines can mediate a diverse array of cellular interactions. For example, platelet PF-4 can render monocytes resistant to apoptosis and induce their differentiation into macrophages (82). In addition, PF-4 can enhance neutrophil adhesion to unstimulated endothelium and granule content release (83). In contrast, platelet-derived β-TGs, which are proteolytic products of inactive precursors, can have either stimulatory or inhibitory activity for neutrophils (84). Finally, platelet-derived MIP-1α can stimulate the release of histamine from basophils (85) and is chemo tactic for T cells (86).

**Platelet transcriptomics**

Platelets express an enormous number of different molecules, many of which can be secreted during platelet activation via various regulated pathways (81, 87–89). These molecules in platelets may come from different sources, such as those inherited from megakaryocytes, those absorbed from the plasma, or those generated de novo. With regard to de novo synthesis of molecules in platelets, although platelets are anucleate, they express significant amounts of RNA, including mRNAs (e.g., premature and mature RNA), structural and catalytic RNAs (e.g., ribosomal and tRNA), regulatory RNAs (e.g., microRNA), and noncoding RNA (e.g., anti-sense RNA) (90–105). More recently, it also was revealed that platelets contain all of the molecular machinery to translate mRNA into proteins, and they have the ability to transfer RNA to recipient cells where it can regulate cellular function (101–104). However, it should be noted that the content of platelet RNA transcript does not fully correspond to the
content of the platelet proteome (106). These molecular attributes of platelets have opened up an entirely new field of platelet genetics, and Schubert et al. (107) provided an excellent recent review on platelet mRNA and its impact on platelet function during health and disease.

**Platelet microparticles**

Pioneer investigations revealed “dust” liberated by platelets upon activation that is capable of supporting thrombin generation, even in the absence of intact platelets (108). Platelet dust, now known as microparticles (also called microvesicles), are small extracellular vesicles produced by cell cytoplasmic blebbing and fission. Microparticles are \( \sim 100–1000 \) nm in diameter, although the majority seem to be \( \sim 200 \) nm in size and are distinct from exosomes, which have smaller dimensions (\( \sim 50–100 \) nm in diameter) and originate from multivesicular bodies through exocytosis (109). The minimal experimental requirements for defining extracellular vesicles and their functions were published by the International Society for Extracellular Vesicles (110).

Although the shedding of microparticles is not unique to platelets, they are particularly potent in this process. Hence, recent examination of human plasma using cryotransmission electron microscopy and gold nanospheres conjugated to Abs directed against the platelet marker CD41 confirmed that microparticles of platelet origin are the most abundant in circulation (111). The formation of microparticles appears to be associated with increased intracellular calcium levels, cytoskeletal rearrangement, and loss of membrane asymmetry resulting in phosphatidylserine (PS) exposure on their surface (112). The exposed PS, given its anionic properties, supports blood coagulation, although microparticles derived from platelets express modest levels of tissue factor (TF) and appear less procoagulant that do monocyte-derived microparticles, which express both PS and TF (113). In a recent study, Tersteeg et al. (114) elegantly examined platelet activation

**Table I. Nonhemostatic roles of platelets in infection and inflammation**

<table>
<thead>
<tr>
<th>Pathogen Reduction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Haboring of pathogens (viruses, bacteria, and parasites) (3, 4, 12–16)</td>
<td></td>
</tr>
<tr>
<td>Clearance of bacterial infections (18)</td>
<td></td>
</tr>
<tr>
<td>Inhibiting growth of S. aureus via ( \beta )-defensin and NET induction (19)</td>
<td></td>
</tr>
<tr>
<td>Bacterial trapping on surface Kupffer cells (5) and via hepatic and pulmonary NETs during sepsis (20)</td>
<td></td>
</tr>
<tr>
<td>Growth inhibition of malarial parasites via erythrocyte invasion (4)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platelet TLRs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen detection (2)</td>
<td></td>
</tr>
<tr>
<td>TLR4: LPS-induced thrombocytopenia and TNF-( \alpha ) production (36), bacterial trapping via NETs in sepsis (6), possible role in thrombopoiesis (34, 43)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platelet MHC Class I</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracellular MHC class I association with platelet ( \alpha ) granules (75)</td>
<td></td>
</tr>
<tr>
<td>Presence of proteasome system with TAP molecules in platelets (75)</td>
<td></td>
</tr>
<tr>
<td>Platelet presentation of malarial peptides to malaria T cells: enhanced immunity toward parasite (76)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platelet Cytokine/Chemokines</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Many chemokines and cytokines involved in pro/anti-inflammatory pathways, including the immunosuppressant TGF-( \beta ), as well as chemokines PF-4, ( \beta )-TG, RANTES, MIP-1( \alpha ) (81). For overview, see Ref. 2.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platelet Transcriptomics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>De novo synthesis of platelet molecules: significant amount of RNA (90–104), contain molecular machinery for mRNA translation and ability to transfer RNA to other cells to regulate cellular function (101–104)</td>
<td></td>
</tr>
<tr>
<td>Impact on health and disease (reviewed in Ref. 107)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PMPs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet activation via GPVI in autoimmune inflammatory arthritis forms PMPs (8)</td>
<td></td>
</tr>
<tr>
<td>LPS stimulation of platelet TLR4 forms PMPs in sepsis (125)</td>
<td></td>
</tr>
<tr>
<td>Increased IL-1 in PMPs indicates role in inflammation (8, 125)</td>
<td></td>
</tr>
<tr>
<td>Immune complexed bacterial components and epitopes of influenza viruses form PMPs via FcYRIa (126, 127)</td>
<td></td>
</tr>
<tr>
<td>PMP's implicated in cell–cell communications via integrin, lactaderhin, and Del-1 (131, 132)</td>
<td></td>
</tr>
<tr>
<td>PMP cargo consists of cytokines, chemokines, lipid mediators, enzymes, receptors, nucleic acids, autoantigens, transcription factors, mitochondria (103, 117–119, 128–130)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platelet Breakdown</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-reactive autoantibodies due to molecular mimicry between viral/bacterial Ags and platelet Ags (135–139)</td>
<td></td>
</tr>
<tr>
<td>H. pylori ITP increased platelet count after eradication of H. pylori (140)</td>
<td></td>
</tr>
<tr>
<td>LPS enhancement of Ab-mediated platelet clearance in vitro and in vivo (37, 141)</td>
<td></td>
</tr>
<tr>
<td>CRP enhancement of Ab-mediated platelet clearance in vitro and in vivo (142)</td>
<td></td>
</tr>
</tbody>
</table>
under physiological flow and observed extremely long (up to 250 μm) membrane strands emerging from platelets, which is substantial considering their small size. These strands, called flow-induced protrusions, also expose PS, recruit neutrophils and monocytes (and not platelets), and appear to break off into PS⁺ microparticles (114). Intriguingly, studies also shed light on PS⁻ microparticles in body fluids (111, 115–117), pointing to the heterogeneity of the microparticles produced by platelets.

The small dimensions of microparticles represent a challenge for the proper assessment of their expression in biological fluids. Primarily using flow cytometry methodologies, platelet-derived microparticles have been observed in different inflammatory conditions in which platelets are activated (118,

![Diagram](image_url)

**FIGURE 1.** The key roles of platelets in modulating inflammatory processes. (1) Platelets can uptake infectious agents, and via the expression of TLRs they can activate neutrophils to, for example, secrete NETs. (2) Platelet CD40L expression allows them to interact with different cells of the immune system and either activate (arrows) and/or suppress (T bar) them. (3) Intact platelet MHC class I molecules are located intracellularly but upon activation are expressed and can activate Ag (e.g., malaria)-specific CD8⁺ T cells. In contrast, the MHC class I molecules on the surface of resting platelets are denatured and lead to CD8⁺ T cell inhibition. (4) Platelets release PMPs under a variety of stress conditions, and these PMPs can carry multiple cargos to other cells and sites of inflammation. (5) Platelets contain many proinflammatory and anti-inflammatory cytokines and chemokines and, upon activation, can release them to the extracellular space. (6) Immune interactions with platelets can lead to severe thrombocytopenic states, such as in the case of sepsis, where infections can bind to platelets and cause their sequestration and/or destruction or ITP, where the combination of Ab and infectious particles or CRP leads to increased platelet destruction. (7) Platelets contain several species of RNA, and these can be exported via PMPs or miRNAs can be translated into nascent protein synthesis. The culmination of these events makes platelets a formidable immunomodulatory host.
In the context of infectious processes, platelets play a complex role in the immune system. They can act as primary mediators of hemostasis, tissue repair, and immune modulation. Platelets are best known as primary mediators of hemostasis and tissue repair, but they also participate in cell–cell communication and immune response. In RA, the activation of platelets through the collagen receptor glycoprotein VI (GPVI) induces the formation of microparticles, whereas in sepsis, microparticles can be produced via the stimulation of platelet TLR-4 by bacterial LPS (8, 125). Interestingly, the microparticles shed through both signals (GPVI and TLR-4) are rich in IL-1, pointing to their role in amplification of inflammation (8, 125). Platelets also participate in adaptive immunity through stimulation of FcRIIA. Indeed, in immunized subjects, bacterial components and well-conserved epitopes expressed by influenza viruses are capable of forming immune complexes that activate FcRIIA (126, 127), leading to the formation of microparticles.

Functionally, platelet microparticles (PMPs) are thought to participate in cell–cell communication. The PMP cargo is vast and includes cytokines and chemokines (e.g., IL-1, RANTES), potent lipid mediators (e.g., thromboxane A2), functional enzymes (e.g., inducible NO synthase), surface receptors (e.g., CD40L), nucleic acids (e.g., microRNA), autoantigens (e.g., citrullinated fibrinogen), transcription factors (e.g., PPARg, RuvB-like2, STAT3, STAT5a), and even respiratory-competent mitochondria, all of them potentially having an impact on the cell targeted by microparticles (103, 117–119, 128–130). Because they express surface receptors and PS (although some are PS–), microparticles interact with other cells through integrin and via the PS-binding proteins lactadherin (131) and developmental endothelial locus-1 (Del-1) (132). Hence, lactadherin+/− and Del-1−/− mice express higher levels of plasma microparticles compared with their wild-type counterparts, suggesting that these proteins are involved in microparticle clearance and in microparticle interaction with other cells (131, 132). Transcription factors packaged inside PMPs can enable transcellular effects, such as PPARg, which was shown to be transported into PMPs and transferred to monocytes where it elicited transcellular effects (129). However, it is unknown whether specific internalization signals exist beyond the initial contact of microparticles with the cellular recipient.

Thus, microparticles can contribute to the dissemination of inflammatory signals derived from platelets. Furthermore, given that they are induced in several inflammatory pathologies, microparticles appear to be potent biomarkers. Understanding the molecular mechanisms implicated in microparticle functions and improvements in their assessment will contribute to the delineation of their physio(patho)logical roles.

Infections and thrombocytopenia
In addition to being suppressed by platelets, acute viral or bacterial infections can often lead to low platelet counts or thrombocytopenia, which might be a viral or bacterial strategy to evade immune responses. The production of platelets is highly regulated, because this is important to prevent serious bleeding when platelet counts are low, as well as to prevent vascular occlusion and organ damage when platelet counts are increased. Recently, it was elegantly shown that platelet production can be regulated by binding of desialylated platelets to the hepatic Ashwell–Morell receptor, which induces expression of TPO in the liver via JAK2-STAT3 signaling (133).

Acute bacterial or viral infections are known to potentiate ITP, an autoimmune bleeding disorder in which platelets are targeted (134). The pathophysiological mechanism of acute infection–associated destruction of platelets is incompletely understood, but several likely scenarios have been suggested. One of them is molecular mimicry between viral/bacterial Ags and platelet Ags, leading to the production of autoantibodies that cross-react (135–139). Also, several patients with Helicobacter pylori (Gram-negative bacterium)–related ITP exhibited increased platelet count following H. pylori–eradication therapy (140). In line with this, LPS, a Gram-negative bacterial endotoxin, enhanced FcγR-mediated phagocytosis of anti-platelet Ab–opsonized platelets in vitro (37), as well as a potent synergistic effect of anti-platelet Abs and LPS, resulting in platelet clearance in vivo (141). Therefore, LPS may be an important mediator of Ab-mediated platelet clearance during Gram-negative infections; despite not knowing the exact working mechanism, triggering of phagocyte and/or platelet TLR4 could be relevant. Recently, C-reactive protein (CRP) was identified as a novel pathogenic serum factor that enhances IgG-mediated platelet destruction in vitro and in vivo (142). CRP is an acute-phase protein, also present in healthy individuals, which increases rapidly during acute infections. CRP was found to be increased in children with ITP, and treatment with IVIg was associated with increased platelet counts, decreased CRP levels, and reduced clinical bleeding severity (142). Moreover, elevated CRP at diagnosis corresponded to slower platelet count recovery after 3 mo (142).

The suggested mechanism of action was independent of platelet FcγRIIA but based on platelet oxidation (triggered by anti-platelet Abs and the phagocyte NADPH oxidase system), which resulted in exposure of platelet phosphorylcholine residues to which CRP could bind and, thereby, enhance IgG-mediated platelet phagocytosis via interaction with phagocytic FcRs (142). Therefore, CRP could be an important factor in Ab-mediated platelet destruction in bacterial (Gram-negative and/or Gram-positive) or viral infections associated with ITP.

A summary of all the above-mentioned characteristics is shown in Table I and illustrated in Fig. 1.

Conclusions
Platelets are best known as primary mediators of hemostasis and thrombin generation; however, like leukocytes, they have multiple functions related to inflammation/immunity. It appears that these anucleate cellular fragments express and secrete several diverse pro- and anti-inflammatory molecules that serve to initiate and modulate immune functions. These aspects of platelets and immunity have initiated a new understanding of the role of platelets in infectious processes and how they can significantly modulate the immune system.

Disclosures
The authors have no financial conflicts of interest.
References


2010. Platelets and megakaryocytes contain functional nuclear factor-kappaB

58. Gambaryan, S. A., K. Nosar, N. Rukoyutkina, S. Herterich, J. Geiger, A. Smolenski,
S. M. Lohmann, and U. Walter. 2010. Thrombin and collagen induce a feedback
inhibitory signaling pathway in platelets involving dissociation of the catalytic
subunit of protein kinase C-e from an NF-kappaB-IkappaB complex. J. Biol. Chem.

P. A. Roche, and S. W. Whiteheart. 2013. IC3 kinase phosphorylation of SNAP-


method for overexpression of peroxisome proliferator-activated receptor-γ in
megakaryocytes. Platelets 23: 288–293. Platelet micro particles achieves transcriptomic

62. Akhyriy, F. D., M. Ray, K. F. Gerttings, N. Blumberg, C. W. Francis, and
Periagomamma, a peroxisomal protein associated with platelet release of CD40 ligand


64. Kao, K. J. 1987. Plasma and platelet HLA in normal individuals: quantitation by


neutralization involving platelet VI. Reactions of maternal isoantibodies responsible
Invest. 41: 1059–1069.


70. Kao, K. J. 1988. Selective elution of HLA antigens and beta-2 microglobulin

of chloroquine or acid treatment of human platelets on the antigenicity of HLA and the

72. Ghino, M., P. Contini, C. Massei, S. Brenci, G. Barberis, G. Filaci, F. Indiveri, and
F. Fumagalli. 1999. 1999. Inactivation of the HLA class I antigens of human platelets

73. Gouttefaissé, C., M. Chiellin, W. Kelhöfer, R. F. Hörmann, S. Stevanovic, and
H. C. Rammen. 2010. Thromboxane A2 metabolites retain platelet aggregating
endogenous peptides of megakaryocyte lineage and do not stimulate direct allo-

fusion-related immunomodulation by platelets is dependent on their ex-

Med. 121: 786–781.

Human macrophage inflammatory protein alpha 1 activates basophils and mast cells.

77. Italiano, J. E., Jr., J. L. Richardson, S. Patell-Herr, E. Battinelli, A. Zaslavsky,
S. Short, S. Roy,man, J. Folkman, and G. L. Klemment. 2008. Angiogenesis is regu-
lated by a novel mechanism involving antiangiogenic protein alpha 1 and separate

78. Schgal, S., and B. Storrie. 2007. Evidence that differential packaging of the major
platelet granule proteins from Willebrand factor and fibrinogen can support their


80. Rowley, J. W., A. O. Nder, N. D. Tolley, B. N. Hunter, E. N. Low, D. A. Nix,


82. Lood, C., S. Amstren, B. Guillermard, A. Jønsen, M. Allinson, L. Truedsson,
G. Bergendal, D. Erlinge, R. Ottesen. 2010. Platelet mRNA: pathophysiology and
protein expression in patients with systemic lupus erythematosus: up-
regulation of the type I interferon system is strongly associated with vascular dis-

83. Ali, F. Y., S. J. Davidson, L. A. Moraes, S. L. Traves, M. Paul-Clark, D. Bishop-
Br. J. Haematol. 143: 308–318. Platelet growth factor receptor-α 1 production by

The beta-thromboglobulins and platelet factor 4: blood platelet-derived CXC
chemokines with divergent roles in early neutrophil regulation. J. Leukoc. Biol. 67:
471–478.


Human macrophage inflammatory protein alpha 1 (MIF-1 alpha) and MIF-1 beta
chemokines attract distinct populations of lymphocytes. J. Exp. Med. 177: 1821–
1826.

Br. J. Haematol. 143: 308–318. Platelet growth factor receptor-α 1 production by


