Published in final edited form as:

Platelets. 2017 March ; 28(2): 155–164. doi:10.1080/09537104.2016.1240766.

Platelet Secretion in Inflammatory and Infectious Diseases

Bhanu K. Manne¹, Shang Chun Xiang², and Matthew T. Rondina^{1,3,4}

¹The University of Utah Molecular Medicine Program, Salt Lake City, Utah

²Qinghai Medical University, Xining, China

³Department of Internal Medicine, Salt Lake City, Utah

⁴The GRECC, George E. Wahlen Salt Lake City VAMC, Salt Lake City, Utah

Abstract

Platelets are small, anucleate circulating cells that possess a dynamic repertoire of functions spanning the hemostatic, inflammatory, and immune continuum. Once thought to be merely cell fragments with responses limited primarily to acute hemostasis and vascular wall repair, platelets are now increasingly recognized as key sentinels and effector cells regulating host responses to many inflammatory and infectious cues. Platelet granules, including α -granules and dense-granules, store hundreds of factors and secrete these mediators in response to activating signals. The cargo packaged and stored within platelet granules orchestrates communication between platelets and other circulating cells, augments host defense mechanisms to invading pathogens and tumor cells, and – in some settings - drives dysregulated and injurious responses. This focused review will highlight several of the established and emerging mechanisms and roles of platelet secretion in inflammatory and infectious diseases.

Keywords

Platelet; Secretion; Inflammation; Infection

Introduction

Platelets are key effector cells for hemostatic and inflammatory responses [1, 2]. The expression of various membrane receptors on the platelet surface mediates platelet activation, adhesion, and aggregation at sites of vascular injury. Platelet activation leads to secretion of granular constituents, the resulting release of newly synthesized proteins, and discharge of membrane bound transcellular signaling molecules, such as p-selectin, to the cell surface. The granular contents secreted by activated platelets include adhesive proteins, growth factors, chemokines, and cytokines (Table 1). Most of these are stored in α -granules and some, such as serotonin, are stored in dense granules. Many of these secreted molecules

Corresponding Author: Matthew T. Rondina, MD, Associate Professor of Medicine, University of Utah Molecular Medicine Program, Eccles Institute of Human Genetics, Room 4220A, Salt Lake City, Utah 84112, (801) 585-0950 (phone), (801) 585-0701 (fax), matthew.rondina@hsc.utah.edu.

Declaration of Interest

The authors have no relevant conflicts of interest to disclose.

that orchestrate hemostasis and thrombosis also mediate platelet participation in systemic inflammatory responses. For example, canonical platelet surface receptors such as GPIb/IX/V, p-selectin, and integrin $\alpha\text{IIb}\beta_3$, which are crucial to hemostasis, are also implicated in numerous other human inflammatory diseases, including rheumatoid arthritis, inflammatory bowel disease, and sepsis [3–9]. Accumulating evidence demonstrates that platelets contribute to the initiation and propagation of both local and systemic inflammatory processes. At times, these may be regulated and augment effective host responses while in other settings, exaggerated platelet activation, adhesion, aggregation, and secretion may contribute to the injurious systemic milieu and adverse clinical outcomes. This focused review will discuss some of the pathways, mechanisms, and functional consequences of platelet secretion. In addition, we will highlight, as examples, several diseases where platelet secretion mediates physiological responses and outcomes.

Platelet Granules and Secretion

α -Granules, unique to the platelet, contain hundreds of proteins, including integral membrane proteins, pro-coagulant molecules, chemokines, mitogenic, growth and angiogenic factors, adhesion proteins, and microbicidal proteins[10–12]. α -Granules are the most abundant granule within platelets, making up about 10% of the platelet volume. There are generally between 50–80 α -granules found in mature human platelets, ranging in size from 200–500 nm[11, 13]. Proteins found within α -granules originate from both synthetic and endocytotic pathways. Intriguingly, emerging data suggests that rather than being homogenous, there may be subpopulations of α -granules within platelets[14–17].

Impairments in α -granule formation are linked to human disease conditions. For example, deficiency of α -granules causes gray platelet syndrome (GPS), a rare congenital autosomal recessive disorder characterized by abnormally large, agranular platelets and bleeding. The genetic basis of GPS was recently mapped to chromosome 3p with a loss of function mutation in neurobeachin-like 2 (*NBEAL2*). *NBEAL2* encodes a BEACH-domain containing protein predicted to regulate vesicular trafficking[18–21]. A mouse model of GPS, where *NBEAL2* is absent, recapitulates the human phenotype as *Nbeal2*^{−/−} mice have macrothrombocytopenia and a deficiency of platelet α -granules and their cargo (e.g. platelet factor 4 (PF4), von Willebrand factor (VWF), and thrombospondin-1)[18]. This murine model is also proving to be a valuable model in revealing new insights into the biogenesis of α -granules[18].

Dense granules are found in smaller numbers and are smaller in size than α -granules. Dense granules contain high levels of cations (including ionized calcium which is essential for activation of the coagulation cascade), polyphosphates, adenine nucleotides, and bioactive amines. Molecules found within dense granules include serotonin, histamine, CD63, and ADP/ATP[11]. A deficiency of dense granules is associated with Hermansky-Pudlak syndrome (HPS), a rare autosomal recessive disorder characterized by oculocutaneous albinism, bleeding, pulmonary fibrosis, and lysosomal accumulation of ceroid lipofuscin. HPS is the most common inherited platelet granule deficiency and the genes involved in HPS code for BLOC (Biogenesis of Lysosomal Organelles Complex) and AP-3 (Adaptor-Related Protein Complex-3), which are necessary for lysosomal-related organelle

formation[11]. There are 9 variants of HPS and the bleeding phenotype is common to all variants but may be least severe in HPS-3[22]. Several other inherited platelet disorder syndromes are associated with dense granule deficiencies, including Griscelli syndrome, thrombocytopenia with absent radii (TAR) syndrome, and Wiskott-Aldrich syndrome.

Granular Secretion Mechanisms in Platelets

Mechanisms of Platelet Exocytosis

Platelet granular secretion, or exocytosis, is required for normal platelet function and in health and disease. The exocytosis mechanisms of platelet α - and dense granules are similar to those used by other specialized secretory cells such as neurons and neutrophils. Platelet granule exocytosis is initiated and regulated through activation of cell surface receptors. Upon platelet activation, exocytosis of granules is initiated by the movement of granules into the plasma membrane, which then leads to granule-plasma membrane fusion and release of intracellular contents (Figure 1). The mechanisms of platelet secretion and the proteins that regulate these events have been elaborately studied using murine models and human patients and some aspects are briefly highlighted below.

SNAREs play crucial roles in platelet granule exocytosis

Platelet secretion occurs primarily through a soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-dependent mechanism[23]. SNAREs play a crucial role in the fusion of the granular and plasma membrane. t-SNAREs and v-SNAREs, which are present on different membranes (t-target and v-vesicle), can form a tight trans-complex that prompts membrane fusion to facilitate secretion[24]. The SNARE proteins are derived from syntaxins, VAMP, and SNAP-25-related genes that orchestrate granule membrane fusion to the plasma membrane or open canalicular system[25]. The precise role(s) of some of the individual proteins mediating these process remains incompletely understood; in part due to the close structural similarities and compensatory mechanisms. The discovery of naturally occurring human variants in SNAREs and the development of knockout murine models have helped us to better understand platelet granular exocytosis mechanisms. For example, VAMP-8, a vesicle-membrane SNARE (v-SNARE), is thought to be the primary regulator of platelet granule release although redundant mechanisms exist. In VAMP-8 knockout mice, platelet granular secretion is impaired with mild agonist stimulation. With stronger stimulation, secretory responses are preserved, albeit in a less efficient manner. This secondary system, which is slower, involves VAMP-2 and VAMP-3[26]. Consistent with this, thrombus formation to laser-induced injury is delayed and reduced, but not completely abrogated, in the absence of VAMP-8[27].

Syntaxin-11 (STX-11) is one of the major t-SNARE expressed in platelets plasma membrane. The significance of STX-11 in secretion was first discovered in patients with Familial Hemophagocytic Lymphohistiocytosis type 4 (FHL-4), a rare genetic disease characterized by cytotoxic T lymphocytes and NK cell dysfunction. Patients with FHL-4 have mutations in STX-11, which makes this protein functionally inactive. Platelet α - and dense granule secretion is substantially impaired in patients with FHL-4[28]. In contrast,

genetically ablating either STX-2 or STX-4 in mice did not inhibit platelet secretion, demonstrating that STX-11 is required for platelet secretion[28].

Munc and Rab proteins regulate SNARE complexes

The Sec1/Munc18 and Rab proteins regulate SNARE interactions. There are three Munc18 (mammalian uncoordinated-18) isoforms in platelets: Munc18a, Munc18b, and Munc18c. Of these three isoforms, Munc18b (also called STXBP2 or Munc18-2) is thought to be the primary isoform in platelets and necessary for platelet secretion. In humans with FHL-3, mutations occur in munc13-4 (UNC13-D). Platelets from FHL-3 patients and munc-13-4 knockout mice exhibit severe impairments in dense granule, α -granule, and lysosome exocytosis[29–31]. In patients with FHL-5, mutations occur in munc18b[32–35]. Patients with FHL-5 also have defects in platelet dense and α -granule secretion, but lysosome exocytosis appears to be only affected in FHL-5 biallelic patients[35]. These findings suggest that munc18b may be a more specific regulator of dense and α -granule secretion machinery. The Rab proteins, which may mediate vesicle docking and participate in secretory events, regulate Munc13 proteins[35–37]. As one example, Rab27b is a small GTPase that is highly expressed in platelets that, when absent, results in defects in dense granule secretion.

Calcium and PKC regulate platelet secretion by phosphorylation of SNAREs

Platelet secretion occurs upon activation by specific agonists (ADP, thrombin, collagen, thromboxane A₂, etc.) through Gq-protein-coupled receptors or other mechanisms (e.g., collagen, fucoidan, rhodocytin)[38–41]. While increases in intracellular [Ca²⁺] are sufficient to induce platelet exocytosis, phosphokinase C (PKC) also appears to act synergistically with calcium to amplify platelet secretion. PKC regulated platelet secretion acts through phosphorylation of SNARE proteins. For example, upon stimulation by thrombin, Munc18c, syntaxin 4, and SNAP-23 undergo PKC-dependent phosphorylation in platelets[33, 42]. In addition, PKC-dependent phosphorylation also mediates the binding of syntaxin 4 to SNAP-23. Recent studies have shown that SNAP-23 at serine residue (Ser95) is phosphorylated by I κ B Kinase 2 is crucial for granular secretion by regulating SNARE complex formation and membrane fusion[43]. Furthermore, Reed and colleagues also used SNAP-23 mutants (Ser²³ → Asp/Thr²⁴ → Asp), which mimic the phosphorylation at Ser23/Thr24 and block syntaxin 4 interactions with SNAP-23. This demonstrates that phosphorylation events at Ser23 also regulate SNARE-complex interactions during membrane trafficking and fusion [44]. These studies suggest that phosphorylation sites on SNARE proteins regulate platelet granular secretion.

Mechanisms of platelet endocytosis

Endocytosis is a cellular process where cells absorb molecular substances from outside the cell by engulfing it with the cell membrane. Platelets not only uptake, or endocytose, particles and solutes from the surrounding environment, but also retain and transport these substances for prolonged period of time[45]. Endocytosis is an important process in platelets and megakaryocytes for loading certain granule cargo, such as fibrinogen (Fg) and vascular endothelial growth factor (VEGF)[46–48]. While the mechanisms of platelet endocytosis remain incompletely understood, recent studies demonstrate that adenosine 5'-diphosphate–

ribosylation factor 6 (Arf6), a small guanosine triphosphate-binding protein, regulates integrin $\alpha 2\beta 3$ trafficking and fibrinogen uptake[49]. Genetic ablation of Arf6 in platelets enhanced clot retraction and spreading, indicating that endocytosis contributes to rapid platelet functions. These findings are consistent with Kanamarlapudi and colleagues who showed that Arf6 regulates P2Y trafficking in platelets as well as dynamin-dependent fission of coated vesicles during endocytosis[50]. Additionally, two Rab proteins (Rab4 and Rab11) are also involved in integrin-mediated fibrinogen uptake and trafficking in platelets[49, 51].

Platelet Secretion during Inflammatory Syndromes

Platelet secretion of granule cargo contents mediates key aspects of cellular responses within the systemic inflammatory milieu through several pathways. These pathways include translocation of proteins from within the α -granule to the platelet membrane surface as well as direct secretion of chemokines, cytokines, and signaling molecules into the systemic milieu. Platelet secretory responses orchestrate homotypic platelet-platelet aggregate formation as well as heterotypic interactions with, and adhesion to, other vascular, immune, and inflammatory cells (Table 1). Below, we will briefly review several cargo proteins secreted by platelets.

P-selectin

Platelet surface p-selectin, also known as CD62P (and previously known as PADGEM or GM-140) is a membrane protein stored within α -granules and, upon secretion, exposed at the cell surface where it mediates platelet interactions with p-selectin glycoprotein ligand (PSGL)-1 expressing cells[12, 52–54]. P-selectin is also stored within Weibel-Palade bodies in endothelial cells and thus is not absolutely specific to platelets. Through expression of p-selectin on their surface, activated platelets bind to circulating immune cells in the blood stream. In this manner, surface-adherent platelets facilitate the recruitment, rolling, and arrest of monocytes, neutrophils, and lymphocytes to the activated endothelium. Platelets also express PSGL-1 and employ this ligand to bind p-selectin on endothelial cells. P-selectin and PSGL-1 are the primary receptor-ligand pair facilitating the formation of heterotypic platelet-leukocyte aggregates (PLAs). The formation of PLAs is a very sensitive marker of *in vivo* platelet activation during human thrombotic and infectious disease[55–58]. Platelet-leukocyte aggregate formation also induces fibrin clot formation via interactions of PSGL-1 on leukocyte-derived microparticles with tissue factor on the platelet surface[59–62].

Through p-selectin, platelets have been shown to play a critical role in the recruitment of neutrophils to damaged lung capillaries. Platelet depletion, p-selectin neutralization, or selective knockout of p-selectin in the hematopoietic compartment reduces neutrophil recruitment and inhibits the development of acute lung injury[63, 64]. Adherence to platelets induces a host of pro-inflammatory responses in immune cells, including activation of pro-coagulant molecules, and promotion of cellular differentiation. These interactions may drive further platelet activation and secretion of granule contents. Below, we briefly review in more detail several cargo proteins secreted by platelets and their roles in human inflammatory and infectious diseases.

RANTES

RANTES (regulated on activation, normal T-cell expressed and secreted, also known as CCL5) contributes to the vascular inflammation associated with atherosclerosis[65, 66]. RANTES is stored in platelet α -granules and released following activation as a component of microparticles. RANTES is a key chemoattractant for eosinophils as well as triggering monocyte and T lymphocyte adhesion and transmigration[12, 67–69]. The packaging and release of RANTES within platelet-derived microparticles (PMPs) provides a mechanism whereby RANTES is transported and then deposited onto areas of injured or activated endothelium[70]. Binding of RANTES to injured endothelium enhances monocyte recruitment and activates monocyte integrins, consolidating their attachment and rolling on the endothelium and, in some settings, incorporation into atherosclerotic lesions[70–72], as further discussed below.

Platelet Factor 4

Platelet factor 4 (PF4, also known as CXCL4) was the first member of the chemokine family identified in platelets and is one of the most abundant proteins contained within platelet α -granules [73]. PF4 is released from activated platelets in a p-selectin dependent manner and exerts effects on numerous other cells. Secreted PF4 can trigger activation and adhesion of neutrophils to endothelial cells, phagocytosis and respiratory burst in monocytes, and chemotaxis of T lymphocytes [74–77]. Other secreted chemokines, including tumor necrosis factor and RANTES, may act synergistically with PF4 to signal to neutrophils and monocytes. For example, PF4 and RANTES may heterodimerize and arrest circulating monocytes on the endothelium[78].

Interleukin-1 β

Several cytokines are also secreted by activated platelets, of which IL-1 β has been the most widely studied[79, 80]. Platelets store IL-1 β in its inactive, precursor pro-IL-1 β form. Upon platelet activation, pro-IL-1 β is rapidly processed to the mature, active form of IL-1 β . Platelets then secrete active IL-1 β in both a soluble form and in association with PMPs[81]. Platelets also possess the ability to synthesis *de novo* IL-1 β from mRNA that is present basally within resting human platelets[82]. Although both forms of IL-1 β enhance endothelial cell adhesiveness for neutrophils, microparticle-associated IL-1 β is significantly more effective at promoting adhesion. While still incompletely understood, this increased adhesive potency may be due to the presence of additional pro-inflammatory factors, such as p-selectin, on microparticles. The conversion of pro-IL-1 β to IL-1 β , and subsequent release of IL-1 β from platelets, occurs in a β 3 integrin-mediated process and, as demonstrated *in vitro*, continues for several hours.

Serotonin

Serotonin, which accumulates in dense granules as platelets circulate, is secreted by platelets as a highly sensitive and specific diagnostic test for heparin-induced thrombocytopenia[83]. Plasma and platelet serotonin levels are decreased in patients with systemic lupus erythematosus (SLE), an autoimmune disorder characterized by systemic inflammation and thrombosis[84]. Serotonin secreted from the dense granules of activated platelets influences

vascular tone and promotes platelet aggregation. This secreted amino acid has also been targeted for clinical therapeutics. Sarpogrelate, an inhibitor of the 5-HT_{2A} serotonin receptor, was shown to inhibit platelet aggregation and reduce the risk of cerebral infarction. Interestingly, bleeding events in this phase III study were lower in patients receiving sarpogrelate than aspirin[85].

Platelet Secretion in Inflammatory and Infectious Human Diseases

Atherosclerosis

In atherosclerosis, activated platelets facilitate recruitment of inflammatory cells, such as leukocytes and progenitor cells, to areas of injured endothelium or at sites of acute plaque rupture (Figure 2) via secretion of cytokines and chemokines from α -granules[86]. For example, the translocation of p-selectin from α -granules to the platelet surface allows platelets to interact with and bind to PSGL-1 on endothelial cells and leukocytes[53, 87, 88]. The canonical role of p-selectin in atherosclerosis is evident in murine models utilizing Apoe^{-/-} mice, where the genetic loss of p-selectin results in smaller lesions [89]. These results suggest that p-selectin expressed upon platelet activation from α -granules is at least partly necessary for platelet-endothelial cell interactions. In murine models, atherosclerosis progression may also depend on CD40L expression by platelets[90]. P-selectin also mediates the formation of platelet-leucocyte aggregates when other chemokines, including SDF-1, RANTES, PF4 and IL-1 β , are concurrently secreted by activated platelets[91]. For example, disruption of PF4-RANTES heterodimers attenuates atherosclerotic lesions in some murine models[92]. RANTES is also deposited within atherosclerotic plaques, driving further monocyte recruitment and plaque progression.

SDF-1 (stromal cell-derived factor 1, also known as CXCL12) is also expressed within atherosclerosis lesions. SDF-1 plays an essential role in neointima formation after arterial injury in murine models[93, 94]. The mechanism involves regulation of neointimal smooth muscle content and expansion of circulating Sca-1⁺ lineage-progenitor cells. In human investigations, recent genomic studies have found an association between genetic variants in SDF and stroke[95].

PF4, a platelet specific chemokine, also localizes in atherosclerotic lesions and its expression within the lesion correlates with disease severity. Mechanistically, PF4 in the presence of TNF- α induces exocytosis and firm neutrophil interaction with endothelium there by enhancing inflammation in the lesion[75]. The secretion of PF4 and RANTES together in concert may synergistically promote atherosclerosis development and progression. Conversely antagonism of RANTES receptors significantly decreases the size of atherosclerotic lesions[96]. The effects of secreted PF4 are not limited to direct interactions with leukocytes. PF4 has also been shown to inhibit the degradation of the LDL receptor, thereby limiting lipoprotein removal with associated pro-atherogenic consequences[97]. PF4 also enhances the uptake of oxidized LDL by macrophages, which increased the foam cells in late atherosclerotic lesions[98].

Tumor Development and Progression

Platelet secretion is a critical driver of tumor biology and progression (Figure 3). Secreted α -granule contents, including vascular endothelial growth factor (VEGF) and p-selectin, stimulate endothelial migration and proliferation, a crucial step for tumor cells metastasis and survival[99]. An interesting early observation was the finding that thrombocytopenia may reduce tumor metastasis[100, 101]. While the exact mechanisms remain only partially understood, tumor cells aggregate and activate platelets - a process which is known as tumor cell-induced platelet aggregation (TCIPA)[102]. TCIPA is correlated with both thrombosis caused by tumor cells and also to the tumor cells' metastatic potential[103]. Published studies demonstrate that platelets protect metastatic tumor cells from destruction by immune cells, as they travel in the blood circulation, and help tumor cells to attach to endothelium at metastatic sites[104–106]. Platelet and endothelial cell adhesion proteins may also transport tumor cells from blood circulation to distant sites of metastasis[107]. The mechanism may be at least partly p-selectin mediated as mice lacking p-selectin have reduced tumor metastasis.

In addition, when platelets come in contact with cancer cells they secrete transforming growth factor β (TGF- β), a potent immunoregulatory molecule which also promotes extravasation of colon and breast cancer cells[108]. The amount of TGF- β stored in α -granules appears to have a regulatory effect on systemic levels of TGF- β in the circulation[109]. Transforming growth factor- β from platelets also diminishes NK granule mobilization, cytotoxicity and interferon- γ secretion[110], key host defense mechanisms critical for detection and clearance of tumor cells. Other soluble mediators, including prostaglandin E2 (PGE2), may have similar activity. The ability of platelets to form heterotypic aggregates with tumor cells may also play a pivotal part in determining tumor cell survival within the microvasculature of affected organs and of tumor metastasis.

Platelet Secretion during Infectious Syndromes

In response to infectious cues, platelets secrete many factors, which activate classical immune cells (Table 1). In addition, platelets also secrete molecules that have direct antimicrobial properties[111]. For example, in experimental models and human studies of acute infectious settings, platelets circulate with increased surface expression of p-selection. Increased p-selectin, translocated from α -granules to the platelet surface, promotes the formation of circulating platelet-leukocyte aggregates and may contribute to adverse outcomes in septic syndromes[56, 57, 112, 113]. Platelet surface p-selectin (as well as endothelial cell p-selectin) mediate host responses to *Klebsiella pneumoniae* sepsis as mice deficient in p-selectin had increased bacterial loads within the pulmonary system, the blood, and organs[114]. P-selectin deficiency was also associated with decreased platelet-monocyte aggregates and, interestingly, increased cytokine release suggesting that p-selectin may attenuate injurious cytokine production and/or secretion during septic syndromes. P-selectin also serves as a trafficking molecule directing neutrophils to the lung during septic conditions[64, 115].

Platelet factor 4 (PF4) and CD40L, two key α -granule cargo proteins secreted upon activation, mediate key aspects of host responses to HIV infection. PF4 is able to bind the

HIV-1 envelop protein, inhibiting the attachment of HIV-1 virus to the cell surface in a concentration-dependent effect[116, 117]. The inhibitory activity of PF4 identifies that platelet secretion augments defense mechanisms to HIV-1 and may extend to other pathogens. In contrast, soluble CD40L, which is increased during HIV-1 infection[118], impairs dendritic cell function and contributes to immune dysfunction in an IL-12 dependent mechanism[119].

Intriguingly, emerging studies suggest that platelets may be immune effector cells during malaria infection. Malaria is a mosquito-borne infectious disease that is widespread in tropical and subtropical regions. Thrombocytopenia commonly occurs in patients with malaria and correlates with adverse outcomes, particularly in settings where plasmodium falciparum is the causative strain[120, 121]. Recent evidence suggests that the primary platelet secretion component responsible for cytotoxic action during malaria infections is PF4[122, 123]. PF4 is released in large quantities by activated platelets when they come in contact with the parasite-infected red blood cells (Figure 4). A recent study has shown that PF4 is internalized by parasite, which then lyses the parasite organ called the digestive vesicle (DV)[124, 125]. Platelet PF4 has also been shown to mediate inflammatory responses in cerebral malaria[126]. PF4 secreted from platelets also orchestrates leucocyte cerebral vascular trafficking in murine models of malaria. Interestingly, in human patients with cerebral malaria, PF4 may be a useful predictive biomarker.

Conclusions and Perspectives for Future Research

Platelets are dynamic effector cells with large granule cargo components that, upon activation, secrete numerous molecules with diverse and dynamic functions. Platelet secretion is integral to normal hemostatic, signaling, and immune activities in the host. Dysregulated or exaggerated secretion of platelet granule contents mediates key aspects driving physiologic and pathophysiologic responses during thrombotic, inflammatory, and infectious human diseases.

While our understanding of platelet secretion has substantially advanced, many knowledge gaps remain. These represent areas where future research may be directed. For example, continued investigation into the basic mechanisms regulating endocytosis is likely to reveal new regulated mechanisms whereby platelets engulf proteins, pathogens, and other molecules from the extracellular milieu. Endocytosis of bacterial and viral pathogens by platelets may uncover insights into the fate of these pathogens and whether platelets uptake of these infectious agents is a host defense mechanism or, as recently demonstrated for dengue, a mechanism for pathogen replication. These studies may also elucidate pathways by which endocytosis regulates key platelet functional responses, such as outside-in-signaling, secretion, and aggregation.

Substantial progress has been made in understanding the mechanisms of platelet secretion. As our knowledge of how platelet secretion influences human inflammatory and thrombotic diseases expands, therapeutic targets may be uncovered. Repurposing or developing agents directed against injurious molecules secreted by platelets, while a difficult challenge, may improve human health.

Acknowledgments

We thank Ms. Diana Lim for her creativity with the excellent figure preparations and Ms. Kendra Richardson for her outstanding editorial assistance. This work was supported by the NIA (AG048022 to M.T.R.), the NHLBI (HL126547, and HL112311 to M.T.R.), the Chinese Foreign Ministry (S.C.X.), and the George E. Wahlen VA GRECC (M.T.R.).

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Figure 1.

Schematic representation of platelet secretion or exocytosis. Upon activating signals, granules fuse to the plasma membrane with the chaperone proteins Rab27a and Munc13-4. Vesicle and plasma membrane fusion is regulated through SNARE proteins (VAMP-8, SNAP-23 and STX-11).

Figure 2.

Platelet secretion in atherosclerosis. Activated platelets roll along the endothelial monolayer via GPIb α /P-selectin. Thereafter, platelets adhere to vascular endothelium via β 3 integrins, release proinflammatory compounds (IL-1 β , CD40L, PF4 and RANTES), and induce expression of chemotaxins and adhesion molecules on endothelial cells, which help recruit circulating leukocytes. These leukocytes transmigration and form foam cells through the uptake of LDL. In this and other mechanisms, platelets provide the inflammatory basis for plaque formation and subsequent thrombosis upon plaque rupture.

Figure 3.

Platelet secretion mediates tumorigenesis. Activated platelets bind to invading tumor cells, secreting growth factors, chemokines, proteases, and microparticles. In some instances, these secreted factors may augment host defense mechanisms to halt tumor invasion while in other settings, these factor may result in injurious tumor cell transendothelial migration.

Figure 4.

Platelet secretion: an innate immune response to malaria. The CD36 receptor on platelets recognizes malaria-infected erythrocytes and secretes platelet factor 4 (PF4), which is basally present in α -granules of resting platelets. PF4 secreted from α -granules of activated platelets lyse the parasite digestive vesicles by killing the parasite within.

Table 1

Factors Secreted by Platelets. This list is not comprehensive and multiple platelet secreted factors have been identified. This table is modified from [127].

Functional Class	Secreted Factor(s)	Target Cells
Adhesion and Signaling Molecule	P-Selectin	PMNs, monocytes, lymphocytes
ITIM-Containing Immunoreceptor	Triggering receptor expressed on myeloid cells – like transcript-1 (TLT-1)	Platelets
Inflammatory modulators	Histamine	ECs, monocytes, PMNs, NK cells, T and B cells, eosinophils
	Serotonin (5-HT)	Monocytes, macrophages, DC
Inflammatory Lipids	TXA ₂	Platelets, T-lymphocyte and macrophage subsets
	PAF	Platelets, PMNs, monocytes, macrophage and lymphocyte subsets
Adaptive immune modulator	CD40L (CD154)	B cells, T lymphocytes, EC, monocytes, DC subtypes, epithelial cells
Growth factors	PDGF	Monocytes, macrophages, T lymphocytes
	TGF- β	Monocytes, macrophages, T and B lymphocytes
Chemokines	PF4 (CXCL4)	PMNs, monocytes, macrophages
	NAP2 (CXCL7)	PMNs
	GRO- α (CXCL1)	PMNs
	ENA-78 (CXCL5)	PMNs
	SDF-1 (CXCL12)	Bone marrow-derived progenitor cells
	RANTES (CCL5)	Monocytes, eosinophils, basophils, NK cells, T-lymphocyte and DC subsets
	MIP-1 α (CCL3)	Monocytes, eosinophils, basophils, NK cells, lymphocyte and DC subsets
	MCP-3 (CCL7)	Monocytes, basophils, NK cells lymphocyte and DC subsets
Cytokines	IL-1 β and IL-1 α	Monocytes, DC and macrophage subsets, T-cell lines, EC, vascular smooth muscle cells, synoviocytes
	MIF	Monocytes, Macrophages
	HMBG1	Macrophages, PMNs, ECs
	GM-CSF	Eosinophils
Antimicrobial peptides	Platelet microbicidal proteins	Microbicidal for several bacteria and fungi
	β -defensin 1	PMNs (NET formation)