The role of platelets in inflammation

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Summary
There is growing recognition of the critical role of platelets in inflammation and immune responses. Recent studies have indicated that antiplatelet medications may reduce mortality from infections and sepsis, which suggests possible clinical relevance of modifying platelet responses to inflammation. Platelets release numerous inflammatory mediators that have no known role in haemostasis. Many of these mediators modify leukocyte and endothelial responses to a range of different inflammatory stimuli. Additionally, platelets form aggregates with leukocytes and form bridges between leukocytes and endothelium, largely mediated by platelet P-selectin. Through their interactions with monocytes, neutrophils, lymphocytes and the endothelium, platelets are therefore important coordinators of inflammation and both innate and adaptive immune responses.

Keywords
Platelets, inflammation, infection, immune response, thrombosis

Introduction
Platelets were traditionally considered to purely have a role in the maintenance of haemostasis. However, there is growing recognition that they also have a critical role in inflammation and immune responses. Indeed, some have even argued that this role may be as important as their role in haemostasis (1). Interest in the role of platelets in inflammation and immune responses has recently returned to the forefront. Findings from the PLATelet inhibition and patient Outcomes (PLATO) study suggested that the novel antiplatelet medication ticagrelor might reduce the incidence of pulmonary infections and infection-related deaths compared to clopidogrel, the previous standard treatment for patients with acute coronary syndromes (ACS) (2–4). Epidemiological evidence also supports the hypothesis that antiplatelet medications affect host immunity, since a recent review of observational studies has suggested that antiplatelet medications are associated with a reduction in mortality from sepsis, without causing an excess of bleeding (5). There are many potential mechanisms for a clinical benefit of antiplatelet medications in systemic inflammation related to infection, which justifies detailed examination of the role of platelets in inflammation and immune responses. The purpose of this review is therefore to summarise the role of platelets in inflammation, with a focus on their role in innate immune responses.

Overview of platelet biology
Platelets have a major role in maintaining vascular integrity and haemostasis. However, platelets also aggregate at the site of atherothrombosis and contribute to plaque rupture, forming an occlusive thrombus, which is central to the pathophysiology of arterial thrombosis and subsequent ischaemia. Antiplatelet therapy has therefore become an integral component of the treatment strategy for arterial thrombosis. Platelets are discoid-shaped fragments derived from bone marrow megakaryocytes. They are released under the regulation of thrombopoietin and circulate for approximately 7–10 days (6). At rest, the human body produces approximately 200 billion platelets per day (7). Platelets can synthesise a limited number of proteins, since they contain messenger RNA (mRNA) but not a nucleus and therefore do not contain DNA (8). Platelets do, however, contain a vast number of pre-formed megakaryocyte-derived molecules in their granules that can be released upon activation.

Platelet adhesion, activation and aggregation
Under resting conditions, the endothelium releases prostacyclin and nitric oxide (NO), which inhibit platelet activation and prevent platelet aggregation. After endothelial compromise, platelets adhere to subendothelial components that have been exposed following vascular injury or atherosclerotic plaque rupture. Under high shear conditions, vWF (Von Willebrand factor) forms a bridge between exposed collagen and the platelet glycoprotein (GP) Ib/V/IX complex on the platelet membrane (9). In addition, exposed collagen binds directly to platelet GP IIb/IIIa and GPVI receptors (10).

The binding of collagen to platelet GPVI receptors induces platelet activation. Additionally, mediators released by activated cells, such as ADP and serotonin, and other plasma mediators, such as epinephrine and thrombin, activate platelet G-protein coupled
receptors (Figure 1). This increases levels of cytosolic calcium and activates specific signalling pathways. These result in platelet shape change and activation of integrins that also promote firm adhesion (11). Upon activation, platelets release the contents of their α and dense granules. ADP from the dense granules then acts on platelet P2Y1 and P2Y12 G-protein-coupled receptors, which triggers further platelet activation and release of ADP. The P2Y12 receptor acts to sustain platelet activation in response to ADP and therefore has a central role in this amplification process (12).

The final common pathway of these agonists is the activation of the GP IIb/IIIa receptor (13) which results in the cross-linking of fibrinogen or vWF between the receptors, leading to platelet aggregation. This promotes the recruitment of additional platelets to the site of vascular injury, which allows the formation of a thrombus.

Platelet granules

Supporting the important role of platelets in inflammation, activated platelets secrete a vast number of inflammatory mediators that have no identifiable role in haemostasis (14). Platelets possess three major types of storage granules: dense granules, lysosomes and α-granules, of which the α-granules are the most abundant. Dense granules contain small non-protein molecules that have important roles in the amplification of platelet responses, such as ADP, ATP and serotonin. Recently platelet serotonin has been shown to have an important role in neutrophil rolling and adhesion to the endothelium (15). Platelet lysosomes contain proteases, glycosidases and other proteins that have a bactericidal effect (16). Platelet α-granules contain a large number of varied proteins that are released during platelet activation and act on thrombosis and haemostasis, inflammation, host defenses and atherosclerosis amongst other effects (17).

There are approximately 50–80 α-granules per platelet, which have heterogeneous contents consisting of membrane-bound proteins that are either expressed on the platelet surface or released upon activation (17). Of the membrane-bound proteins, most are already present on the resting membrane, whilst others, such as the adhesion molecule P-selectin, are only minimally expressed prior to platelet activation.

Many of the proteins contained within platelet α-granules have an important role in haemostasis. However, α-granules also have a significant role in innate immunity, mostly either by modulating the expression of platelet adhesion receptors that interact with leukocytes or by releasing cytokines that affect leukocyte function. Detail of the full contents of α-granules is incomplete, but they are known to contain a diverse range of chemokines, including CXCL1, platelet factor 4 (PF4; also known as CXCL4), CXCL5, CXCL7, interleukin (IL)-8 (also known as CXCL8), CXCL12, macrophage inflammatory protein (MIP)-1α (also known as CCL3) and RANTES (also known as CCL5) (17). The predominant effect of these cytokines is to regulate leukocyte movement, migration from the vasculature into the tissues and other pro-inflammatory functions, such as phagocytosis and generation of reactive oxygen species (Table 1). This affects the recruitment of leukocytes to sites of inflammation and mostly upregulates their pro-inflammatory functions. In addition, α-granules also contain small, cationic microbicidal proteins that can directly disrupt the membrane of Staphylococcus aureus (18).

Major platelet-derived cytokines

Many of the major platelet-derived cytokines affect monocytes in particular (Table 1 and Figure 2). PF4 is one of the most
abundant proteins contained in platelet α-granules. PF4 is a CXC chemokine which shares sequence similarities with the chemokine IL-8, albeit with different functional effects (19). As well as having a role in thrombosis and haemostasis, PF4 has a broad range of activities related to innate immunity, including effects on monocyte and neutrophil chemotaxis (20). PF4 promotes neutrophil granule release and adhesion to endothelial cells, mediated by L-selectin and leukocyte function-associated molecule 1 (LFA-1) (21). In addition, PF4 prevents monocyte apoptosis, promotes monocyte differentiation into macrophages and induces phagocytosis and generation of reactive oxygen species (22). PF4 induces monocyte release of cytokines (including CXCL8, CXCL3, IL-1α, IL-1β, IL-6, IL-19, tumour necrosis factor (TNF) -α, CCL2, CCL3 and CCL22) (23). In combination with regulated on activation, normal T cell expressed and secreted (RANTES), PF4 also promotes monocyte arrest on the endothelium (24) and may upregulate endothelial E-selectin expression (25). RANTES is a chemokine that has a role in atherosclerosis and is found in large quantities in platelet α-granules. Platelets either directly release RANTES or form microparticles containing RANTES, which can be immobilised on activated endothelium and promote monocyte recruitment, mediated by P-selectin (26). T cells that express CD40L can also induce platelet RANTES release, which promotes T cell recruitment to the endothelium in a process that is amplified by RANTES (27).

Activated platelets release the pro-inflammatory cytokine IL-1β in vitro (28), although it has been suggested that this may be at least partly dependent on contaminating leukocytes (29). IL-1 is central to the cytokine cascade and has a major role in vascular inflammation (30). Activated platelets induce IL-6 and IL-8 release from vascular smooth muscle cells, mediated by release of IL-1 (31). In addition, IL-1 is known to mediate vascular NO production (32) and promote neutrophil adhesion to endothelial cells (33). Activated platelets have also been shown to induce CCL2 secretion and intercellular adhesion molecule (ICAM-1; also known as CD54) expression in endothelial cells in a process mediated by IL-1 (34). CCL2 is the major chemokine that regulates monocyte and macrophage chemotaxis and acts on monocyte CCR2 receptors (35).

### Adhesion molecules

One of the key constituents of platelet α-granules is P-selectin (also known as CD62P), which has a key role in linking thrombosis and haemostasis and inflammation. P-selectin and P-selectin ligand-1 (PSGL-1) are a receptor and its respective ligand that have a central role in the interaction between platelets, leukocytes and endothelial cells (36). α-granules also contain other adhesion molecules, such as platelet endothelial adhesion molecule-1 (PECAM-1), GPIIb/IIIa and vWF (16).
Direct platelet-leukocyte interactions

P-selectin and PSGL-1

P-selectin is contained within the α-granules of platelets and is expressed on the surface membrane upon platelet activation (37). Monocytes, neutrophils, eosinophils and haematopoietic progenitor cells have all been shown to possess the corresponding ligand, PSGL-1 (38, 39). P-selectin cross-links platelets and leukocytes and is therefore a major mediator of platelet-leukocyte aggregate formation and its action is described in more detail in the following sections.

CD40 and CD40L

CD40 and CD40L (also known as CD154) are a receptor and its respective ligand that are important mediators of interactions between lymphocytes and antigen-presenting cells (40) and have also been shown to have a role in atherothrombotic disease (41). Activated platelets express CD40L, which has a similar structure to TNF-α and a similar effect. Platelet CD40L expression induces monocyte expression of tissue factor, which in turn initiates the extrinsic coagulation cascade (42). Platelet-expressed CD40L has also been shown to affect dendritic cells as well as B lymphocytes and T lymphocytes, suggesting that it provides a communicative link between innate and adaptive immunity (43). In addition to its direct effects on leukocytes, platelet-expressed CD40L also interacts with CD40 on endothelial cells to promote secretion of chemokines, such as IL-8 and CCL2, and express adhesion molecules, such as E-selectin (also known as CD62E), vascular cell adhesion molecule 1 (VCAM-1; also known as CD106) and ICAM-1 (44). This promotes migration of leukocytes to the site of vascular injury and subsequent adhesion. As well as expressing CD40L on their surface membrane, platelets also release soluble CD40L, which can induce vascular cells to express E-selectin and P-selectin and release IL-6 (45, 46). Indeed, it has been suggested that activated platelets are the predominant source of soluble CD40L (46, 47). A role of CD40 and CD40L in ACS has been suggested by reports of increased levels in patients with ACS (48, 49).

TREM1

Platelets interact with triggering receptor expressed on myeloid cells 1 (TREM1) that is primarily expressed on monocytes and neutrophils, although the natural ligand of TREM1 is unknown (50). Platelets have been shown to express a ligand for TREM1, which potentiates lipopolysaccharide (LPS) -induced neutrophil respiratory burst and IL-8 release but does not mediate platelet-leukocyte aggregate formation (51).

Platelet-leukocyte aggregate formation

Binding of platelets to leukocytes

The initial binding of platelets to leukocytes is mediated by platelet P-selectin binding to leukocyte PSGL-1. This is followed by firm adhesion, which is mediated either by leukocyte CD11b/CD18 binding to platelet GPIb or platelet-bound fibrinogen, or by platelet ICAM-2 binding to leukocyte CD11a/CD18 (52). The initial capture and rolling of leukocytes on the endothelium is largely mediated by endothelial selectins. In addition to the direct effect of platelet P-selectin on promoting leukocyte adhesion to
endothelium, endothelium-bound immobilised platelets can also bind leukocytes via P-selectin, acting as a bridge and further promoting leukocyte adhesion (53). Therefore, P-selectin/PSGL-1 interaction has a functionally important role in leukocyte rolling and adhesion to platelets and endothelium, which are critical steps in the process of leukocyte extravasation (54–57).

**Effect of platelet-leukocyte aggregate formation on leukocyte function**

The interaction between platelet P-selectin and PSGL-1 increases the adhesive properties of monocytes, by promoting expression of beta integrins and adhesion to fibronectin, VCAM-1 and ICAM-1, and promotes transendothelial migration (58). Similarly, P-selectin interaction with neutrophil PSGL-1 increases the adhesive properties of neutrophils by upregulating CD11b/CD18 and promoting adhesion to fibrinogen and ICAM-1 (59, 60). Neutrophils that have formed platelet-neutrophil aggregates shed L-selectin, show increased phagocytic activity and produce more reactive oxygen species (61). Interaction between P-selectin and PSGL-1 also regulates monocyte cytokine production. P-selectin potentiates monocyte secretion of CCL2 (also known as monocyte chemotactic protein-1) and TNFα in response to platelet activating factor (PAF), possibly by upregulating nuclear translocation of nuclear factor-κB (62). Monocytes and neutrophils roll over long, negatively-charged platelet flow-induced protrusions (FLIPRs) in a P-selectin/PSGL-1 dependent manner, which induces leukocyte CD11b and L-selectin shedding; the leukocytes retain fragments of the FLIPRs as microparticles on their surface (63). Monocyte-platelet aggregate formation also appears to induce a change in monocyte phenotype to the pro-inflammatory CD14high CD16+ phenotype (64).

**In vivo sequelae of platelet-leukocyte interactions**

The innate immune system is essential for the resolution of microbial infection. However, in sepsis, excessive innate immune activation can cause excessive collateral tissue damage and, in particular, neutrophils have been implicated in the microvascular pathology that results in multi-organ failure (65). Platelet P-selectin has been shown to mediate leukocyte recruitment into post-ischaemic tissue, due to its effects on transendothelial migration (66), and blocking platelet P-selectin reduces post-ischaemic neutrophil infiltration of kidneys and subsequent acute kidney injury (67). Platelets appear to have a particularly prominent role in pulmonary neutrophil sequestration. In an animal model, blocking P-selectin reduces pulmonary neutrophil recruitment during abdominal sepsis (68). Acute lung injury also appears to be mediated by P-selectin in a murine model; inhibiting P-selectin expression and the subsequent formation of platelet-neutrophil aggregates improves gas exchange, decreases neutrophil recruitment and improves survival (69).

In ACS, plaque rupture induces the formation of platelet-monocyte aggregates and platelet-neutrophil aggregates by both P-selectin- and non-P-selectin-dependent mechanisms, although the physiological role of these aggregates is not clearly established (70). In patients with ACS, the platelet P2Y12 inhibitor clopidogrel reduces levels of CRP and TNFα, which may be related to a reduction in P2Y12-mediated platelet-leukocyte interactions or may be related to reduced myocardial necrosis secondary to the anti-thrombotic effects of clopidogrel (71). Patients with ACS who have high platelet reactivity, as shown by increased expression of platelet P-selectin despite treatment with clopidogrel, have been shown to have a higher risk of adverse cardiovascular events (72). At antiplatelet doses, aspirin also has anti-inflammatory effects that appear to be mostly related to its inhibition of platelet thromboxane A2 synthesis, by inhibiting COX-1 (73). Since thromboxane A2 is a potent platelet agonist, this may indirectly reduce inflammation that results from thrombosis. Additionally, thromboxane A2 and other thromboxane prostanoid receptor agonists mediate vascular inflammation (74), which may also be to some extent inhibited by aspirin. Even antiplatelet doses of aspirin may have additional anti-inflammatory effects mediated by COX-2, especially when used at higher doses, as reviewed by Hohlfeld et al. (73). Stable coronary artery disease and atherosclerosis are also associated with low grade inflammation, which in turn is associated with an increase in platelet reactivity, as reviewed by Larsen et al. (75). It has also been suggested that platelet-leukocyte interactions, mediated by platelet-expressed P-selectin and CD40L, may contribute to the pathogenesis of a number of other inflammatory conditions. This is covered in more detail in another review by Schrotta et al. (76). In addition, cross-talk between monocytes, neutrophils and platelets activates the extrinsic coagulation cascade, which is a critical mediator of the initiation and propagation of deep vein thrombosis (77).

**Role of platelets in sterile inflammation**

Tissue damage and cell death are major initiators of sterile inflammation, which is central to a number of pathological processes, including ischaemia, atherosclerosis, gout and Alzheimer’s disease (78). Cell death, particularly necrosis, initiates the release of damage-associated molecular patterns (DAMPs), which act on monocyte/macrophage intracellular and extracellular receptors, thereby triggering an inflammatory response. The most clearly characterised DAMPs include high-mobility Group Box-1 (HMGB1), IL-1α, S100 proteins, heat shock proteins (HSPs), dsDNA and uric acid (79). HMGB1 is released extracellularly upon cell necrosis, but it has also been shown that platelets contain HMGB1 and express it on their outer membrane upon activation (80). HMGB1 is a highly potent inflammatory mediator that acts on receptor for advanced glycation endproducts (RAGE), which activates a number of signalling pathways, including MAP kinases, and activates NF-κB (81). It has recently been shown that activated platelets present HMGB1 to neutrophils, which induces the formation of neutrophil extracellular traps (NETs) (82), which are discussed in more detail in later paragraphs. Platelets also express receptors for other DAMPS, including the heat shock protein Gp96 (83). These receptors appear to have an important role in...
mediating dendritic cell activation, although the mechanism is unclear and appears to be independent of soluble platelet factors and cell-to-cell contact (83).

Response of platelets to pathogens

Bacterial interaction with platelets

The immediate activity of platelets at the site of a wound also means that they are ideally located to act as first-responders to invading microbes. Bacteria interact directly with platelets causing platelet activation, which allows platelets to release pro-inflammatory mediators and act as sentinel cells. However, this also directly contributes to the pathology of disseminated intravascular coagulation and infective endocarditis (84). Bacteria, such as Streptococcus pyogenes, bind fibrinogen that can then interact with platelet GPIIb/IIIa to trigger platelet activation (85), whilst other bacteria such as Streptococcus epidermidis are capable of interacting directly with platelet GPIIb/IIIa causing platelet activation (86). Similarly, S. aureus can bind vWF, which can then interact with platelet GPIIbα (87), whereas some species of streptococcus interact directly with platelet GPIIbα to cause platelet activation (88). The knowledge-base regarding platelet signalling after the adherence of bacteria is relatively incomplete (84). Platelet activation by Streptococcus sanguinis and Streptococcus gordonii results in platelet aggregation and release of α-granules (containing RANTES, PF4, sCD40L, soluble P-selectin and platelet-derived growth factor (PDGF)-AB) and dense granules (containing ADP and ATP) (89, 90). Thrombocytopenia is common in patients with sepsis and is associated with increased mortality (91). Patients with sepsis have higher levels of platelet P-selectin expression and leukocyte CD11b and there is some evidence that levels of these markers correlate with severity of sepsis (92).

Platelet TLR

Toll-like receptors (TLR) are a major family of receptors that recognise pathogen-associated molecular patterns (PAMPs). It has been demonstrated that platelets possess TLR4 (93), as well as TLR2, TLR3, TLR7, TLR8 and TLR9 (94). TLR4 mediates leukocyte response to the bacterial product lipopolysaccharide (LPS), which is a classical initiator of innate immune responses (95). However, LPS has not been consistently demonstrated to have a clear effect on traditional aspects of platelet function, such as platelet aggregation and P-selectin expression or cytosolic concentrations of calcium (96). Conversely, other studies have shown that activation of platelet TLR4 by LPS may increase platelet adhesion to fibrinogen (97) and the formation of neutrophil extracellular traps (NETs) that ensnare bacteria in sepsis (98). NETs, which are composed of cytoplasmic proteins and nuclear contents, including DNA, are expelled by activated neutrophils into the extracellular space, possibly as a last resort to control bacterial infections (99). Important roles of NETs have been identified in a number of pathological processes, including autoimmune disorders, chronic lung diseases and vascular disorders (100). Recent studies have demonstrated an additional platelet-dependent component of NET formation that is mediated by platelet chemokines, including RANTES and PF4 (101–103). There is also an increasing recognition of a major role of NETs in the pathophysiology of thrombosis, particularly DVT (104). However, very recent studies also demonstrate a major role of NETs in coronary thrombosis (82, 105). Coronary thrombus from patients with acute myocardial infarction (MI) contains numerous neutrophils and high levels of NETs, which contribute to the thrombus scaffold (82). Additionally, there are increased levels of NETs at the site of coronary plaque rupture during ST-segment elevation myocardial infarction and the NET burden predicts infarct size (105).

TNF-α production in response to LPS is significantly impaired in mice rendered thrombocytopenic by an antiplatelet antibody and this can be reversed by platelet transfusion, suggesting a role of platelets in LPS-induced cytokine production (93). In accordance with this, reducing platelet reactivity by inhibiting platelet P2Y12 receptors with clopidogrel and prasugrel also reduces TNF-α production in animal models of mice (106) and rats (107) respectively. However, this is not the case in pigs (108), suggesting that this process may be species-dependent.

Platelets and the complement system

The complement system is part of the innate immune system and acts as an immune surveillance system that eliminates infectious microbes, cellular debris, immune complexes and apoptotic cells (109). However, complement activation also contributes towards vascular inflammation and atherosclerosis, particularly mediated by the potent inflammatory mediators C3a and C5a (110). Emerging evidence suggests that platelets may have an ability to interact with both the classical and alternative pathways of complement (110). This appears to be an amplificatory role, whereby platelets become activated by complement and then induce further complement activation (111). Platelet activation and expression of P-selectin can initiate complement activation by increasing C3b deposition, C3a generation and C5b-9 formation (112). There is evidence to suggest that this activation of the complement system is mediated by platelet release of chondroitin sulfate (113). It has been demonstrated that platelet microparticles express gC1qR, which activates the classical complement cascade, and complement components such as C1q and C5b-9 are deposited on microparticles that are exposed to plasma (114). This therefore demonstrates that both platelets and platelet microparticles can support complement activation, which may have a crucial role in microbial clearance, but may also contribute to the pathophysiology of vascular inflammation and atherosclerosis.

Role of platelets in malaria

Malaria has long been recognised to cause thrombocytopenia, although the mechanisms for this are unclear. Cerebral malaria in particular has a poor prognosis and platelets may have a central role in initiating and accelerating the cerebral inflammatory injury (115). However, platelets also play a critical role in killing...
Table 2: Summary of major platelet mechanisms that modulate inflammation and immunity.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Main actions of mechanism</th>
</tr>
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<tbody>
<tr>
<td>Platelet α-granule release</td>
<td>Platelet α-granules contain multiple mediators of inflammation (see Table 1), which have a diverse range of mostly pro-inflammatory effects.</td>
</tr>
<tr>
<td>Platelet P-selectin expression</td>
<td>Platelet P-selectin interacts with leukocyte PSGL-1, which is critical to the formation of platelet-leukocyte aggregates. Additionally, forms cross-links between leukocytes and the endothelium, thereby facilitating adhesion (59).</td>
</tr>
<tr>
<td>Platelet-leukocyte aggregate formation</td>
<td>Upregulates a wide range of pro-inflammatory functions of leukocytes, including release of pro-inflammatory cytokines, reactive oxygen species production, phagocytosis and endothelial adhesion (1).</td>
</tr>
<tr>
<td>Platelet expression of CD40L</td>
<td>Interacts with leukocyte CD40 and induces monocyte expression of tissue factor and activation of the coagulation system (123). Influences several important T cell functions, including antigen presenting cell activation.</td>
</tr>
<tr>
<td>Platelet TLR4-mediated NET formation</td>
<td>Emerging evidence suggests an important role of platelets in the formation of NETs (98), which aid the clearance of bacteria. However, NETs also have prothrombotic effects and contribute to the scaffold of a thrombus (82,105).</td>
</tr>
<tr>
<td>Platelet P-selectin-mediated activation of the complement system</td>
<td>Platelets releases chondroitin sulfate, which activates the complement system (113). This may have an important role in the clearance if microbes, but may also contribute towards vascular inflammation.</td>
</tr>
<tr>
<td>Platelet release of HMGB1</td>
<td>Platelets present HMGB1 to neutrophils, which induces the formation of NETs (82). Additionally, HMGB1 is a potent inflammatory stimulus that activates MAP kinases and NF-κB (81).</td>
</tr>
<tr>
<td>Platelet activation in response to binding of GPIb and GPIIb/IIIa by bacteria</td>
<td>Platelets aggregate, in response to bacteria directly or indirectly binding GPIb and GPIIb/IIIa (124). This may contribute towards thrombocytopenia and may allow bacteria to become surrounded by platelets and inaccessible to leukocytes.</td>
</tr>
<tr>
<td>Platelet expression of TREM1 ligand</td>
<td>Mediates leukocyte activation and engagement of leukocyte TREM1 induces secretion of IL-8, TNFα and CCL2 (125).</td>
</tr>
<tr>
<td>Platelet release of microparticles</td>
<td>Presents IL-1β (126), RANTES (26) to the endothelium. Play a key role in signalling between platelets and the innate immune system (127,128).</td>
</tr>
</tbody>
</table>

Plasmodium falciparum parasites and survival from malaria is lower if platelets are inhibited by aspirin or depleted in certain models (116). The role of platelets in killing P. falciparum is in part dependent on platelet factor 4 (117).

Role of platelets in malignancy

Patients with metastatic cancer have an increased risk of thrombosis. Platelets interact with tumour cells, resulting in platelet activation, P-selectin expression and formation of platelet-tumour microthrombi, which may protect tumour cells from the innate immune system (118). The metastatic potential of tumour cells is dependent on their ability to leave the circulation to form deposits in peripheral tissues. Whilst tumour cell-endothelial interactions differ from leukocyte-endothelial interactions, selectins and integrins are also thought to play an important role in metastasis (118). Heparin attenuates metastasis in certain models, which may be mediated by P-selectin (119). Aspirin is also associated with a reduced risk of distant metastasis in patients with cancer, particularly of colorectal origin (120), although the mechanism for this has not been established. At low doses aspirin primarily inhibits cyclooxygenase (COX)-1, whilst at higher doses aspirin progressively inhibits COX-2, both of which may effect tumour progression (121).

Conclusion

Platelets have a major role in coordinating inflammation and immune responses. Platelet P-selectin expression and subsequent formation of platelet-leukocyte aggregates upregulates leukocyte pro-inflammatory functions. In addition, platelet α-granules contain a wide range of cytokines that have a predominantly pro-inflammatory effect (Table 1). It is known that platelet P2Y12 inhibitors reduce platelet P-selectin expression, platelet-leukocyte aggregate formation and release of α-granule contents. However, the effect of this on host immunity is not yet established. The major role of platelets in inflammation and immune responses (Table 2) provides a clear rationale for further studies to determine whether modulation of platelet function can improve patient outcomes in inflammatory disorders, particularly inflammation related to infection.
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