PLATELET DISORDERS

Platelets in sepsis

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Abstract
Platelets are circulating blood cells that will normally not interact with the intact vessel wall but that may swiftly respond to vascular disruption by adhering to subendothelial structures, followed by interaction with each other, thereby forming a platelet aggregate. The activated platelet (phospholipid) membrane may form a suitable surface on which further coagulation activation may occur. These processes are part of the first line of defence of the body against bleeding but may also contribute to pathological thrombus formation in vascular disease, such as thrombus formation on top of a ruptured atherosclerotic plaque. In case of systemic inflammatory syndromes, such as the response to sepsis, disseminated intravascular platelet activation may occur, which will contribute to microvascular failure and thereby play a role in the development of organ dysfunction. In addition, in this situation platelets may be directly involved in the inflammatory response by releasing inflammatory mediators and growth factors.

Introduction
Under normal conditions $1 \times 10^{12}$ platelets continuously flow along 1000 m$^2$ of vascular surface in the human body without adhering or aggregating. However, upon disruption of the integrity of the vessel wall, a swift and complex interaction between circulating platelets, endothelial cells and subendothelial structures occurs [1] {2071 /id}. The result of this interaction is platelet adhesion to the vessel wall and forming aggregates with each other, thereby materializing a first line of defense against blood loss. The interaction between platelets and the vessel wall is mediated by cellular receptors on the surface of platelets and endothelial cells, such as integrins and selectins, and by adhesive proteins, such as von Willebrand factor and fibrinogen.

Platelet aggregation under pathological conditions
Platelets play a pivotal role in the pathogenesis of acute atherothrombosis, which is the pathological substrate of acute vascular events, such as acute myocardial infarction and stroke. Although the mechanism by which platelets adhere to the vessel wall to achieve hemostasis is fairly well understood, the exact pathways that contribute to platelet adhesion and activation in thrombosis, e.g. upon rupture of an atherosclerotic plaque, are still unclear [2] {1966 /id}. The essential aspects of platelet activation and aggregation are for the major part the same as those in response to hemorrhage. However, in case of pathological thrombus formation there may be modifying factors, such as increased shear stress around atherosclerotic plaques and local dysfunction of endothelial cells, potentially in association with inflammatory mechanisms are probably important in pathological thrombus formation [2,3] {1966 /id; 2232 /id}. Besides playing a role in thrombus formation upon a ruptured atherosclerotic plaque, platelets also play a role in the formation of the atherosclerotic plaque itself. Platelets can release adhesive ligands, such as P-selectin and may, upon activation, provide a suitable phospholipid surface for the recruitment of mononuclear cells and lymphocytes, that contribute to the local inflammatory processes associated with atherosclerosis [4,6] {3220 /id; 3221 /id}. In addition, platelet granules contain growth factors, such as platelet-derived growth factor, which is important...
for cellular proliferation in the expanding atherosclerotic lesion.

**Platelets in sepsis**

Most clinicians will recognize that platelets are involved in the pathogenesis of sepsis, if only by the fact that marked thrombocytopenia is a common feature of sepsis. The incidence of thrombocytopenia (platelet count $<150 \times 10^9 \text{ l}^{-1}$) in critically ill medical patients is $35–44\%$ [7,8] (2257 /id; 1810 /id). A platelet count of $<100 \times 10^9 \text{ l}^{-1}$ is seen in 20–25 of patients, whereas 12–15 of patients have a platelet count $<50 \times 10^9 \text{ l}^{-1}$. Typically, the platelet count in patients with sepsis decreases during the first 4 days on the intensive care unit [9] (1209 /id). Sepsis is a clear risk factor for thrombocytopenia in critically ill patients and the severity of sepsis correlates with the decrease in platelet count [10] (2274 /id). The mechanism by which thrombocytopenia in sepsis occurs, however, is not completely clear. Impaired production of platelets from within the bone marrow may seem contradictory to the high levels of platelet production-stimulating pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-$\alpha$ and interleukin (IL)-6, and high concentration of circulating thrombopoietin in patients with sepsis. These cytokines and growth factors should theoretically stimulate megakaryopoiesis in the bone marrow [11] (2275 /id). However, in a substantial number of patients with sepsis marked hemophagocytosis may occur, consisting of active phagocytosis of megakaryocytes and other hematopoietic cells by monocytes and macrophages, hypothetically due to stimulation with high levels of macrophage colony stimulating factor (M-CSF) in sepsis [12] (2261 /id). Platelet consumption may also play an important role in patients with sepsis, due to ongoing generation of thrombin (which is the most potent activator of platelets in vivo) [13,14] (2276 /id; 511 /id). Of note, the involvement of platelets in the sepsis-associated coagulopathy was already identified more than 30 years ago, focusing on the interaction of platelets with endotoxin. [15] (3124 /id). In the setting of inflammation-induced activation of coagulation, platelets can be activated directly by endotoxin [16] (2002 1895 /id) or by pro-inflammatory mediators, such as platelet activating factor [17] (2002 1896 /id). Release of inflammatory mediators and growth factors may be another link between activation of coagulation and inflammation. Recent studies have shown that expression of P-selectin on the platelet membrane not only mediates the adherence of platelets to leukocytes and endothelial cells but also enhances the expression of tissue factor on monocytes [18]. Tissue factor expression is the triggering event in the activation of blood coagulation, resulting in the generation of thrombin, which may further activate platelets. P-selectin can be relatively easily shed from the surface of the platelet membrane and soluble P-selectin levels have indeed been shown to be increased during systemic inflammation [19].

Hence, platelets seem to occupy one of the essential cross-roads in the complex interaction between inflammation and coagulation, not only by facilitating and propagating thrombin generation but also by being an important mediator of growth factor and adhesion molecule activity. More research on the role of platelet activation in sepsis will undoubtedly be helpful in further unraveling the pathogenesis of sepsis and in the understanding of the tight cross-talk between inflammation and coagulation.

**References**


[14] Levis J, Poore TE, Young NS, Margolis S, Zauber NP, Townes AS, Bell WR. Gram-negative sepsis: detection of


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