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Chapter 3

Role of Platelets in Inflammation

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Additional information is available at the end of the chapter

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1. Introduction

1. 1. Inflammation

Inflammation is a complex of responses of the innate immune system to pathological stimuli such as microbes, pathogens or damage-associated molecular patterns (DAMPs). Local inflammation includes the following classical symptoms: *dolor* (pain), *calor* (heat), *rubor* (redness), *tumor* (swelling) and *functio laesa* (loss of function). Systemic inflammation occurs in different contexts like massive trauma, chronic disease, or as a response to an infection, in which case it is designated as sepsis. Clinical responses during systemic inflammation (systemic inflammatory response syndrome, SIRS) include altered body temperature, elevated pulse rate, elevated respiratory rate, abnormal white blood cell count and other symptoms. [1] The inflammatory response includes (but is not limited to) recruitment of immune cells, such as neutrophils and monocytes, by the vessel wall, followed by their extravasation to tissues. Although inflammation involves multiple mechanisms beyond this process (e. g. , involving complement and kinin systems as well as changes in vascular tonus), we will concentrate herein on the platelet role in vascular endothelial activation and interactions with leukocytes, with a special focus on *in vivo* data.

2. Platelet-derived mediators regulating inflammation

Platelets have multiple roles beyond hemostasis and thrombosis and were described as inflammatory cells several decades ago. [2] Platelets contain a number of inflammatory peptide and protein mediators, some of which they retain the capability of synthesizing *de novo*, whereas others are stored and secreted from granules (dense granules, α-granules or lyso-

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somes). [3] The release of these cytokines and chemokines, as well as eicosanoids, upon activation enables platelets to recruit leukocytes to the site of inflammation or injury. The table below lists some of the platelet-derived inflammatory mediators:

Molecule	Family	Location
IL-1β	Cytokine	Synthesized
Thromboxane A2	Eicosanoid	Synthesized
PF4/CXCL4	Chemokine	α- granules
β-thromboglobulin (CXCL7/ NAP-2)	Chemokine	α- granules
RANTES (CCL5)	Chemokine	α- granules
CD40L	Cytokine	α- granules
PDGF	Growth factor	α- granules
TGF-β	Growth factor	α- granules
TNF-α	Cytokine	α- granules
IL-1α	Cytokine	α- granules
GRO-α (CXCL1)	Cytokine	α- granules
ENA-78 (CXCL5)	Cytokine	α- granules
SDF-1 (CXCL12)	Cytokine	α- granules
MIP-1α (CCL3)	Chemokine	α- granules
MCP-3 (CCL7)	Chemokine	α- granules
NAP-2 (CXCL7)	Chemokine	α- granules
TARC (CCL17)	Chemokine	α- granules
Interleukin-8 (CXCL8)	Chemokine	α- granules
Polyphosphates	Phosphates	Dense granules
ATP	Nucleotide	Dense granules
Serotonin	Monoamine	Dense granules
Glutamate	Amino Acid	Dense granules

Table 1. Inflammatory mediators synthesized by and stored in platelets

Platelet α-granules contain large proteins, many of which are involved in regulation of the inflammatory response. [4, 5] Among them, Platelet Factor 4 (PF4) is the most abundant protein secreted by activated platelets (accounting for ~25% of α-granule content). [6] It functions as a chemoattractant for monocytes. PF4 accelerates atherogenesis by causing vascular inflammation and promoting retention of lipoproteins in the vascular wall, which contributes to atherosclerosis. PF4 prevents full interaction of LDL with its receptor, causing lipoproteins to be retained on the cell surface rather than being catabolized. [7]

Platelet-originating thromboxane A2 (TxA2), which is made *de novo* from arachidonic acid upon activation, induces platelet activation and aggregation. [8] This may form a positive feedback loop facilitating further release of stored cytokines.

Platelet-derived IL-1α has been shown to mediate cerebral inflammation *in vivo*. [9] IL-1α secreted from platelets promotes expression of the adhesion molecules ICAM-1 and VCAM-1 on endothelial cells. It also accelerates transendothelial migration of neutrophils and contributes to chronic inflammatory diseases, such as multiple sclerosis. [9] Platelet IL-1α and IL-1β have proinflammatory roles in rheumatoid arthritis; it has been shown that platelet depletion attenuates the disease in mice. [10]

Besides storage, platelets can also synthesize biologically active proteins. For example, thrombin activation results in synthesis of pro-IL-1β. [11] Interestingly, synthesis of pro-IL-1β was inhibited by neutralization of the beta-3 integrin, which implies that direct anti-platelet therapy could have an anti-inflammatory effect. Platelets contain the splicing machinery allowing for cytokine mRNA maturation. [12] IL-1β potentiates its own synthesis in platelets by an autocrine loop, and its production by activated platelets occurs *in vivo*, where it accumulates in thrombus in the ferric chloride-treated carotid artery. [13] This represents a link connecting sterile thrombotic process with formation of proinflammatory milieu. IL-1β from platelets causes both up-regulation of endothelial adhesion receptors and release of proinflammatory IL-6 and IL-8 from endothelial cells. IL-1β is also responsible for activation of NF-κB in endothelial cells, which is required for transcription of inflammatory genes MCP-1 and ICAM-1. [7]

Platelet derived growth factor (PDGF) is able to chemoattract monocytes and eosinophils. [4] The chemokine RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted) recruits monocytes to the inflamed endothelium in a P-selectin-dependent fashion. [14] RANTES plays a role in many inflammatory disorders including asthma, atherosclerosis and delayed-type hypersensitivity reactions. [15]

Among other platelet-derived chemokines, Macrophage Inflammatory Protein (MIP)-1α induces leukocyte chemotaxis *in vivo*. [8, 16] MIP-1α is a chemoattractant for monocytes, macrophages, T-cells and neutrophils and is involved in transendothelial migration at sites of inflammation. [17] MIP-1α is required for a normal inflammatory response to certain types of viruses. MIP-1α-null mice develop a reduced inflammatory response to influenza virus and coxsackievirus-induced myocarditis. [17]

Platelets store large amounts of the pro-inflammatory molecule CD40 ligand (CD40L). Interaction of CD40L with CD40 on endothelial cells and macrophages causes release of IL-8 and MCP-1, which attract neutrophils and monocytes. [18] Similarly to IL-1β, CD40L induces adhesion receptor expression on endothelium and release of chemokines thus mediating leukocyte recruitment.

Platelets contain Polyphosphate (polyP) in their dense granules. [19] Proinflammatory and procoagulant functions of polyP have recently been demonstrated. [20] PolyP, released upon platelet stimulation, binds to factor XII activating the FXII-driven contact activation system. The resulting release of the inflammatory mediator bradykinin culminates in the accumulation

of neutrophils and increased vascular permeability through binding its receptor BR2. Targeting polyP, for example, with phosphatases may be of potential therapeutic benefit for treating such diseases as rheumatoid arthritis and atherosclerosis. [20] However, the role of polyP in activating the contact phase system has recently been questioned. [21]

Thus, platelets store and release a substantial repertoire of inflammatory mediators. These molecules may contribute to multiple inflammation-related diseases, which make platelets important players in the field of inflammation.

3. Platelet-endothelium interactions

Under physiological (non-inflammatory) conditions, production of platelet inhibitors (such as prostacyclin and nitric oxide) by endothelial cells limits platelet interaction with intact endothelium. Adhesion of activated platelets to intact Human Umbilical Vein Endothelial Cells (HUVEC) was demonstrated *in vitro*. [22] Mechanisms of this involved $\alpha_{IIb}\beta_3$ integrin (glycoprotein (GP) IIb/IIIa) on platelets, ICAM-1 and $\alpha_v\beta_3$ integrin on the endothelium and von Willebrand Factor (VWF), fibrinogen and fibronectin as bridging molecules. Platelet GPIbα, which is constitutively expressed and does not require activation, was reported to be a receptor to endothelial P-selectin. [23] There is a report demonstrating that platelets contain P-selectin glycoprotein ligand (PSGL)-1 (although 25-100-fold fewer than leukocytes). [24] Blocking PSGL-1 down-regulates the number of rolling and captured platelets on stimulated venule endothelium suggesting that this route can also be implicated in platelet-vessel wall interaction under inflammatory conditions. Integrin $\alpha_v\beta_3$, a vitronectin receptor on the endothelial cells, was shown to participate in platelet recruitment to stimulated endothelium. [25]

In vivo, platelets do not spontaneously interact with intact endothelium in murine mesenteric venules. [26] Stimulation of murine vessels with Weibel-Palade body secretagogues calcium ionophore or histamine results in rapid platelet adhesion followed by rolling, peaking 1 min after stimulation. This "stop-and-go" platelet translocation on stimulated endothelium was absent in VWF-null mice. Cleavage of GPIbα from platelet surface also prevented platelet binding to the vessel wall. Therefore, interaction of platelets with activated endothelium *in vivo* is mediated by binding of platelet GPIbα to endothelium-expressed VWF. [26]

Another pathway of platelet binding to the vascular wall involves the glycoprotein VI (GPVI), a major platelet receptor for collagen. This route is most important in platelet interactions with atherosclerotic plaques. Inhibition of GPVI by infusion of GPVI-Fc, a dimeric soluble form of GPVI fused with human Fc fragment, to ApoE$^{-/-}$ mice decreased transient platelet interactions with atherosclerotic artery wall by about half. [27] Long-term administration of a GPVI-blocking antibody also improved endothelial function and prevented propagation of atherosclerosis. [27] GPVI binds activated endothelium through vitronectin and improves cardiac function in a mouse model of heart ischemia-reperfusion by reducing inflammation in the infarcted myocardium. [28] Infusion of soluble GPVI-Fc in either ischemia or reperfusion phase substantially decreased infarct size.

In a model of cerebral ischemia-reperfusion, platelet tumbling on and adhesion to the brain vascular endothelium has been demonstrated. [29] This was specific to veins and no platelet-vessel wall interactions were observed in arteries of different diameter. This interaction was almost entirely dependent on P-selectin as administration of anti-P-selectin antibody abolished it. Neutralization of $\alpha_{IIb}\beta_3$ had certain inhibitory effect too, though less manifested than blocking P-selectin. Rolling and adhesion of platelets was reported also during reperfusion period after retinal ischemia. This process was dependent on endothelial P-selectin, and the time course of P-selectin *de novo* synthesis in the endothelium corresponded to the kinetics of platelet-endothelial interactions. [30]

Platelet adhesion to endothelium of atherosclerotic plaques can also be mediated by the glycoprotein α_{IIb}. [31] Platelet adhesion to the atherosclerotic plaque in apoE$^{-/-}$ α_{IIb}-double deficient mice was virtually abolished as compared with apoE$^{-/-}$ $\alpha_{IIb}^{+/+}$ controls. Formation of atherosclerotic lesions was reduced in the absence of α_{IIb}. Platelet-vessel wall interactions through α_{IIb} are also implicated in the pathogenesis of such thromboinflammatory disease as ischemic stroke as shown in a model of cerebral ischemia-reperfusion in mice. The exact mechanism of α_{IIb} involvement in interactions with inflamed but non-denuded endothelium remains to be clarified. It is known that ischemia promotes fibrinogen deposition on the vessel wall, which leads to platelets recruitment. [32] Local hypoxia and pro-inflammatory shift (like generation of reactive oxygen species (ROS)) result in VWF expression on the endothelium mediating platelet accrual. [33, 34] Thus, two major ligands for $\alpha_{IIb}\beta_3$, fibrinogen and VWF, can appear on the endothelial surface during inflammation and recruit platelets via this integrin.

Platelet accumulation in lung and cerebral vasculature was described in a murine model of malaria[35] as well as in patients. [36] Platelets might damage endothelium and support leukocyte accumulation in the brain vessels thus promoting cerebral inflammation as a part of malaria pathogenesis. [37] Platelet depletion protects mice from disease progression. [38] The role of platelets in malaria may be complex depending on the stage of the disease: platelets could attenuate parasite growth at the early stages whereas at later stages platelets support disease-related inflammation. [39]

Activated platelets can be found in circulation in patients with various inflammatory diseases, such as sepsis, cerebrovascular ischemia and diabetes. [40-42] Besides posing a danger for excessive thrombosis, circulating activated platelets confer a proinflammatory signal. Activated platelets infused into mice stimulate release of Weibel-Palade body constituents and form complexes with leukocytes, leading to elevated recruitment of leukocytes to the vessel wall. [43] Thrombin-activated platelets accumulate at the atherosclerotic carotid artery wall. This process is dramatically inhibited when platelets lack CD40L. [44]

Interaction of platelets with endothelium mediates accumulation of monocytes and deposition of proinflammatory cytokines (e.g. , RANTES) at the vessel wall (Figure 1). It was directly demonstrated in mice using repeated infusions of activated platelets or bone marrow transplantation techniques, that platelets promote the development of larger atherosclerotic plaques. [45, 46] This effect is predominantly mediated by platelet P-selectin.

Thus, platelets bind to the activated/inflamed vascular wall by a set of receptors including P-selectin, glycoproteins Ibα, α_{IIb} and VI as well as CD40L. Activated platelets are able to induce

a pro-inflammatory shift in the endothelium. Platelet-mediated endothelial activation plays a role in the development of various diseases that have an inflammatory component in their pathogenesis.

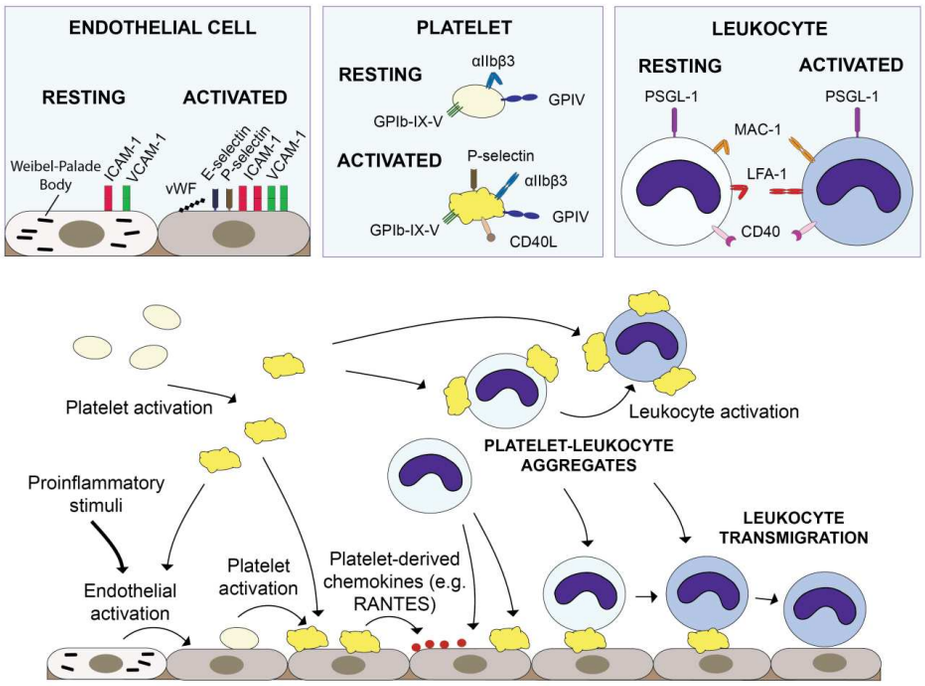


Figure 1. Platelet cross-talk with endothelium and leukocytes.

4. Platelet-leukocyte interactions

Under physiological conditions, platelets and leukocytes do not bind to each other. Such interaction becomes possible in prothrombotic or proinflammatory state with increased number of blood platelet-leukocyte aggregates (PLA) (Figure 1) observed in such diseases as diabetes mellitus, stroke and others. [47-49]

Binding of platelets to leukocytes can mediate recruitment of the latter to the vessel wall and render leukocytes more prothrombotic promoting synthesis of tissue factor by monocytes. [50] This interaction starts by binding of P-selectin on activated platelets to PSGL-1 on leukocytes initiating a signaling cascade inside leukocytes, which leads to activation of integrins, in particular, Mac-1 and LFA-1 on leukocyte membrane. [51-53] Mac1 can bind platelet receptor GPIbα directly or $\alpha_{IIb}\beta_3$ through fibrinogen bound to the integrin on platelets. [54, 55] Platelet-leukocyte binding is an active process as pre-activation of leukocytes potentiates this interaction whereas tyrosine kinase inhibitors down-regulate it. Full activation of the integrins triggers outside-in signaling regulating multiple leukocyte functions such as transmigration, production of ROS and phagocytosis. [56] Platelet-mediated activation of Mac-1 can lead to sequestration and activation of coagulation Factor X resulting in thrombin generation. [57]

This phenomenon suggests that platelet-leukocyte interaction triggers also the coagulation cascade.

In vivo, interactions between platelets and leukocytes occur in various thrombo-inflammatory conditions. For example, blood stasis in the carotid artery induces P-selectin-dependent accumulation of leukocytes surrounded by platelets in the vicinity of the vessel wall. [58] Platelet depletion almost completely abrogates leukocyte recruitment suggesting that development of the inflammatory response in this model is platelet-dependent. Platelet P-selectin is implicated in recruiting leukocytes not only to the inflammation site but also in pure thrombosis. Thrombi in ferric chloride-challenged carotid arteries of P-selectin-deficient mice contained less leukocytes than in control animals. [59] This confirms the central role of P-selectin in platelet interactions with leukocytes.

Formation of platelet-leukocyte rosettes *in vivo* depends on platelet activation. It has been reported that plasma level of circulating PLA more specifically reflects platelet activation than platelet P-selectin expression. [60] Resting platelets infused into mice do not associate with leukocytes. [61] Intravenous injection of collagen together with $\alpha_{IIb}\beta_3$ antagonist to prevent formation of platelet aggregates, results in rapid development of platelet-leukocyte conjugates. These conjugates roll on the vascular wall both in C57BL/6 and aged ApoE-deficient mice prone to atherosclerosis. In both cases, this rolling was mediated by P-selectin. Binding of activated platelets to leukocytes supported leukocyte recruitment by the endothelium through VCAM-1, and elevated leukocyte interactions with vessel wall in inflammation and atherosclerosis. [45] Infusion of activated P-selectin positive but not P-selectin deficient platelets elevated monocyte binding to atherosclerotic endothelium in mice. Formation of PLA resulted in deposition of chemokines, such as RANTES and PF4, on the endothelium thus supporting development of atherosclerosis. Besides leukocytes, activated platelets mediate lymphocyte homing in peripheral lymph nodes. [62] Again, all these phenomena were dependent on platelet surface P-selectin.

Cell activation in leukocyte-platelet interaction is bi-directional, i. e. , not only platelets activate leukocytes but also vice versa. [56] In particular, various leukocyte-derived molecules can activate platelets and promote platelet-mediated fibrin deposition. Activated platelets stimulate neutrophils to release their chromatin designated as Neutrophil Extracellular Traps (NETs), [63] at least in part by presenting High Mobility Group Box 1 (HMGB1). [64] NETs can recruit and activate platelets. [65] Histones, an integral part of NETs, directly activate platelets and induce platelet aggregation. [66]

In conclusion, platelets interact with both endothelium and leukocytes mediating accumulation of the latter at the inflammatory site, thus supporting the central step in the inflammatory response.

5. Platelet Toll-like receptors

Toll-like receptors (TLRs) are a family of innate immunity pattern-recognition receptors that trigger inflammation in response to microbial products or products of inflamed tissues. TLRs

function as front-line sensors of infection, as they recognize conserved structures in pathogens designated as pathogen-associated molecular patterns (PAMPs). [67] TLRs can also sense DAMPs, released by activated or necrotic host cells and upregulated following tissue damage. [68] Human and murine platelets express TLR2, TLR4, TLR7 and TLR9. [69-76] TLR6 has been detected in human platelets. [69] Expression of TLR1 has been reported in one[69] but not in another[77] study.

Platelet TLR2. Pam3CSK4, a synthetic agonist of the TLR2/1 complex, triggers platelet activation including integrin $\alpha_{IIb}\beta_3$ transition to an active state, aggregation, alpha- and dense granule release and CD40L expression. [78-80] These responses are inhibited in TLR2-deficient murine platelets and in human platelets by pretreatment with TLR2-blocking antibody. [79] Pam3CSK4 also triggers formation of platelet–neutrophil aggregates (PNA). [79, 80]

In periodontitis, a chronic inflammatory disease of the supportive dental tissues, the gram-negative periodontopathogens directly induce TLR2- and TLR4-dependent surface expression of CD40L in human platelets. [81] *In vivo* challenge with live *Porphyromonas gingivalis* induced formation of PNA in wild-type but not TLR2-deficient mice. [79] *Ex vivo* experiments showed that platelet TLR2 mediated formation of PNA and enhanced phagocytosis of periodontopathogens. [81]

Human cytomegalovirus (HCMV), a widespread pathogen that correlates with various diseases including atherosclerosis, binds TLR2-positive platelet subpopulation. This results in platelet degranulation, release of proinflammatory CD40L and IL-1β and proangiogenic vascular endothelial–derived growth factor (VEGF). Murine CMV activates wild-type but not TLR2-deficient mouse platelets. HCMV-activated platelets bind to and activate neutrophils, supporting their adhesion and transmigration through endothelial monolayers. [82] In an *in vivo* model, CMV increased the number of PLA and plasma VEGF levels and demonstrated a trend to enhance neutrophil extravasation in a TLR2-dependent fashion. [82]

Platelet TLR4. Platelet activation with thrombin causes increase of TLR4 surface expression in one [83] but not another [72] study. Lipopolysaccharide (LPS), a cell wall component of gram-negative bacteria, is a natural ligand for TLR4. *In vitro*, some studies have reported no [77, 84] or even inhibitory effect[85] of LPS on platelet aggregation whereas others have shown that LPS can potentiate platelet aggregation induced by low doses of other agonists. [86, 87] *In vivo,* intravenous injection of LPS in mice induces formation of platelet aggregates mainly in lung and liver microvasculature. [88, 89] Platelet TLR4 mediated microvascular LPS-induced thrombosis in murine cremaster muscle venules. [84, 90]

LPS present on platelets and leukocytes from patients with hemolytic uremic syndrome (HUS) caused PLA formation. [91] LPS binds human platelets through a complex of TLR4 and CD62, leading to platelet activation. The specificity of LPS binding to platelet TLR4 was confirmed *in vivo* using TLR4 deficient mice. [92]

Platelet TLR4 contributes to LPS-induced thrombocytopenia *in vivo*. [71, 72] In one study, LPS induced thrombocytopenia in wild-type but not TLR4-deficient mice. [71] TLR4-positive but not TLR4-negative platelets accumulated in the murine lungs in response to LPS in a neutrophil-dependent fashion. In another study, LPS produced thrombocytopenia and increased

serum levels of TNFα in LPS-sensitive mice but not in mice carrying mutated TLR4. [72] LPS-induced TNFα production in LPS-sensitive mice was reduced by platelet depletion and could be restored by platelet transfusion. [72]

In mouse endotoxemia, TLR4-positive but not TLR4-negative platelets accumulate in the lungs. [71] LPS induces platelet binding to sequestered neutrophils primarily in the liver sinusoids and pulmonary capillaries leading to formation of NETs, [93] which are able to trap and kill microbes. [63]

Platelet TLR7. A recent study showed that platelet TLR7 mediates platelet activation in response to the single stranded RNA encephalomyocarditis virus (EMCV). [74] This interaction led to platelet granule release, P-selectin surface expression, and increase in PNA, both in mouse and human blood, but did not induce platelet aggregation. There were, however, implications to the host immune response and survival. TLR7 expressed on platelets is implicated in protection against EMCV-induced mortality. Transfusion of TLR7-positive platelets into TLR7-null mice prolonged survival after infection with EMCV whereas transfusion of platelets lacking TLR7 into wild-type mice did not affect the survival rate. [74]

Platelet TLR9. In platelets, TLR9 is located in intracellular compartments. [75] TLR9 responds to carboxy(alkylpyrrole) protein adducts, an altered-self ligand generated in oxidative stress, in both human and mouse platelets. This interaction results in aggregation *in vitro* and thrombosis *in vivo*. [76] Physiological platelet agonists synergize with TLR9 ligands by increasing TLR9 expression on the platelet membrane. [76]

6. Platelets in sepsis

Sepsis is an uncontrolled systemic reaction to an infection. It can progress into severe sepsis with multiple organ dysfunction and cognitive impairment. Septic shock, in which patients suffer vascular collapse and often are irresponsive to fluid resuscitation and vasopressor therapy, is often the terminal event of severe sepsis. [1] Sepsis is a complex process presenting with multiple pathogenic features, such as dysregulation of the immune and coagulation systems, thrombosis, disruption of endothelial barrier function, increased vascular permeability, microvascular sequestration, tissue damage, etc. [94] This complexity is likely to be responsible for the failure to find new treatments for sepsis, [95] and for the lack of good animal models. [96, 97]

Platelets are both cellular effectors and cellular targets in the pathophysiology of sepsis. Regardless of the initiating events in sepsis, platelets play an important role in the development of multiple organ failure via their haemostatic and thrombotic potential, resulting in thrombotic microangiopathy and disseminated intravascular coagulation. [98, 99, 100] Evidence for an important role of platelets is provided by clinical studies and animal model data demonstrating beneficial effect of antiplatelet agents in sepsis (reviewed in [101]).

Sepsis is frequently accompanied by thrombocytopenia, which is closely associated with disease severity and mortality rate. [98, 99] Multiple mechanisms may contribute to thrombo-

cytopenia in sepsis: disseminated intravascular coagulation with peripheral consumption and destruction of platelets, impaired thrombopoiesis, direct activation by bacteria or their products, phagocytosis, etc. [102-104] Thrombocytopenia is also detected after injection of LPS in mice (a common model for sepsis) [88, 89] through a TLR4-dependent mechanism. [71, 72]

Alterations in circulating platelets occur in septic patients. CD62P expression was elevated in septic platelets in some studies[105, 106] but not in the others[107, 108] Other platelet activation markers found in sepsis include membrane expression of thrombospondin (TSP)[109, 110] and CD63, [106] elevated soluble CD40L level[108] and an increase in beta-thromboglobulin and the beta-thromboglobulin-to-PF4 ratio. [111] Increased VEGF release by agonist-stimulated platelets from septic samples has been reported. [107] Moreover, triggering receptor expressed on myeloid cells (TREM)-like transcript-1 (TLT-1), secreted upon platelet activation, is found in the plasma of patients with sepsis in levels that correlate with disseminated intravascular coagulation. [112, 113]. Animal studies suggest that TLT-1 dampens inflammation and augments platelet aggregation, reducing local hemorrhage. [112] Furthermore, soluble TLT-1 increases platelet adherence to the endothelium[114] and is involved in the regulation of inflammation in the course of sepsis by suppressing leukocyte activation and affecting platelet-neutrophil crosstalk. [115]

An *in vitro* study showed that platelets from septic patients are hyper-adhesive to cultured endothelium. [110] Alterations in platelet aggregation [107, 116] and increase in PLA level, which both might contribute to inflammation and vascular injury, have also been found in sepsis. [105, 109]

Changes in platelet transcriptome have also been reported in sepsis. [117] Expression of spliced tissue factor mRNA in platelets from septic subjects was associated with tissue factor-dependent procoagulant activity. [118] This may be one of the mechanisms by which platelets contribute to microvascular thrombosis in sepsis. [119, 118]

It is likely that different platelet-activating pathways cooperate during sepsis. Platelets are activated by some (but not all) bacteria or their products, and by NETs. [65, 103, 104] This could have beneficial roles in fighting infection (i. e. , pathogen capture within thrombus, pathogen killing, etc). However, uncontrolled thrombus formation in response to bacteria or NETs could have detrimental effects in sepsis. Other processes, such as imbalance between plasma level of high molecular weight VWF and its cleavage protease ADAMTS-13, imbalanced coagulation, systemic endothelial activation, and leukocyte activation, might contribute to potentiating platelet activation in sepsis. [99, 100]

7. Platelets and neurovascular inflammation

The central nervous system (CNS) is an immune-privileged site, separated from blood by the blood brain barrier (BBB). Under pathological conditions, BBB may be disrupted. This lets cells from blood into the cerebral tissue and facilitates innate and adaptive immune responses in the CNS. [120, 121]

Platelets are present in the inflamed CNS microvasculature in mice and are capable of activating brain endothelial cells via IL-1α release. Platelets, as inflammatory cells, participate in neural diseases associated with pathogen-induced and sterile inflammation. [122-124]

Sterile neurovascular inflammation accompanies such neural disorders as stroke, multiple sclerosis, and Alzheimer's disease (summarized in [125]). Ischemic stroke elicits a strong inflammatory response. [126] Inhibition of platelet adhesion to the injured vessel wall by blocking surface receptors GPIbα or GPVI protected mice from ischemic injury, implying that platelets are involved in stroke-related cerebral inflammation. [127] The lack of ADAMTS13, an enzyme cleaving VWF rendering it less proadhesive, promoted brain damage whereas infusion of ADAMTS13 ameliorated the defect, [128] further suggesting that platelet adhesion is an important pathogenetic step in ischemic stroke.

Interestingly, limiting platelet aggregation with $\alpha_{IIb}\beta_3$ inhibitors did not protect from stroke in mice[127] and humans. [129] Altogether there are several candidates on the platelet surface or inside platelet granules, including GPIb, GPVI, and VWF that could be potential targets for stroke treatment through reducing thrombo-inflammation without inducing bleeding complications[126, 130-133]

Neuronal loss is accompanied by BBB breakdown and vascular inflammation in age-related **Alzheimer's disease** (AD). [134] Platelet function in AD is altered, and platelet activation state (determined by plasma soluble GPVI levels) is considered a potential biomarker for the disease progression. [135-138] Platelets contain substantial amounts of amyloid precursor protein[139] and various forms of tau protein that could have diagnostic value as biomarkers and/or play a role in disease pathogenesis. [140]

Multiple sclerosis (MS) is a devastating T-cell mediated autoimmune neuroinflammatory disease. [141] High levels of platelet activation markers (surface expression of P-selectin) and increased plasma content of platelet-derived microparticles (PMP) were detected in MS patients. [142] Chronic lesions of MS patients contain tissue factor, as has been demonstrated by proteomics approach, [143] and elevated levels of platelet-specific α_{IIb} and β_3 transcripts were detected by microarray. [144] These findings are in concert with platelet presence in human MS lesions and in the murine brain in experimental autoimmune encephalomyelitis (EAE), rodent model of MS. [145] Platelet depletion as well as blocking GPIbα or $\alpha_{IIb}\beta_3$ by antibody Fab fragments in the inflammatory rather than immunization phase of the disease resulted in decreased EAE severity. Intravital microscopy revealed that platelets directly contributed to leukocyte rolling and adhesion to endothelium of the inflamed postcapillary venules via GPIb-Mac-1 interaction. [145]

Platelet activation in neuroinflammation may result from direct recognition of specific structures of damaged tissue. For instance, massive platelet activation and degranulation was induced upon systemic administration in mice of sialated glycosphingolipids (gangliosides), components of astroglial and neuronal lipid rafts of BBB. The cerebral gangliosides GT1b and GQ1b are specifically recognized by platelets with P-selectin playing the central role. [146]

The pathogenesis of **migraine**, the third most frequent disease worldwide, [147] involves sterile inflammation and hypersensitization of pain pathways. [148] Spontaneous platelet

activation and aggregation in migraine patients have been known for years [149, 150] and expression of platelet receptors to fibrinogen and serotonin are altered in migraine patients. [151] PLA accumulating in the blood of patients with migraine[152] may link severe headaches and stroke. [152, 153] Preliminary observations suggest that antiplatelet therapies may be effective to reduce the severity of migraine. [154]

8. Platelets in allergic inflammation

Allergic diseases include a variety of conditions (atopic dermatitis, asthma, etc) that are caused by immune responses to environmental antigens. The hallmarks of allergy are the activation of T_H2 lymphocytes and the production of allergen-specific IgE antibodies, with the latter causing excessive activation of mast cells, eosinophils and basophils. This may become fatal when hypersensitivity results in systemic response designated as anaphylaxis. In chronic allergic inflammation, large numbers of immune cells accumulate at the affected site, causing substantial tissue damage. [155] The link between platelet activation and allergy has been studied for many years. [156, 157]

Independent studies report elevated plasma levels of platelet activation blood markers (β-thromboglobulin (β-TG), PF4, P-selectin, and PMPs) in patients with atopic dermatitis (AD) and psoriasis. [158-160] as well as in a mouse model of AD. [161] Plasma β-TG and PF4 may be markers for the severity of AD and psoriasis. [158]

In AD, it is possible that platelets contribute to an itch–scratch–hemorrhage cycle via release of pruritogenic factors such as histamine, 5-HT, acid proteases, IL-1β, TGF-β, PAF, and prostaglandin E2. [157]

While studies on platelet activation markers in asthmatic patients are inconclusive likely due to differences in experimental design, [162-167] the role of platelets in lung allergic inflammation has been established in mouse models. [168-171] There is a significant association between activation of platelets and eosinophils in the airways of individuals with asthma. [164] Moreover, circulating PLA are detected in the blood of allergen-challenged asthmatic patients and mice. [168] Platelets are essential for leukocyte recruitment to human and murine lungs in allergic inflammation [168, 170] and to the skin in chronic hapten-induced dermatitis, another mouse model of AD. [172] PLA circulate in the blood of asthmatic patients and in allergen-challenged mice. [165, 168] In all cases, the role of platelets was P-selectin-dependent.

Platelets express functional low (FcεRII) and high affinity (FcεRI) receptors for IgE at low level [173-175] Murine platelets can chemotactically respond to the sensitizing allergen via FcεR *in vitro* and *in vivo*, with platelet influx preceding the influx of leukocytes. [171] Upon engagement of IgE receptors, platelets release a variety of biologically active mediators[175, 176] including RANTES, a potent eosinophil chemoattractant. [177] IgE is stored in platelet *α*-granules and released upon activation, which may potentially amplify the allergic response. [178]

Multiple products released by activated platelets are able to exacerbate the allergic response, e. g. , thromboxanes, histamine, and serotonin. [179, 180, 181] PAF is a potent mediator of allergic inflammation that is both released by and activates immune and inflammatory cells, including platelets [55, 182, 183]. In mice, platelets, and not mast cells, are the main source of serotonin released during allergic inflammatory response. [184] Besides allergic mediators platelets also contain substances limiting inflammation, for example, lipoxins, produced during platelet-leukocyte interactions. [185-188]

In asthma, platelets have been found to actively participate in most of its main features, including bronchial hyperresponsiveness, bronchoconstriction, airway inflammation and airway remodelling. [169, 189]

In conclusion, delineation of platelet contribution to the allergic response may be beneficial in developing more effective therapies, [190] as well as diagnostic and prognostic tools to evaluate efficacy of treatment of various allergic diseases. [191]

9. Concluding remarks

Platelets are important players in the development of inflammation. They store multiple inflammatory molecules that, upon release, chemoattract key innate immune cells leukocytes and stimulate endothelium. Platelets interact with leukocytes and support their interaction with vessel wall and egression to tissues. Platelets play a pivotal role in various inflammation-related diseases and targeting platelets could be a promising approach to manipulate the inflammatory response.

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