Small but mighty: Platelets as central effectors of host defense

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Summary
Platelets actively participate in inflammatory processes and drive diseases such as atherosclerosis, rheumatoid arthritis and cancer metastasis. However, platelets also have anti-inflammatory and anti-infective properties, which have received less consideration in the past. In this review, we highlight recent findings on the role of platelets in host defense and describe regulatory pathways modulating immune responses. Furthermore, we discuss the role of platelets for the resolution of inflammation and tissue repair. These conceptual changes contribute to our understanding of platelet biology in disease.

Keywords
Platelet immunology, inflammation, platelet physiology, sepsis, leukocyte function / activation

Introduction
Platelets are key cellular mediators of haemostasis and thrombosis. However, they are also increasingly recognised as an integral component of the immune system (1, 2). Platelet actions are thereby viewed predominantly in a pro-inflammatory context, in which they initiate and accelerate innate and adaptive immune responses. In fact, platelets promote a variety of immune diseases including atherogenesis (3), rheumatoid arthritis (4), transfusion-related acute lung injury (5) and tumour growth (6). Several structural characteristics of platelets support this perspective (Table 1). The expression of immunoreceptors on the cell surface of platelets such as complement, Fc and Toll-like receptors (TLRs) allow sensing of pathogens (7). Further, P-selectin and multiple adhesion receptors such as glycoprotein (GP)Ibα, GPVI, CD40L and the integrin αIibβ3 enable direct platelet-leukocyte-interactions leading to leukocyte activation and recruitment (8). This can induce cellular effector functions such as production of reactive oxygen species (ROS) and formation of neutrophil extracellular traps (NETs) (1, 9). Furthermore, platelets express soluble immunomolecules such as chemokines CCL3 (MIP-1α), CXCL4 (Platelet factor 4, PF4), CCL5 (RANTES), CXCL5 and CXCL7 (β-thromboglobulin) as well as cytokines like interleukin (IL)-1β and transforming growth factor (TGF)-β1 (1). Those factors are harbored in platelet granules and may also be newly synthesised (10). Cytokine secretion initiates inflammation and may affect all subsets of leukocytes resulting in their recruitment (1, 8, 11), activation (1, 8, 12), differentiation (2) and survival (13, 14).

However, an increasing body of evidence suggests that platelet immune functions not only contribute to inflammation. In fact, platelets can directly protect from infections and actively participate in the clearance of pathogens from the blood. Thereby they support the development of adaptive anti-microbial immunity. Further, platelets provide anti-inflammatory molecular cues to limit the body’s immune response. This review provides a perspective on platelets as central effectors and regulators of immunity with a focus on their anti-inflammatory properties.

I – Platelets assist in the clearance of pathogens and protect from infections

In healthy individuals blood is sterile. Disruption of the endothelial barrier due to injury or disease provides the risk for pathogen invasion into the vasculature. With a high concentration of 150–400 × 10⁶ cells per litre of human blood, platelets outnumber all leukocyte subsets manifold. Thus, numerous platelets may encounter pathogens, which are immediately bound following their intrusion to prevent pathogen dissemination and protect the host from further infection. Moreover, platelets assist in the clearance of pathogens to reinstate sterility of the blood.

To fulfill those tasks, platelets execute a variety of defense mechanisms. One is direct pathogen attack (Figure 1). Platelets internalise pathogens such as Staphylococcus aureus (S. aureus) or human immunodeficiency virus (HIV) into their open canalicular system without their elimination (34). In contrast, platelets can directly eliminate Escherichia coli (E. coli), particularly when the bacteria are opsonised by IgG (17). The bactericidal activity is dependent on the IgG receptor FcyRIIA and actin rearrangement processes in platelets (17). Generally, the process of direct pathogen attack is not solely receptor dependent, but also involves platelet secretion of oxidants and antimicrobial proteins including...
thrombocidins, defensins and kinocidins (35–39). Further, the platelet released chemokine platelet factor 4 (PF4) induces killing of the intraerythrocytic malarial parasite (40).

Besides contributing directly to the elimination of pathogens, platelets can also bind to circulating pathogens via pattern-recognition receptors, which are then presented to innate immune cells promoting microbial killing (41, 42). Platelets thereby support the recruitment of innate immune cells to sites of infection (1, 8, 25). Accumulated neutrophils and monocytes initiate a major element of intravascular immunity referred to as immunothrombosis (Figure 2) (25, 43). It relies on the interaction of platelets with innate immune cells and blood coagulation factors, leading to intravascular fibrin generation and thrombus formation within microvessels (25, 43). Platelets are pivotal in this pathophysiological condition. They not only form platelet-rich thrombi but also induce leukocyte recruitment into the growing thrombus via expression of adhesion molecules (e.g. P-selectin) and release of chemokines (1, 25, 44). Importantly, platelets bind neutrophils and trigger release of prothrombotic scaffolds (neutrophil extracellular traps, NETs), which are of central relevance during immunothrombosis (25, 43, 45, 46). Platelets contribute to NET formation by interaction of P-selectin with P-selectin glycoprotein ligand-1 (PSGL-1) on neutrophils (47), release of β-defensins (33) or involvement of the high mobility group box 1 protein (HMGB1) signalling pathway (48). NETs encircle intravascular microbes and promote their killing via antibacterial proteins including myeloperoxidase, neutrophil elastase and pentraxin (25, 43, 45, 49, 50). NETs also induce a strong procoagulant response through multiple molecular mechanisms and activate platelets, which further maintains immunothrombosis (25, 46, 51). Besides induction of NET formation, platelets support immunothrombosis via additional pathways. One is the secretion of thiol isomerases, which drive fibrin generation via activation of intravascular tissue factor (52–55). Another is the release of platelet-derived polyphosphates, which activate the factor XII-dependent contact pathway of coagulation and enhance fibrin polymerisation (25, 43, 56, 57). The physiological functions of immunothrombosis during host defense include capturing and entrapment of circulating pathogens within microvessels in order to limit pathogen dissemination and to prevent their entry into extravascular compartments (25, 46). Following their spatial concentration, pathogens are then exposed to multiple antimicrobial strategies in

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<table>
<thead>
<tr>
<th>Platelet immunoreceptors</th>
<th>Platelet-released molecules</th>
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<tr>
<td>Complement receptors (15, 16)</td>
<td>CCL3 (MIP-1α) (1)</td>
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<tr>
<td>Fc receptors, e.g. FcγRIIA (17)</td>
<td>CXCL4 (Platelet factor 4, PF4) (18, 19)</td>
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<td>Toll-like receptors (20)</td>
<td>CCL5 (RANTES) (21), CXCL5 (22)</td>
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<tr>
<td>P-selectin (23, 24)</td>
<td>CXCL7 (β-thromboglobulin) (19)</td>
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<tr>
<td>Glycoprotein (GP)Ibα (24, 25)</td>
<td>Interleukin (IL)-18 (10)</td>
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<td>GP VI (26)</td>
<td>Transforming growth factor (TGF)-β1 (1, 27)</td>
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<td>CD40L (CD154) (28)</td>
<td>High-mobility group box 1 protein (HMGB1) (29)</td>
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<td>Integrins, e.g. β3 integrin alibβ3 (30)</td>
<td>Stromal derived factor 1 (SDF-1) (31)</td>
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<td>Intercellular adhesion molecule (ICAM)-2 (32)</td>
<td>Antimicrobial proteins, e.g. β-defensins (33)</td>
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**Table 1**: Selection of surface-expressed platelet immunoreceptors and platelet-released molecules.
volving both innate immune cells and activated platelets (25, 46, 58–60).

The potentially beneficial process of immunothrombosis needs to be tightly balanced, since its dysregulation may result in disseminated intravascular coagulation (25). Furthermore, entrapment of viable pathogens within thrombi may contribute to the pathogenesis of septic thrombotic diseases such as endocarditis (61). As a side note, significant amounts of innate immune cells and NETs have also been identified in thrombi of large arteries and veins (43, 62–64). Inhibition of leukocyte recruitment and NET formation reduced both thrombus formation and tissue injury in mice (65, 66). Thus, immunothrombotic mechanisms seem to contribute to clinically relevant conditions such as myocardial infarction and deep-vein thrombosis.

Platelet interactions with pathogens play a critical role in infection. In line with this, mice with low numbers of circulating platelets are more susceptible to bacterial and parasite infection than mice with normal cell counts (67, 68). Furthermore, platelet-depleted animals show increased organ damage and bacterial burden (67). In a model of experimental infective endocarditis with Streptococcus sanguis infection of the aortic valve, thrombocytopenia was associated with higher bacterial densities in vegetations (69).

This further supports the concept that platelets reduce bacterial spreading. Further, platelets release antimicrobial proteins, which may act directly on bacteria (69–71).

In addition to protecting the host from infections, platelets assist in the clearance of pathogens from blood. In doing so, they collaborate with intravascular phagocytes, namely liver Kupffer cells (72). While platelets interact transiently with Kupffer cells in steady state, bacterial infection induces firm platelet adhesion, which promotes encapsulation of bacteria on the Kupffer cell surface (72). Platelets thereby impede bacterial infection, pathogen-induced endothelial permeability and liver dysfunction, resulting in reduced mortality (72). Furthermore, platelets shuttle blood-borne pathogens to secondary lymphoid organs to induce adaptive antibacterial immunity (73). In contrast to the rapid bacterial elimination by liver Kupffer cells, promotion of adaptive immunity requires prolonged antigen exposition. Therefore, platelets enable an additional “slow clearance pathway” for pathogens regulated by bacterial opsonisation. This allows sufficient exposure to splenic CD8α+ dendritic cells, which then induce adaptive immunity (74).

Figure 2: Platelets are crucial elements in immunothrombosis. Platelets drive intravascular immunity in collaboration with innate immune cells and blood coagulation factors. Platelets recruit neutrophils and induce formation of neutrophil extracellular traps (NETs). NETs ensnare pathogens and promote their killing. Further, NETs support recruitment and activation of platelets and induce a strong pro-coagulant response supporting intravascular thrombus formation within microvessels. Platelets secrete factors such as protein disulfide isomerase (PDI) and polyphosphates, which support blood coagulation. This leads to fibrin generation and contributes to microvascular thrombus formation. The elements of immunothrombosis directly attack pathogens but also capture and ensnare circulating pathogens within microvessels in order to limit pathogen dissemination and to prevent their entry into extravascular compartments.
II - Platelets modulate the immune response and limit inflammation

In the event of acute infection, an immediate immune response involving leukocytes and platelets aims to eliminate invading pathogens and ensures host integrity. However, uncontrolled as well as persistent inflammation might be detrimental to host organs. In critical conditions such as sepsis, amplification of the immune response is certainly necessary. On the other hand, an exaggerated immune response with imbalanced cytokine production may promote inflammation resulting in septic shock (75, 76). Elevated serum levels of pro-inflammatory cytokines including tumour necrosis factor (TNF)-α, IL-6, IL-17 and interferon (IFN)-γ are associated with poor prognosis in septic patients and related mouse models (67, 77, 78). Similarly, elevated cytokine levels are associated with persistent inflammation and contribute to chronic inflammatory (79, 80) and autoimmune diseases (81, 82). Therefore, tight regulation of the acute inflammatory response is important for the maintenance of a balanced immune continuum.

In septic patients, adverse clinical outcomes including mortality correlate with the severity of thrombocytopenia (83, 84). Disseminated intravascular coagulation during severe sepsis is a major cause of mortality and commonly presents with thrombocytopenia (85, 86). Further, local haemorrhage in inflamed tissues is induced by severe thrombocytopenia during sepsis, suggesting its contribution to excess mortality (87). However, platelet counts of 10–15% of the normal platelet number are sufficient to prevent inflammatory bleeding during sepsis (87, 88), while mortality rates remain unchanged pointing to additional mechanisms associated with thrombocytopenia (89). In line with this, induction of thrombocytopenia in mouse sepsis models demonstrated that platelets can limit systemic inflammation (67, 89, 90). Application of thrombocytopenia to septic animals increased mortality (67, 89), while platelet transfusions improved survival (89). The anti-inflammatory properties of platelets leading to downregulation of immune responses can be mediated either by whole cells or platelet ectosomes (PLT-Ect). PLT-Ect are small cell blebs released during the activation process of platelets and are the most abundant cell-derived microvesicle subtype within the vasculature (91). The immunosuppressive actions of platelets and their PLT-Ect affect a variety of leukocyte subsets (Figure 3).

In monocytes and macrophages, platelets can elicit anti-inflammatory properties via several molecular mechanisms (Figure 3a). Among those are platelet GP Ibα-dependent interactions with monocytes (90). Interestingly, interaction of platelet CD40L with monocyte CD40, which has formerly been recognised solely in a pro-inflammatory context, has recently been found to also limit the inflammatory capacity of leukocytes (92). Furthermore, platelet cyclooxygenase 1 (COX-1)-dependent generation of prostaglandin E2 (PGE2), which binds to the macrophage prostaglandin receptor EP4, mediates similar immunosuppressive effects (89). In the absence of platelets, serum levels of pro-inflammatory cytokines including TNF-α (67, 89, 90), IL-6 (89, 90) and IFN-γ (67) are significantly increased in severe inflammation. In line with this, platelet infusion leads to systemic reduction of pro-inflammatory cytokines (89). Several in vitro studies suggested that this modulation of cytokine level is due to an anti-inflammatory influence of platelets towards monocytes and macrophages. Co-culture of platelets or PLT-Ect with macrophages induces a profound reduction in the release of pro-inflammatory cytokines including TNF-α and IL-6 in response to zymosan A or lipopolysaccharide (LPS), which are ligands to TLR-2 or TLR-4, respectively (93, 94). Similar observations can be made, when activated platelets are co-cultured with blood monocytes during exposure to LPS or the bacterium Porphyromonas gingivalis (92). Here, pro-inflammatory cytokines including IL-6 and TNF-α are reduced, while secretion of the anti-inflammatory cytokine IL-10 is increased (92).

In addition to the modulation of cytokine release, platelets can suppress macrophages in their production of anti-microbial nitric oxide (94). Furthermore, PLT-Ect modulate the differentiation of blood monocytes into immature dendritic cells (iDC), i.e. towards a less inflammatory phenotype (93). Expression of CD80, which provides costimulatory signals for T cell activation and survival, as well as human leukocyte antigen (HLA)-expression and phagocytic activity of iDCs is reduced when PLT-Ect are present (93). Since PLT-Ect can induce a long-lasting reduction in monocyte cytokine secretion (> 24 hours), it has been suggested that they may induce a persistent switch in these myeloid cells towards an anti-inflammatory phenotype (93). It is important to note, that anti-inflammatory effects of platelets seem to depend on the context but also the intensity of the inflammatory response. In this regard platelets potentiate TNF-α production and inflammation when mice are challenged with low-dose LPS injections (41, 95, 96). In contrast, upon induction of severe sepsis with high-dose LPS or after application of the cecal ligation and puncture (CLP) technique, platelets inhibit macrophage secretion of pro-inflammatory cytokines and improve clinical outcome (89, 90).

In addition to the influences on monocytes, platelets can also exert immunosuppressive effects on neutrophils (Figure 3b). Platelets limit the inflammatory activity of neutrophils via platelet GP Ibα-mediated downregulation of the neutrophil β2 integrin Mac-1 (CD11b/CD18) (90). Furthermore, platelets may indirectly limit the systemic inflammatory activity via NET formation. While the latter are known for their pro-inflammatory functions in host defense (25, 45), NETs degrade cytokines and chemokines reducing the inflammatory response (97).

Besides their pivotal influence on myeloid leukocyte subsets, platelets and PLT-Ect also perform immunosuppressive effects towards lymphocytes, especially CD4+ T cells (Figure 3c). This is mediated by platelets suppressing the release of pro-inflammatory cytokines including TNF-α, IL-6 and IFN-γ, while generation of the mainly anti-inflammatory cytokine TGF-β1 is induced (98). Additional platelet influences refer to CD4+ T cell differentiation. Naïve CD4+ T cells can differentiate into T helper 1 (Th1), Th2, Th17 or regulatory (Treg) cells. Earlier, it has been suggested that activated platelets inhibit CD4+ T cell proliferation (92) and differentiation towards Th17 cells (99). Therefore, platelets may be involved in the limitation of inflammatory and (auto)immune conditions via Th17 suppression. However, the mechanisms of...
Figure 3: Anti-inflammatory regulatory pathways of platelets and platelet ectosomes (PLT-Ect) modulate leukocyte activity, cytokine release and differentiation. A) Immunosuppressive effects of platelets towards monocytes and macrophages aggravate the release of anti-inflammatory cytokines and inhibit the release of pro-inflammatory cytokines. Further, platelets may inhibit nitric oxide production and differentiation of monocytes towards immature dendritic cell (iDC). Involved molecules mediating anti-inflammatory effects towards monocytes and macrophages include platelet GPIb, CD40L-CD40 interaction as well as Cox-1-induced PGE2 ligation to the corresponding EP4 receptor. B) Neutrophil extracellular traps (NETs) may degrade cytokines limiting the immune response. Thereby, NET formation is induced by platelets releasing β-defensins or HMGB1 as well as ligation of PSGL-1 by P-selectin. Additionally, platelets may directly reduce the inflammatory activity of neutrophils due to GPIb-mediated downregulation of the β2 integrin Mac-1. C) Anti-inflammatory strategies of platelets towards CD4+ T cells lead to inhibited secretion of pro-inflammatory cytokines and induced secretion of the anti-inflammatory cytokine TGF-β1. Platelets limit lymphocyte differentiation towards inflammatory Th17 cells and promote differentiation towards immune regulatory Treg cells. Further, platelets limit Treg plasticity towards inflammatory IL-17- and IFN-γ-producing T cells. The immunosuppressive effects of platelets towards lymphocyte biology rely on P-selectin-PSGL-1 interaction and release of PF4, which is a ligand to the chemokine receptor CXCR3.
PF4-mediated Th17 suppression seem to be complex and context-dependent. This can be illustrated by the fact, that PF4 deficiency enhances Th17 differentiation after cardiac or bone marrow transplantation, but not in response to parasite infection (99, 100). Furthermore, PLT-Ect induce the differentiation of naive CD4+ T cells into Forkhead box P3 (FOXP3) positive Tregs (98), but prevent Treg differentiation into pro-inflammatory subsets (101). Tregs are important in the limitation of immune responses and generation of immune tolerance (102), and FOXP3 has emerged as the master regulator of Treg development and function (103). Mechanistically, the effects of PLT-Ect on Treg differentiation are partly dependent on platelet-derived TGF-β1 and P-selectin (98, 101). T cell plasticity towards IL-17- and IFN-γ-producing cells is associated with a variety of diseases including multiple sclerosis (104), inflammatory bowel diseases (105) and psoriasis (106). Hence, platelets may be involved in the regulation and limitation of those diseases.

In summary, increasing evidence suggests that platelets together with PLT-Ect actively regulate the immune response during inflammation by modulating both the innate and adaptive immune system. In this regard platelets target leukocyte subsets within the vasculature, e.g. at the vascular wall or within microthrombi. Beyond that, PLT-Ect may extravasate and also reach leukocytes in tissues or organ cavities. Absence of the anti-inflammatory effects of platelets on leukocytes contributes to dysregulated inflammatory conditions and autoimmune diseases.

The immune functions of platelets are modulated through direct and indirect (via soluble mediators) interactions with immune cells and microbes. However, they also seem to depend on the "configuration" of their precursor cells located in the bone marrow. Megakaryocytes express a variety of immunomolecules including CD40L (107), IL-1 receptor (108) and several TLRs such as TLR-1, TLR-2, TLR-3 and TLR-6 (20, 109, 110). Inflammation and infection shapes the maturation and differentiation of megakaryocytes via IL-1β and TLR ligands, and thereby alters the molecular repertoire passed on to the forming platelets (108, 110). Specifically, transferred messenger RNAs (mRNAs) and microRNAs have been established as key players modulating platelet protein levels and function, which has been reviewed in detail by Rondina et al. (111). Thus, the immune regulatory capacity (i.e. pro- and anti-inflammatory functions) of platelets is already modulated at the progenitor state in the bone marrow. Notably, mRNA can be passed on to PLT-Ect where it remains functional (112, 113). By these means microvesicles are expected to influence gene expression in neighboring cells (endothelium, immune cells) and could therefore contribute to shaping the local immune response.
III – Platelets support the resolution of inflammation and assist in tissue repair

Following the inflammatory phase, controlled resolution of inflammation and subsequent tissue repair are critical steps in order to restore tissue homeostasis (114, 115). Temporal or spatial disruption of resolution potentially leads to persistent inflammation and may result in chronic inflammatory diseases. Historically, the resolution of inflammation has been considered a passive process following the removal of pro-inflammatory mediators (114). In a modern perspective the resolution of inflammation is regarded as a carefully managed active program leading to reduced tissue infiltration and increased apoptosis of neutrophils (114, 116), non-phlogistic recruitment of monocytes (116), and induction of macrophage phagocytosis of debris and apoptotic cells (117–119). The process starts shortly after acute inflammation is initiated and involves the biosynthesis of pro-resolving mediators (120, 121). These are diverse in nature and include lipid mediators such as lipoxins (e.g. LXA4), resolvins (e.g. RvE1), protectins and maresins (122, 123), proteins such as annexin A1 (124, 125), gaseous mediators such as hydrogen sulfide (126, 127) and carbon monoxide (128, 129), adenosine (130–132) as well as neuromodulators released under control of the vagus nerve (133, 134).

Main effector cells in the resolution phase are lymphocytes and especially macrophages, which promote chemokine clearance and perform efferocytosis (135). Yet, platelets play an underestimated role in this condition. Due to their ability to generate several of the aforementioned pro-resolving mediators, platelets likely participate in the initiation and maintenance of resolution programs (▶Figure 4a).

Platelet degranulation increases lipoxin generation (136, 137). For instance, biosynthesis of the lipoxin LXA4 is processed by the platelet enzyme 12-lipoxygenase during platelet-leukocyte-interactions (138) or upon microparticle transfer (139). LXA4 was among the first anti-inflammatory and pro-resolving lipoxins recognised. On the one hand LXA4 limits neutrophil recruitment and chemoattraction at sites of inflammation, on the other hand non-phlogistic recruitment of mononuclear cells is induced and macrophage engulfment of apoptotic neutrophils enhanced (123, 140). Maresin 1 (MaR1) is another lipoxin generated by platelet 12-lipoxygenase following platelet-leukocyte-interactions (141). MaR1 and Maresein-like lipid mediators generated by platelets act in an organ-protective manner, e.g. during acute respiratory distress syndrome (141, 142) and restore reparative functions of impaired macrophages in the setting of diabetes mellitus (143). Moreover, platelets store the pro-resolving protein ANXA1 (144, 145), which inhibits neutrophil trafficking during inflammation (124, 146, 147).

Besides the ability to initiate and maintain resolution programs, platelets also receive pro-resolving signals during the resolution phase (▶Figure 4b). Platelets respond to the mediator RvE1 via expression of the corresponding receptor ChemR23 (148). Receptor ligation then leads to reduced platelet aggregation and P-selectin surface expression, suggesting a limitation of platelet activation following the receipt of pro-resolving signals (148). Another target for ligands promoting the resolution of inflammation is the peroxisome proliferator-activated receptor γ (PPARγ), which is also expressed in platelets (149). PPARγ-igation dampens platelet activation and secretion (150). Concordantly, treatment of diabetic patients with the PPARγ agonist rosiglitazone reduces platelet P-selectin expression (151), circulating CD40L (152) and platelet-leukocyte-interactions (153). Interestingly, platelets can package PPARγ in microparticles, which are then taken up by leukocytes and other cells (154).

The resolution of inflammation sets the stage for subsequent regeneration and tissue repair. Platelets are critically involved in the regenerative process and release a multitude of growth factors and angiogenic mediators upon activation. Therefore, platelets modulate the activation of fibroblasts, which impacts on the organization and remodelling of the extracellular matrix (155). The migration and proliferation of other cell types required for tissue repair such as mesenchymal stem cells (MSCs) (156) and smooth muscle cells (SMCs) (157) is also modulated by platelets. Furthermore, platelets balance angiogenesis in damaged tissues due to the release of pro- and anti-angiogenic factors (158, 159). The chemokine CXCL12, also known as stromal cell-derived factor-1α (SDF-1α), is critical for recruitment of CD34+ bone marrow derived progenitor cells to sites of inflammation or injury and induces their differentiation into endothelial progenitor cells (160, 161). In this line, inhibition of SDF-1α binding to the corresponding receptor CXCR4 has been shown to retard diabetic wound healing due to prolonged inflammation and impaired cellular migration (162). Platelet derived growth factor (PDGF) is another prominent mediator in tissue repair. It regulates SMC migration and proliferation, enhances fibroblast activity and is particularly relevant for blood vessel maturation (163). PDGF also contributes to the recruitment of pericytes to capillaries in vivo and thus increases vascular integrity (164, 165). Other factors secreted by platelets and considered to be pro-angiogenic are vascular endothelial growth factor (VEGF) (166), epidermal growth factor (EGF) (167), hepatocyte growth factor (HGF) (168) and insulin-like growth factor-1 (IGF-1) (168). The regenerative potential of platelets is harnessed in a variety of clinical scenarios ranging from acute trauma management to treatment of chronic wounds as in the case of diabetic ulcers (169, 170), e.g. via the administration of autologous platelet-rich plasma gels or recombinant platelet-derived growth factors (170, 171).

IV – Can anti-inflammatory platelet functions be differentially induced?

As noted in the introduction, platelets have both pro- and anti-inflammatory properties. For the sake of clarity this review focused on platelet functions that limit inflammation and reduce the immune response. Under which conditions do platelets act in a pro- or anti-inflammatory manner? Can these functions be separated? Are there specific triggers favoring either phenotype? To date, there is no clear answer to these questions and the various immune functions of platelets are subject to ongoing investigations. It could be speculated that ligation of specific surface receptors during immune cell or pathogen interactions induces the differential
secretion of immunomolecules by platelets. This is supported by the findings that agonist stimulation has differential effects on platelet protein abundance and secretion (172–174). Likewise, interactions with bacteria elicit multifaceted platelet responses (7). Thus, dependent on the respective agonist platelets might provide a more inflammatory phenotype. The release of immunomodulatory molecules from platelet granules could thereby play an important role (175, 176). Interestingly, platelets differentially store and release their granule content, which has been demonstrated for pro- and anti-angiogenic factors as well as larger proteins such as von Willebrand factor (VWF) and fibrinogen (177–179). However, high-resolution microscopy recently suggested that tight spatial control of the canalicular system during platelet activation allows the differential release of proteins rather than their separated packaging (180). By these means, platelets might differentially respond to immune stimuli in either a pro- or anti-inflammatory manner. Spatially controlled mechanisms (e.g. local delivery of coagulant factors or chemokines) seem to play a role in a variety of platelet-immune cell interactions and could potentially separate pro- and anti-inflammatory platelet functions (181, 182). Further, platelets might be provided with a phenotype favoring pro- or anti-inflammatory functions already at the time of separation from megakaryocytes. Infections and inflammatory conditions alter the megakaryocyte phenotype (see Section II) and platelet functions may consequently be modulated through RNAs provided by their ancestor cells (111).

Conclusion

The involvement of platelets in the immune continuum has been accepted for some time. In host defense platelets fulfill a variety of critical functions ranging from direct pathogen attack to cooperation with innate immune cells and soluble factors to establish intravascular immunity. However, platelets exceed their role as sensors of infection and activators of leukocytes functions. Platelets also provide the capacity to limit inflammation and suppress the host immune response. Dependent on the context and extent of inflammation, platelets reduce myeloid cell activation, trigger the release of anti-inflammatory cytokines, and even affect lymphocyte differentiation. In addition to the well-known pro-inflammatory effects of platelets, these recent findings create an alternative perspective on platelets and establish them as central effectors of the immune system. A future challenge will be to dissect the detrimental and beneficial roles of platelets in diseases. Particularly, future studies need to determine the cause and contributing factors directing platelets to either exacerbate or limit inflammation. Specifically, the molecular mechanisms underlying immune regulative functions of platelets remain to be addressed. This could guide the development of novel therapies in inflammatory conditions.

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