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Platelets and their interactions with other immune cells

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Abstract

Platelets are anucleate blood cells, long known to be critically involved in hemostasis and thrombosis. In addition to their role in blood clots, increasing evidence reveals significant roles for platelets in inflammation and immunity. However, the notion that platelets represent immune cells is not broadly recognized in the field of Physiology. This manuscript reviews the role of platelets in inflammation and immune responses, and highlights their interactions with other immune cells, including examples of major functional consequences of these interactions.

Introduction

Platelets are small anucleate blood elements, known since the late 19th century to participate in blood clot formation (17). They are critical mediators of the physiologic response of cessation of bleeding following blood vessel injury (hemostasis) as well as pathologic formation of blood clots (thrombosis) (175). Platelets are traditionally viewed in the context of hemostasis and thrombosis, while leukocytes are regarded as primary immune cells mediating the body's response to pathogens. In recent years, increasing evidence supports the notion that platelets participate in immune responses, and interactions between platelets and leukocytes contribute to both thrombosis and inflammation. Despite these data, much general teaching of the physiologic roles of platelets and leukocytes is limited to the original descriptions. In this manuscript, we will focus on platelets from a perspective of immunity and inflammation, including the mechanisms of their interactions with leukocytes and the functional consequences of these interactions. We will devote little attention to the role of platelets in hemostasis and thrombosis and instead refer readers to available reviews on these traditional functions of platelets (25, 125). We will highlight numerous examples that support the premise implied in the title of this manuscript, that platelets should be regarded as immune cells.

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Overview of Platelets

Human platelets are the smallest blood cells with ~2–5 μm in diameter, 0.5 μm in thickness and ~6–10 femtoliters in mean cell volume. They are derived as fragments from megakaryocytes and are released into the circulation with an average life span of ~7–10 days (reviewed in (221)). A primary and critical function of platelets is to sustain hemostasis. This is achieved by forming a stable platelet plug at the site of vascular injury via adhesion and aggregation to the exposed sub-endothelial matrix proteins. However, similar processes at the site of rupture of an atherosclerotic plaque can lead to occlusive platelet thrombi and cause thrombosis. Whereas the normal count for human platelets range from 150,000 to 400,000/μl, hemostasis can be achieved with platelet counts more than 10,000/μl (187). This observation suggests that platelets likely have roles beyond hemostasis and thrombosis, a theme that is addressed in this review. Despite their small size and limited life span, platelets display an elaborate structure that provides clues to their biological role.

Platelet structure

Resting platelets reveal a unique discoid shape cell, in part, due to the robust cytoskeletal structure encompassed by several loops of the microtubular coils (marginal microtubule bands) (106). However, platelet activation is associated with major shape change due to cytoskeletal changes that enable filopodial and lamellopodial extensions to occur (Fig. 1). The phospholipid bilayer of the platelet membrane embeds cell surface receptors that engage soluble ligands or fixed ligands on other immune cells and the endothelium. The functional consequences of receptor-ligand engagement include activation of platelets and complexes of activated platelets with leukocytes, erythrocytes, or endothelial cells and contribute to inflammation. Also present on the plasma membrane are numerous openings or pores that lead to several invaginations in platelets called the open canalicular system (OCS), which provide the small-sized platelets with a much greater surface area (218, 219). Distinct from the plasma membrane-associated OCS, platelets also display a channel system called dense tubular system (DTS). The DTS is believed to be a remnant of megakaryocyte smooth endoplasmic reticulum and stores calcium and enzymes that support the activation of platelets (42, 169). Most importantly, electron microscopy images of platelets disclose the notable absence of nucleus and a chockfull presence of organelles including mitochondria, glycosomes and secretory granules (Fig. 2).

Platelet granules

The anuclear feature of platelets, including the inability to replicate does not impede their ability to respond effectively to the external stimuli. Platelets are endowed with presynthesized proteins within their granules, which can be secreted to the extracellular milieu or expressed on the platelet surface following their activation. Certain proteins like platelet factor 4 (PF4) are synthesized by the megakaryocytes and carried over to platelet granules, while immunoglobulins (IgG) are endocytosed from the plasma by platelets. One recent proteomic study concluded the presence of eight hundred and twenty seven proteins in the granules (234). This suggests that secretion events can facilitate the cross talk of platelets with a variety of cell types, including the immune and endothelial cells, and thus

influence a wide range of physiological functions. Platelets possess three types of granules: α granules, dense granules, and lysozymes.

α granules—α granules are the most abundant granules (~50–80/platelet), measuring 200–500 nm in diameter (18). Their contents include proteins that support platelet adhesion, aggregation and coagulation, which are required for hemostasis and thrombosis function. Some examples include fibrinogen, von Willebrand factor (VWF), vitronectin, fibronectin, thrombospondin, factor V, factor VIII, and cell adhesion molecules like integrins $\alpha_{IIb}\beta_3$ (GPIIb/IIIa) and $\alpha_v\beta_3$. α granules also contain proteins and peptides that recruit, localize, or activate immune cells and thus modulate inflammatory or immune function. One of these granular proteins is P-selectin, which is expressed on the platelet surface following activation of platelets (93). As discussed in detail below, P-selectin on activated platelets can engage its ligand P-selectin glycoprotein ligand-1 (PSGL-1) expressed on neutrophils and monocytes and activate these leukocytes (140, 208, 230). Chemokines (PF4 or CXCL4) and β-thromboglobulin, [neutrophil activating peptide (NAP), CXCL7] secreted from the granules can recruit and activate neutrophils, suppress neutrophil apoptosis (24, 79, 177) and participate in the homing of endothelial progenitor cells (EPC) (90). Chemokine CCL3 [Macrophage inhibitory protein-1 α (MIP-1α)], CCL5 (RANTES) and CXCL1 (GRO α) can recruit monocytes (73, 92), while CXCL-5 can modulate chemokine scavenging and neutrophil chemotaxis (137, 165). α granules also contain proteins that exhibit anti-microbial effects and thus influence innate immune function. Examples include thrombocidin 1 and 2, which have anti-bacterial and anti-fungal actions (115). α granules also contain proteins that possess mitogenic and angiogenic abilities and thus regulate wound healing and angiogenesis function. Platelet derived growth factor (PDGF), transforming growth factor beta (TGF-β), epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) could influence the effector cells like monocytes macrophages, and endothelial cells (10, 61, 129). α granules contain hundreds of distinct proteins, including substances with opposing physiological roles (e.g., pro- and anti-angiogenic, pro- and anti-coagulant (18)). Recent studies demonstrate that platelets possess the ability to store α granule contents differentially, which enables differential release of α granule content in response to various stimuli (180). Differential storage and release of platelet alpha granule proteins has important implications for the role of platelets as immune cells; the mechanisms responsible for these complex processes remain to be fully characterized.

Dense granules—These granules appear as dense bodies on electron microscopy due to the elevated contents of calcium and phosphate. They are ~10 fold less abundant than α granules and about ~150 nm in diameter (70, 88). The contents of these granules are also released into the extracellular environment upon activation of platelets. These granules store nucleotides (ATP and ADP) (169). ATP can modulate inflammatory pathways by activating dendritic cells, while ADP provides a feedback mechanism that activates platelets. Serotonin can mediate vascular tone and also recruit neutrophils at sites of inflammation (14, 58). Other constituents include cations, like calcium and magnesium that can support signal transduction processes.

Lysosomes—These granules are approximately 200–250 nm in diameter and can be microscopically identified by staining for lysosomal enzymes, like acid phosphatase or arylsulfatases (12). Lysosomes contain the lysosomal-associated membrane proteins, LAMP1, LAMP2 and LAMP-3 (CD63) (183). CD63 is translocated to the platelet surface following stimulation with strong stimuli. Lysosomes are home to proteases like carboxylpeptidases, cathespin D and E that contribute to the inflammatory potential of platelets (169, 186, 213) and enzymes that remodel the extracellular matrix (37).

Platelet membrane receptors

Receptors on platelets enable them to sense the external environment and respond to biological changes. For the purpose of this review, we broadly classified platelet receptors into receptors that support hemostasis and receptors that sustain the interaction with other immune cells or participate in immune function. Several receptors are constitutively expressed on the platelet surface, although some receptors are stored in the granules and surface expressed only after activation.

Receptors involved in hemostasis—Given the prominent role of platelets in hemostasis, the major receptors on platelets have a direct role in their activation and/or supporting the adhesive interaction of platelets with adhesive proteins at the site of injury.

Some platelet receptors involved in hemostasis primarily mediate platelet activation. These include receptors that engage platelet agonists (agents that activate platelets). At the site of vascular injury, activation of coagulation pathways generates a serine protease thrombin. Platelets express two thrombin receptors, namely protease-activated receptor 1 (PAR1) and PAR4 (101). PAR1 responds to lower levels of thrombin ~1 nM while PAR4 is sensitive to at least 10 times higher concentration of thrombin. Interestingly, differential expression of PAR is noticed among species. Mouse platelets express PAR3, instead of PAR1, along with PAR4 (94). Thrombin is a potent activator of platelets, and activated platelets degranulate their contents including ADP and metabolize arachidonic acid to generate thromboxane A2. Platelets express two ADP receptors, P2Y1 and P2Y12, and a thromboxane receptor, TP (8, 76, 145). Binding of ADP and thromboxane A2 to their respective receptors enables critical autocrine platelet activation processes to occur. Exposed collagen at the site of injury can be recognized by integrin $\alpha_2\beta_1$ and an immunoglobulin type receptor glycoprotein VI (GPVI) on platelets (4, 141, 192).

Other platelet receptors are involved in hemostasis by mediating stable platelet adhesion. These include receptors that engage in platelet-extracellular matrix or platelet-platelet interactions. Given that platelets often have to accomplish hemostasis in the context of a high shear stress environment, it is imperative that they possess a shear responsive receptor. A leucine–rich repeat family member, glycoprotein GP Ib-IX-V complex that includes GPIα (~145 kD) as well as GPIbβ (~22 kD), GPIX (~17 kD), and GPV (~82kD), endows platelets to adhere von Willebrand factor (VWF) exposed at the site of injury under high shear stress (3). The interaction of GPIbα with VWF transduces signals, which activate another class of cell adhesion molecules on platelets or integrins, specifically $\alpha_{IIb}\beta_3$ (75). Platelets express the integrin family of receptors, namely $\alpha_{IIb}\beta_3$, $\alpha_v\beta_3$, $\alpha_5\beta_1$ and $\alpha_6\beta_1$. Integrin $\alpha_{IIb}\beta_3$ is the

most abundant receptor with 50,000–80,000 copies on the platelet surface with an additional pool in the α granules (150, 207). $\alpha_{IIb}\beta_3$ is in an inactive state on platelets, and agonist stimulation leads to integrin activation via a conformational change in the structure. This enables the binding of $\alpha_{IIb}\beta_3$ to soluble plasma fibrinogen and the sustain platelet–platelet aggregation. Integrin $\alpha_v\beta_3$ integrin primarily supports adhesiveness to vitronectin (45, 166), while $\alpha_5\beta_1$ and $\alpha_6\beta_1$ have supplementary roles in adhesion to fibronectin and laminin at the injury site (162, 189). Integrins are often in complex with four membrane-spanning receptors called tetraspanins, which include CD9 and CD63, which may support signal transduction and stable integrin adhesion (81, 95).

Receptors that enable platelet interaction with immune cells, the endothelial cells, or participate in immune function—Emerging evidence indicates that platelets also possess receptors that enable stable interaction of platelets with other immune cells or complexes in the circulation as well as adhesion to the vascular endothelium. In some cases, these receptors are only expressed on the surface of activated platelets, such as P-selectin, which can bind PSGL-1 on leukocytes (78, 120). Some receptors are expressed constitutively, such as GPIbα, which can bind with β2 integrin Mac 1 (CD11b/CD18; $\alpha_M\beta_2$ integrin) on neutrophils (184). Intercellular adhesion molecule-2 (ICAM-2) expressed on platelets (52) can support leukocyte tethering via leukocyte function antigen 1 (LFA1) (212). In other cases as described above for $\alpha_{IIb}\beta_3$, receptors can be expressed in an inactive form and upon activation they become active; $\alpha_{IIb}\beta_3$ can support adhesion to leukocytes via fibrinogen (212). Platelets may also interact with endothelial cells under inflammatory conditions; for example, GPIbα expressed on platelets can interact with activated endothelial cells that express P-selectin and VWF (170). Activated platelets express a 39 kD membrane glycoprotein of the tumor necrosis factor (TNF) family called CD40L (CD154), which can interact with CD40 on endothelial cells and trigger an inflammatory response (83). Platelets also express a C-type lectin receptor CLEC-2 (197) that interacts with podoplanin on lymphatic endothelial cells and participates in blood-lymphatic separation, via lymphovenous hemostasis during development (16). Platelet CLEC-2 can engage with tumor cells expressing podoplanin, contributing to cancer metastasis (104). Interaction of platelet CLEC-2 with podoplanin expressing inflammatory macrophages can activate platelets (107). Consistent with an immune role for platelets, CLEC-2 on platelets can also capture human immunodeficiency virus type 1 (34). Please see Table 1 and associated text for details of adhesive mechanisms mediating platelet adhesive interactions with immune cells and endothelium.

Certain receptors on platelets mediate platelet-immunoglobulin (Ig) or platelet-complement interaction and thus participate in modulating immune complexes and/or function. These include FcγRIIA, the low affinity receptor for the IgG Fc domain (171), FcεRI high affinity receptor for IgE (99) and FcαRIA receptor for IgA (167). FcγRIIA engaged on platelets may provide immunological defense against bacteria, while activation of platelets via FcεR1 trigger release of RANTES (regulated on activation, normal T cells expressed and secreted) and serotonin, mediators that promote pro-inflammatory response in other immune cells (80). Crosslinking of platelet FcαRI led to production of prothrombotic mediators like tissue factor and interleukin-1β via pre-mRNA splicing and protein synthesis (167); a topic that

will be discussed in the next section. Platelets also possess receptors for complement components including a 33kD receptor to complement protein C1q (C1qR) (156) that can facilitate the classical complement activation (158). Platelet C1qR can also interact with protein A from *Staphylococcus aureus* enabling direct interaction of platelets with bacteria (147). Decay accelerating factor (DAF or CD55) is another glycosyl phosphatidylinositol (GPI) anchored receptor on platelets (109), which likely protects platelets from complement attack during defense against bacteria. Thus, platelets share some common receptors with primary phagocytes like neutrophils and monocytes and participate in immune functions.

Protein synthesis by platelets

In addition to containing proteins pre-stored in their granules or on their membrane, platelets have the ability to synthesize proteins, despite lacking a nucleus. This concept was first described in the late 1960s (211); however, it was not widely accepted until several decades later (217). Further, the notion that anucleate platelets have the capability to synthesize proteins is rarely addressed in traditional physiology textbooks. Platelets possess messenger RNA (mRNA) and can synthesize proteins upon activation, including proteins involved in inflammatory responses (152, 179, 214). For example, activated platelets can synthesize interleukin-1β, which can promote inflammatory responses in other cell types including leukocytes and endothelial cells (89, 128). For a broader review of protein synthesis by platelets, including a historical perspective, please refer to the following recent review (217).

Other mediators in platelets

Platelets also possess mediators that are not specifically located on the membrane or the three granules. These mediators can also regulate the interaction of platelets with other immune cells and influence inflammatory process. For example, β defensin 1 was reported to be located in an extragranular compartment in platelets, and upon release by activated platelets, it induces the release of neutrophil extracellular traps (NET) from neutrophils and limit bacterial growth (112). High mobility group box 1 (HMGB1) expressed on activated platelets causes neutrophil extracellular trap (NET) formation in neutrophils and commit them to autophagy (173). These features represent additional characteristics in support of the premise that platelets represent immune cells.

Platelets as Immune Cells

As exemplified in this review, there is abundant evidence that platelets have important roles in a broad range of immune responses, in addition to their well-established role in hemostasis and thrombosis. There is a gradually increasing awareness that platelets can function as immune cells (as the most abundant immune cells in blood), although this concept is not uniformly considered in traditional physiology teaching (57). Herein, we review some mechanisms by which platelets participate in immune responses.

Release of chemokines/cytokines

Chemokines are small (8–10 kD) proteins with four cysteine residues in the conserved positions and are known to induce chemotactic response on effector cells by engaging the chemokine receptors. Depending on the spacing of the N-terminal cysteine residues,

chemokines are grouped into four categories: CC, CXC, CX3C, and XC. CC chemokines have two adjacent conserved cysteines, while CXC and CX3C have either one or three residues between the two conserved cysteines. The latter, XC, is a variant chemokine with only one N-terminal cysteine and a second cysteine downstream (123). Platelets store chemokines of the CC and CXC class within the α granules, and these mediators are released upon platelet activation (20, 23). CC chemokines such as MIP-1 α, monocyte chemotactic protein-3 and RANTES recruit and activate leukocytes (73, 92, 102, 178, 215, 216). CXC chemokines such as PF4 and β-thromboglobulin can recruit neutrophils and suppress neutrophil apoptosis (24, 79, 177). CXCL-5 can modulate neutrophil chemotaxis (137). Platelets also release other growth factors with immune modulating activities such as PDGF (134) and TGF β (7) and immune mediators such as histamine (134) and serotonin (14). Interleukin-1 β from platelets can promote inflammatory responses in leukocytes and endothelial cells (89, 128). Platelets can activate peripheral B cells and potentiate IgG production probably through sCD40L and RANTES (44). Thus, platelets contribute to the immune function by releasing the mediators that recruit, localize, or activate immune cells and thus modulate inflammatory or immune function chemokines.

Toll-like receptors

Toll-like receptors (TLRs) are transmembrane pattern recognition receptors responsible for a variety of responses against microbial cell wall components and are critically involved in innate immune responses (72, 196). Ten TLRs (i.e., TLR-1, through TLR-10) have been identified in humans; they are expressed on a broad range of cell types, though their sub-cellular localization and function has been best characterized on “traditional” immune cells (36, 72, 196). Platelets have also been shown to express various TLRs with evidence of a functional role; these include TLR-2, TLR-4, TLR-7, and TLR-9 (2, 19, 43, 111). Stimulation of platelet TLR-2 and TLR-9 has been reported to induce platelet aggregation responses to various agonists (19, 105, 154, 181). Similarly, platelet TLR-4 has been shown to participate in a number of responses to bacterial endotoxin, including platelet recruitment to inflamed or injured vascular walls (2, 193) and platelet release of IL-1β-containing-microvesicles (27). Further, platelet TLR-4 was shown to promote release of neutrophil extracellular traps (NETs) capable of trapping bacteria during bacterial infection (40). Recently, platelets were shown to express TLR-7 and to mediate host responses to viral infections without detectable effects on platelet aggregation (111). The evidence of functional toll-like-receptors on platelets provides further support to the notion that platelets are important immune cells.

Release of microvesicles

Another mechanism by which platelets may participate in immune responses is the release of microvesicles, also known as microparticles. They are sub-micrometer particles released not only by platelets, but also endothelial cells, leukocytes, and tumor cells (151). A functional role for platelet microvesicles in hemostasis was proposed by the observation that patients with Scott syndrome, a hemostatic disorder, had defective platelet microvesiculation (185). Microvesicles of platelet origin represent a major fraction of circulating microvesicles (48, 149). Based on proteomic analyses, microvesicles derived from human platelets contain nearly 600 distinct proteins (71), raising the intriguing possibility that microvesicles may

recapitulate many of the known functional roles of platelets. Despite technical challenges and variability in methods to quantify microvesicles (29), there is considerable clinical research interest in quantification of circulating microvesicles. Elevated platelet-derived microvesicles have been demonstrated in the circulation of patients with a variety of thrombotic and inflammatory disorders (130, 144, 148, 149, 190). Release of microvesicles is another mechanism by which platelets contribute to immune responses; as mentioned earlier, platelets were shown to release IL-1β-enriched microvesicles following stimulation by bacterial (27). Interleukin 1 enriched microvesicles from platelets activated by collagen amplify inflammation in a model of rheumatoid arthritis (21).

Expression and transfer of microRNA

Since the 1960s, platelets were known to contain mRNA (22); however, limited information was available of the mechanisms for regulation of mRNA and consequently protein synthesis in platelets. Recently, human platelets were shown to contain a broad range of functional microRNA (miRNA, reference (118)). MiRNA are short non-coding RNAs that regulate mRNA translation by a variety of mechanisms reviewed in detail elsewhere (176). Human platelets have been described to contain >200 distinct miRNA despite using stringent criteria for miRNA identification (38, 146, 195). Platelet miRNA may regulate protein translation on platelets (146) and can be secreted or delivered via microvesicles and influence gene expression in endothelial cells (74, 146, 153). Whether platelet miRNA mediates gene expression in other cell types, including other immune cells, remains to be defined.

Direct interactions with microorganisms

Aside from their ability to modulate the immune response, several studies have examined how platelets directly interact with microorganisms, specifically bacteria and fungi. Early studies on the antimicrobial properties of platelets focused on the presence of microbicidal proteins. One of these is β-lysin, a small (6 kDa), cationic, thermostable protein whose main function is to kill gram-positive bacteria, namely *Staphylococcus aureus* and *Bacillus spp* (55). Processes that stimulate release of β-lysin include coagulation, inflammation, antigen-antibody complex formation, the generalized Shwartzman reaction, and bacteremia. Once released, β-lysin induces plasma membrane disruption of Gram-positive bacteria and eventual cell lysis. This process is synergistic with lysozyme, complement and antibody, as removal of β-lysin decreases the bacteriocidal effect of serum (54, 62, 87).

Platelet microbicidal proteins are another class of bacteriocidal peptides, similar to β-lysin. They are small, cationic peptides that are released from platelet α granules by thrombin stimulation and have the ability to kill *Staphylococcus aureus* through the disruption of the plasma membrane (225, 227). Studies in infective endocarditis suggest that platelet microbicidal proteins are also important in fighting viridans *Streptococci* infections (47), whereas the development of resistance to platelet microbicidal protein by *S. aureus* may lead to persistent bacteremia (64). Not only are platelet microbicidal proteins antibacterial, they also possess antifungal properties (226, 228). Included within the class of platelet microbicidal proteins are thrombocidin-1 and -2, CXC chemokines stored within platelet α granules. These proteins are related to neutrophil-activating peptide-2 (NAP-2) and

connective tissue-activating peptide III (CTAP-III), respectively, and are able to kill both Gram-positive (*Bacillus subtilis*, *S. aureus*) and Gram-negative (*Escherichia coli*) organisms and are effective against some species of *Candida* (113).

In addition to microbicidal proteins, platelets also have direct cell-cell interactions with microbes. It has been well described that bacteria can induce platelet aggregation, leading to sequestration of the bacteria. Additionally, studies have shown that platelets are also able to engulf bacteria and the human immunodeficiency virus (HIV) (229, 233). However, the consequences of these interactions have been debated. Although sequestration of bacteria by platelets may assist removal of bacteria by the reticuloendothelial system (202), sequestration may also protect bacteria from bacteriocidal agents. This concept has been suggested by the retrieval of viable organisms from platelet-bacterial aggregates *in vitro* (41). Additionally, there are data suggesting that platelet-bacterial aggregation propagates and protects the development of vegetative lesions in bacterial endocarditis (86, 100, 198). The engulfment of bacteria by platelets appears distinct and less effective than the phagocytic capability of leukocytes (220); the functional consequences of pathogen engulfment by platelets remain to be clearly delineated.

Interactions with complement

Platelets have also been shown to interact with the complement system to enhance innate immunity. One method is through platelet activating factor, which enhances phagocytosis of complement-bound erythrocytes (RBC) by monocytes through complement receptor 1 (31). Another method is through phosphorylation of complement C3 and C3b; activated platelets promote activation of the complement system via release of protein kinases and ATP and phosphorylation of C3 and C3b (60). In addition to phosphorylation of C3b, platelets are also able to bind to C3b via P-selectin; platelet activation induces activation and propagation of the complement system via P-selectin (51). Platelets have also been shown to bind C1q and activate the classical pathway of complement (158). The interactions between platelets and the complement system are complex; platelets can activate complement and vice-versa; the interactions between platelets and the complement system remain to be fully characterized (157).

Interactions between Platelets and Leukocytes

In addition to platelets' innate ability to interact with microorganisms, complement, and endothelium; platelets also modulate inflammation through their direct interactions with leukocytes in circulation and tissue. In this review, we will discuss the molecules involved in platelet-leukocyte interactions and the prototypical functional consequences.

Mechanisms of platelet-leukocyte interactions

A variety of mechanisms has been described to participate in platelet-leukocyte interactions and can be divided into two broad categories: adhesive and soluble mechanisms. Although we will discuss these mechanisms separately, many of them work in unison to activate platelets and leukocytes. And while a multitude of mechanistic interactions have been

identified between platelets and leukocytes (1, 132, 135, 230), this review will emphasize selected interactions that have been most actively studied.

Adhesive mechanisms of platelet-leukocyte interactions—There have been several adhesive molecules described to participate in platelet-leukocyte interactions (Figs. 3 & 4) (85). We will discuss the main adhesive interactions in this section.

One adhesive mechanism involves the interaction between P-selectin on platelets to P-selectin glycoprotein ligand-1 (PSGL-1) on leukocytes. P-selectin (also known as granule membrane protein-140 (GMP-140), PADGEM protein, and CD62) is a membrane glycoprotein found in secretory granules of platelets (α-granules) (15, 136) and endothelial cells (Weibel-Palade bodies) (82) that is upregulated on the platelet surface after activation. The counter-ligand for P-selectin is PSGL-1, a homodimeric mucin composed of two ~120 kDa subunits (140) and expressed on microvilli on most leukocytes (122, 139). PSGL-1 is important for mediating neutrophil rolling on platelets and endothelial cells in the microcirculation (30, 139). When bound to P-selectin, PSGL-1 induces a signaling pathway to activate leukocytes by inducing a conformational change of the β2 integrin, Mac-1, to an active state (133, 209) as well as clustering of Mac-1 on the leukocyte surface (224). In addition to their effect on leukocyte capture and rolling, P-selectin-PSGL-1 interactions between platelets and neutrophils promote neutrophil transendothelial migration (116) independent of effects on neutrophil adhesion to endothelial cells.

Another adhesive mechanism involves the interaction between platelet glycoprotein Ibα (GPIbα; CD42b) and Mac-1 (CD11b/CD18; $\alpha_M\beta_2$ integrin). GPIbα is the α-subunit of the heterodimeric transmembrane protein GPIb located on platelets (65). It is part of the GPIb-IX-V complex and binds to von Willebrand factor for thrombus formation (138). In addition to its role in thrombosis, GPIbα has recently been described to bind to the β_2 integrin, Mac-1, on leukocytes to promote microvascular inflammation and thrombosis (210). Mac-1 is a heterodimer that consists of an alpha (CD11b; α_M) and beta subunit (CD18; β_2). It is found on moderate levels on the surface of leukocytes with preformed stores expressed on the surface after stimulation (98). Mac-1 serves as both a complement receptor to iC3b (11) as well as for firm adhesion and transmigration by binding to ICAM-1 on endothelial cells (188). In addition to GPIbα, platelets also bind to Mac-1 (as well as LFA-1) via ICAM-2 (52, 222). ICAM-2 is found on the membrane surface of resting platelets and does not change after activation. Binding of platelets to ICAM-2 may assist in leukocyte transendothelial migration (96).

Adhesive interactions between platelets and leukocytes may also be mediated by CD40L (CD154; gp39) on platelets and CD40 on leukocytes. CD40L was first described on the surface of activated T cells (5), but has also been described on platelets (83). CD40L is a member of the tumor necrosis factor (TNF) family and is the ligand for the TNR receptor, CD40. CD40 is found on a variety of cells, including B cells and endothelial cells, and the interaction between CD40 and CD40L is important in the regulation of the adaptive immunity (reviewed in (66)). CD40 has also been found on neutrophils, possibly contributing to the pro-inflammatory effects of platelets (204). However, recent data have demonstrated its importance in the formation of atherosclerosis (28) as well as of acute

inflammatory conditions, such as inflammatory bowel disease (206). In addition to its surface-bound state, CD40L is also cleaved by metalloproteinases and can be found in solution as sCD40L and able to exert its effects (108).

Depending on the molecules involved, the attachment of platelets onto leukocytes may alter the behavior of the latter; the functional consequences of these interactions are summarized in Figure 5. As described previously, P-selectin-PSGL-1 interactions lead to activation and clustering of Mac-1 on leukocytes. Neutrophils may actively scan the vasculature for activated platelets in order to promote inflammation via clustering of PSGL-1. *Ex vivo* observations in the late 1990s showed that activated neutrophils demonstrated clustering of P-selectin ligand at the uropods, resulting in polarized neutrophils with platelets bound to the uropod. (56). Similar findings were recently described *in vivo*, with evidence that neutrophil polarization in activated venules induced organization of a protruding domain that bound platelets and resulted in a PSGL-1-mediated signal transduction that drove neutrophil migration; neutrophils from platelet-depleted mice were less motile than those from untreated mice (191). Similar to observations by others, survival in acute lung injury in mice is improved after platelet depletion, suggesting their importance in propagating the proinflammatory response after injury (191, 231).

Soluble mechanisms of platelet-leukocyte interactions—In addition to the adhesive elements described above, platelets can release soluble factors that activate, modulate, or assist with capture of circulating leukocytes. A large number of the hundreds of biologically active mediators contained in platelet granules (see Table 1) are capable of inducing these effects. In this section, we will highlight a few selected examples:

Platelet factor 4 (PF4; CXCL4) is a protein belonging to the CXC-subfamily of chemokines and is released from α-granules after platelet activation. PF4 activates neutrophils by binding to the proteoglycan chondroitin sulfate on the surface of neutrophils as tetrameric PF4 (159). In isolated neutrophils, the addition of tumor necrosis factor-α (TNF-α) appears to be necessary for PF4-induced activation (160), however, TNF-α co-stimulation is not required in the presence of endothelial cells (159). This leads to enhanced neutrophil adherence to endothelial cells and secondary granule exocytosis (measured by lactoferrin release) without an increase in intracellular calcium levels or chemotaxis. A second receptor for PF4, CXCR3B, has been described, although it has been primarily described in microvascular endothelial cells and important for regulating angiogenesis (121, 203).

Fibrinogen, released from platelets and endothelial cells, is traditionally thought of as a hemostatic element. However, neutrophils are also able to adhere to bind fibrinogen via the CD11b/CD18 integrin (114), and neutrophils binding to fibrinogen is regulated in a shear stress-dependent manner (232). These studies suggest that fibrinogen-CD18 interactions may be a way for leukocytes to adhere to both platelets and endothelium at sites of vascular injury.

Neutrophil extracellular traps (NETs) have recently been described as important effectors of innate immunity. NETs are primarily composed of both nuclear (histones and DNA) and granular products (e.g. neutrophil elastase, myeloperoxidase, matrix metalloproteinases) and

are released predominantly by neutrophils, although other leukocytes are able to release them (26). Neutrophils release NETs through an NADPH oxidase-dependent mechanism, as neutrophils from patients with deficiencies in this enzyme (chronic granulomatous disease) are unable to form NETs (67). In addition to the oxidative burst, decondensation of chromatin by peptidylarginine deiminase-4 (PAD4) is required for proper NET formation (124). Once released, NETs play an important role in the capture and clearance of bacteria and fungi (155, 161, 201), but may also promote thrombosis and coagulation. Histones, as part of NETs, may be particularly thrombogenic as they have been shown to promote platelet aggregation and thrombosis (68, 117); the toll-like receptors TLR2 and TLR4 appear to mediate these effects of histones on platelets (181, 223). In addition to histones, DNA also appears to be prothrombotic (69) whereas degradation of DNA by recombinant DNAse I is protective against stroke in mice (50).

Functional consequences of platelet-leukocyte interactions

Interactions between platelets and leukocytes have been shown to contribute to a broad range of physiologic and pathologic conditions. In this review, we will highlight some prototypical examples of these interactions, resulting in both beneficial and detrimental responses.

Acute lung injury—Acute lung injury (ALI) is a potentially fatal condition in which the body is unable to oxygenate or ventilate appropriately to support the metabolic demands of the body. ALI is a consequence of a variety of different diseases, including infection, chemical pneumonitis, and trauma (110, 174). On histology, it is characterized by leukocytic infiltrates into the lung parenchyma and airspaces with edema formation. Animal studies have demonstrated that platelets contribute to the development of ALI, since depletion of platelets resulted in improved organ function and reduced leukocyte infiltration in experimental ALI (6, 231); P-selectin (231) and sCD40L (168) have been implicated in these responses. Further, platelets and their released products have been associated with the development of (blood) transfusion-related ALI (TRALI) via sCD40L (108). These effects may be through platelet-induced NET formation, as suggested by an improvement in lung injury and NET formation after the use of GPIIb/IIIa inhibitors or aspirin in experimental models of TRALI (32).

Infection—As described above, interaction of platelets with bacteria can induce neutrophils to release neutrophil extracellular traps (NET). The formation of NETs appears to be another mechanism by which the innate immunity combats infections. Recent data demonstrate that platelets, via toll-like receptor 4, promote trapping of *Escherichia coli* by neutrophils in the liver sinusoids (40). This suggests a role of platelets as an integral component of the innate immunity.

Sterile inflammation—Platelets and leukocytes are often recruited to sites of inflammation, particularly in the microcirculation, with close spatial and temporal correlation. Recruitment of platelets and leukocytes to sites of inflammation can be inter-dependent. For example, in a model of corneal abrasion, depletion of platelets reduced leukocyte recruitment while depletion of leukocytes reduced platelet recruitment (126).

Efficient recruitment of both platelets and leukocytes was necessary for effective wound healing (126). These findings exemplify a closely coordinated effort by leukocytes and platelets in response to sterile inflammation. Similarly, platelet-dependent leukocyte recruitment was shown in experimental autoimmune encephalomyelitis, a model of a demyelinating disease; recruitment of platelets and leukocytes mediate inflammation in that model (119). Platelet-leukocyte interdependence has been described in a variety of other models; these interactions have been reviewed elsewhere (175, 194).

Allergic inflammation—Platelets have been studied in the context of allergic asthma; platelets contain a number of mediators that can lead to bronchial smooth muscle hyperreactivity and mucus production, such as platelet activating factor (35) and histamine (13). Further, there are some reports that platelet factor 4 and β-thromboglobulin are increased in patients with asthma, particularly those with most airway hyperreactivity (97, 143, 200), though these data have been questioned (103, 131). In mouse models of allergic lung inflammation, platelet depletion reduced measures of lung inflammation, including eosinophil and lymphocyte recruitment (164) as well as epithelial and smooth muscle thickening (163). However, platelet depletion did not affect the degree of airway hyperresponsiveness (163). These data suggest that platelets may contribute to allergic inflammation, though much remains to be clarified about these processes.

Atherosclerosis—Atherosclerosis is a chronic inflammatory disease of the blood vessels in which platelet-leukocyte interactions play a central role, in addition to the role of platelets in thrombosis associated with atherosclerosis (reviewed in (49, 172)). The interaction between activated platelets and both circulating leukocytes as well as the vascular endothelium propagates vascular inflammation, leading to plaque formation. Several platelet-dependent mechanisms have been suggested to mediate these responses. One of the key molecules in this interaction is platelet CD40L (cell-bound and soluble). Platelet CD40L binds to endothelial CD40, inducing surface expression of a number of key adhesion molecules (E-selectin, VCAM-1, and ICAM-1) as well as cytokine release (IL-8, MCP-1). This activation of the endothelium then attracts circulating neutrophils, T-cells, and monocytes into adhering to the inflamed endothelium, leading to vascular inflammation and plaque formation (83, 127). Platelet P-selectin also plays an important role in the pathogenesis of atherosclerosis by binding to monocyte PSGL-1 to help capture monocytes, form platelet-monocyte aggregates, and to induce inflammation via a cyclooxygenase-2 (COX-2) pathway (53, 63). A variety of platelet-derived chemokines have also been suggested to participate in atherogenic responses (reviewed in (91)). These represent important pathways through which platelets promote the inflammation seen in the development of atherosclerosis; a greater understanding of these mechanisms may impact prevention and management of this common clinical entity.

Inflammatory bowel disease—The inflammatory bowel diseases (IBD; ulcerative colitis and Crohn’s disease) are a set of chronic inflammatory disorders that encompasses complex interactions between genetic, microbiotic, and environmental factors; increasing evidence supports the notion that platelets play an important role in the inflammatory responses associated with IBD. Increased blood platelet counts in humans with IBD was

shown in the 1960s (142). Subsequently, a variety of qualitative changes in platelets have been described in IBD (205), including elevated levels of platelet CD40L and a higher number of CD40L-positive platelets in inflamed intestinal mucosa, as compared to control subjects (46). In a mouse model of colonic inflammation, blockade of the CD40-CD40L pathway or deficiency of either CD40 or CD40L led to decreased inflammation and damage of the colonic mucosa in experimental colitis. Furthermore, absence of CD40 or CD40L resulted in less platelet and leukocyte adhesion to inflamed colonic venules (206). A number of platelet-derived mediators have been suggested as possible mediators of inflammatory responses in IBD (reviewed in (205)); however, the mechanisms involved remain to be clearly delineated.

Conclusion

In addition to their role in hemostasis and thrombosis, platelets are key mediators of inflammation and warrant to be recognized as immune cells. They can interact with pathogens, regulate the function of other immune cells, and mediate a broad range of physiologic processes. Interactions between platelets and other immune cells contribute to a broad range of important human diseases and may provide targets for future therapies in these conditions. Greater awareness of the role of platelets as key components of the immune system is warranted.

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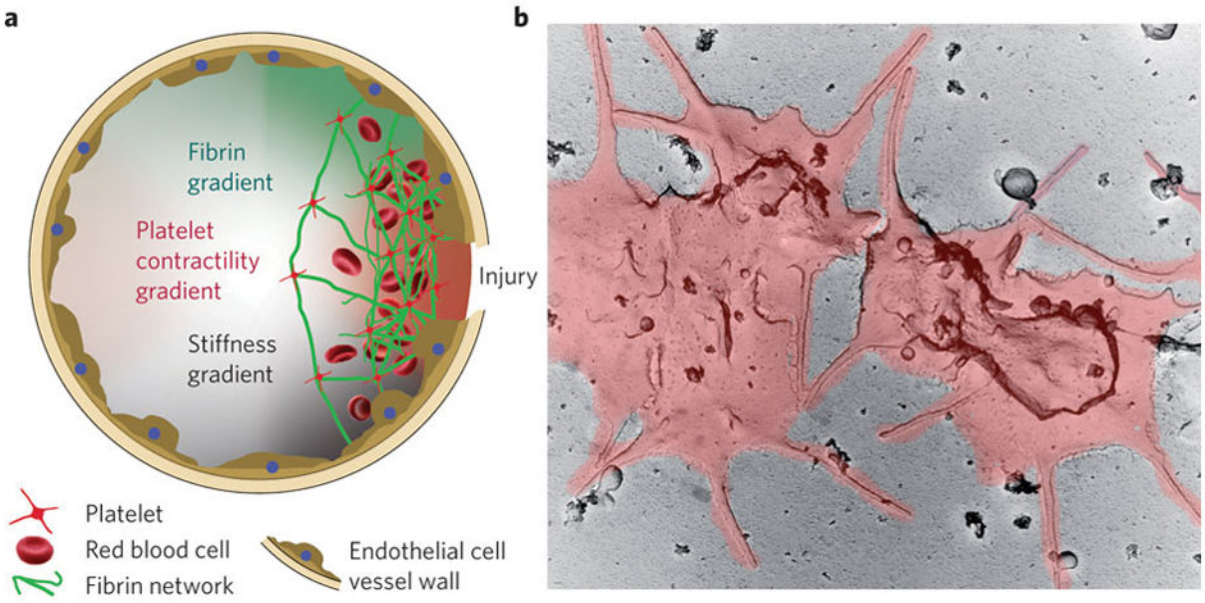

Figure 1.

(A) Platelets localize to the site of injury, binding to fibrin, and forming a hemostatic plug. (B) Electron micrograph of activated platelets, which spread out over an injured area and extend filopodia. Reprinted by permission from Macmillan Publishers Ltd: Nature Materials (59), 2010.

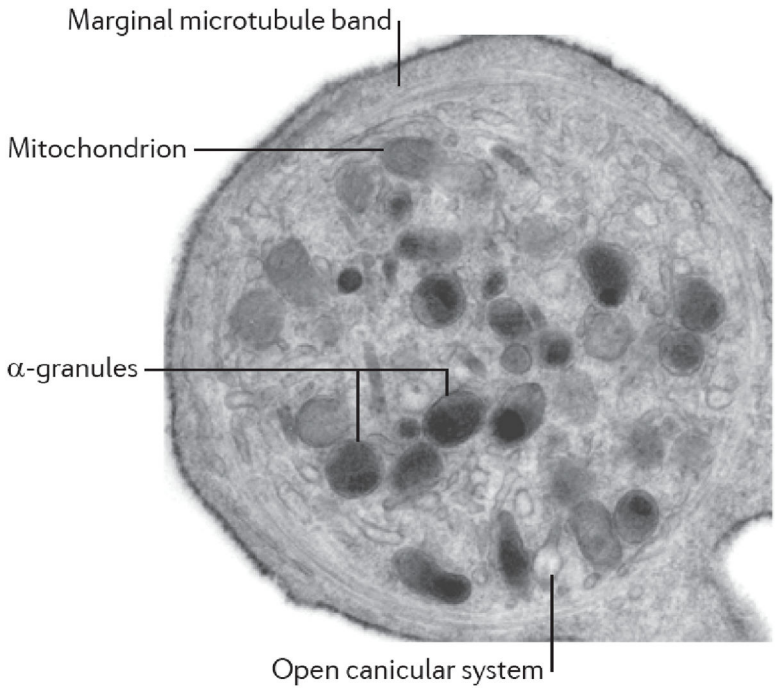

Figure 2.
Ultrastructural features of a discoid platelet showing α granules, mitochondrion, the marginal microtubule band, and open canicular system. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology (182), 2011.

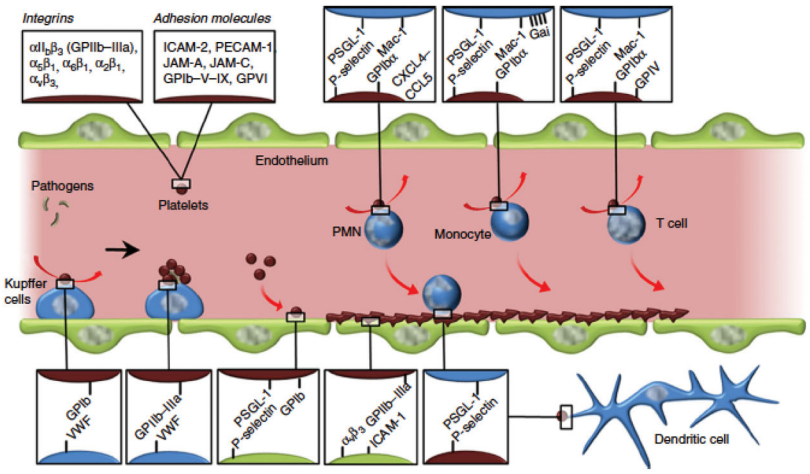

Figure 3.

Examples of adhesive interactions between platelets (red) and leukocytes (blue). Platelets contain a number of integrins and cell adhesion molecules on their surface which bind to both leukocytes and endothelial cells (green). Major cell adhesion molecule interactions include (platelet-leukocyte) P-selectin-PSGL-1 and GP1bα-Mac-1. Platelets also adhere to endothelial cells and help capture flowing leukocytes from the circulation. Reprinted from reference (85) with permission from Wiley.

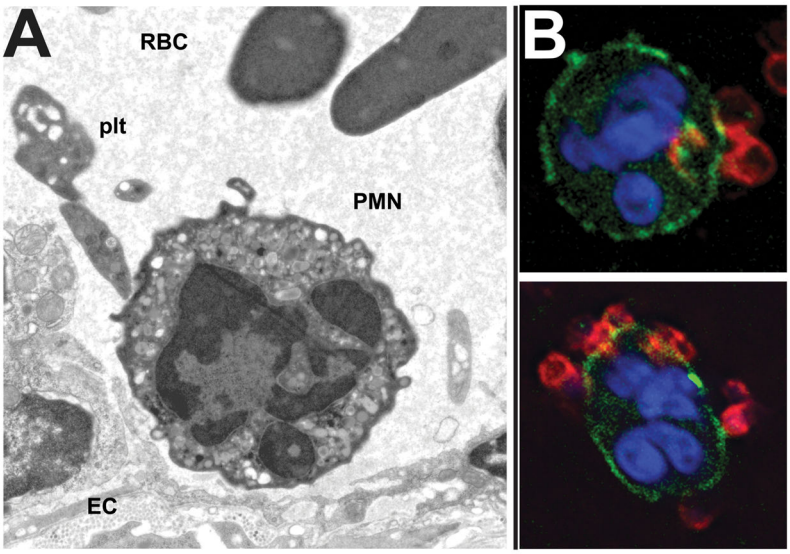

Figure 4.

Adhesive interactions between activated platelets and neutrophils. (A) EM image of an inflamed mouse cremaster venule, demonstrating platelet-neutrophil-endothelial cell interaction. Image courtesy of Dr. Alan Burns, University of Houston College of Optometry. (B) Platelet (red)-neutrophil (green/blue) interactions in suspension after platelet activation.

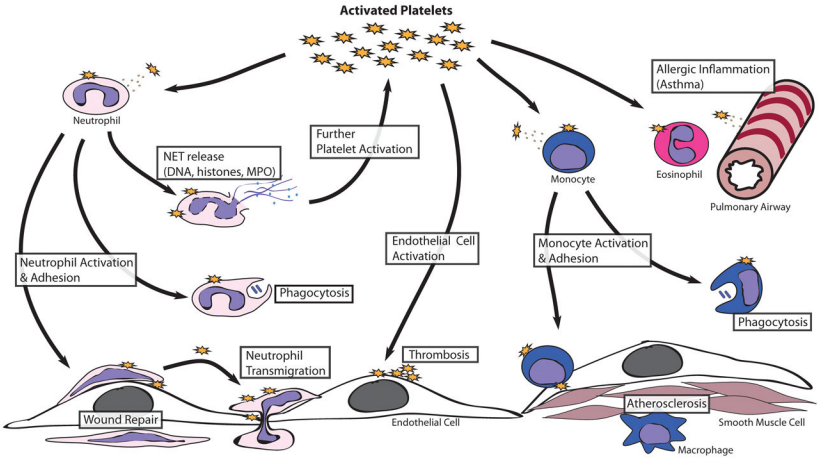

Figure 5.

Selected examples of pro-inflammatory effects of platelets resulting in functional consequences on leukocytes. Platelets interact with leukocytes through both adhesive mechanisms as well as release of cytokines/chemokines. This results in leukocyte activation and enhanced leukocyte-endothelial adhesion. Through these mechanisms, platelets participate in several normal and pathologic immune functions including microbial killing, leukocyte homing, wound healing, allergic inflammation, and atherosclerosis, among others.

Table 1

Selected examples of soluble element-mediated interactions between platelets and leukocytes

Platelet Element	Leukocyte Element	Effect (References)
sCD40L	CD40	Atherosclerosis (28) Inflammatory bowel disease (206)
Platelet factor 4	Chondroitin sulfate (neutrophils)	Activation of neutrophils (159)
	CXCR3B (microvascular endothelial cells)	Regulating angiogenesis (121, 203)
Fibrinogen	Mac-1 (neutrophils)	Neutrophil adhesion to fibrin deposits (114, 232)
TLR4	Histones (neutrophils)	Platelet activation and thrombosis (68, 117, 223)
?	DNA (neutrophils)	Thrombosis (50, 69)
RANTES (CCL5)	CCR5 (monocytes, endothelium)	Monocyte arrest on HMVEC (9) Development of atherosclerosis (77)
	CCR5 (endothelium, leukocytes)	Cerebral microvascular dysfunction and inflammation in I/R (199)
LIGHT (TNFSF14)	Herpes virus entry mediator (HVEM; neutrophils, monocytes)	Enhances phagocytosis and bactericidal activity (84)
	HVEM (endothelial cells) Lymphotoxin beta receptor (LTβR; endothelial cells)	Platelet-endothelial interactions; Levels elevated in STEMI (33)
?	Myeloperoxidase (MPO; neutrophils) Hydrogen peroxide (H_2O_2)	MPO and H_2O_2 induce platelet secretion of serotonin and adenine (39)
LPS-stimulated platelet	??? (neutrophils)	Release of neutrophil extracellular traps (40)
Platelet activating factor	CR1 (monocytes)	Enhances phagocytosis (31)