Platelets

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Global Spotlights

Platelets: from simple fragments to inflammation regulators

Rory R. Koenen *

Department of Biochemistry, CARIM School for Cardiovascular Diseases, Maastricht University, PO Box 616, 6200MD Maastricht, Zuid Limburg, The Netherlands

It has been roughly one and a half centuries ago that platelets were first described as cellular components of animal blood that mediate hemostasis, and their medical importance both for bleeding and thrombosis was recognized soon after.[1] Being readily obtainable and highly responsive cellular elements of blood, observations in platelets have boosted research on e.g. signal transduction, cytoskeleton, and adhesion in other fields of cell physiology. The outstanding relevance of platelets for human healthcare is highlighted by the number of transfused platelet concentrates exceeding 2 million yearly both in the USA and in the EU. In cardiovascular medicine, antiplatelet drugs are first choice for the prevention of recurrent adverse events after myocardial infarction (MI) and stroke. Of note, despite the numerous cell types implicated in the pathophysiology of cardiovascular disease, platelets are among the few that have specific drugs directed against them.

Although the physiologic importance of platelets is undebated, they are often designated as 'fragments', and platelet researchers still find themselves confronted with remarks disqualifying platelets as true cells.[1] Despite their small size, short half-lives, and the absence of a nucleus with genetic information, platelets have numerous abilities that would do many a cell proud. For example, they not only have receptors for hemostatic cues but also for molecular danger patterns derived from microbes or tissues, allowing them to quickly sense damage and respond almost instantaneously, thereby closely interacting with a vast number of molecular and cellular partners even under high shear flow conditions. In addition, platelets are packed with molecular effectors that can be rapidly released from their secretory granules or through extracellular vesicles upon activation. Considering their large numbers in circulation, platelets have major significance in their roles in hemostasis and thrombosis and beyond.

The sheer versatility of the platelet would be impressive by itself, yet recent research has uncovered unexpected abilities, particularly in inflammation and intercellular communication. Platelets quickly undergo interactions with leucocytes when activated, altering their functions and modulating inflammation. For example, platelet binding was recently found to drive the activation of the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome in monocytes and in neutrophils, leading to interleukin 1β production.[2] In neutrophils, inflammasome activation also leads to the release of neutrophil extracellular traps (NETs), structures containing of DNA, histones, and neutrophil antimicrobial factors. NETs promote blood coagulation activation, platelet adhesion, and endothelial inflammation, the latter leading to tissue factor exposure and propagation of thrombotic responses. Interestingly, circulating NETs, interleukin 1β, and NET-bound tissue factor were recently found to be elevated in a group of patients with MI and elevated C-reactive protein, indicating a tight interplay between inflammation and thrombosis supported by these factors.[3] A direct contribution of platelets to the formation of NETs in this setting is likely, since they are chiefly responsible for the clinical manifestations of atherothrombotic adverse cardiovascular events, as is indicated by studies in patients and in animals[4,5] and platelet-derived factors are instrumental in the induction of NETs (*Figure 1*).

Another aspect of the platelet–neutrophil axis is the recently described modulation of platelet production by neutrophils during inflammation. For example, neutrophils were found to be located around megakaryocytes within the bone marrow in mice.[6,7] The bone marrow neutrophils were able to enter (and exit) the megakaryocytes in a process that is termed 'emperipolesis', a process that resembles transmigration rather than phagocytosis. The neutrophils entered the cytoplasm of the megakaryocytes in the process, and part of their membranes and surface proteins was transferred to the nascent platelets during their production. Emperipolesis was shown to be increased during systemic inflammation and was associated with enhanced platelet production. Apart from entering the megakaryocytes, bone marrow neutrophils were recently shown to exert pulling forces on the developing pro-platelets, thereby 'plucking' off fresh platelets from megakaryocytes and accelerating their formation.[6] Depletion of neutrophils resulted in a reduced platelet growth speed in mice. Intriguingly, experimental MI led to enhanced platelet production that was caused by an increased megakaryocyte plucking by neutrophils in the bone marrow. These newly formed platelets were enriched in reticulated platelets, which are RNA-rich and more responsive to stimuli. An increase in the reticulated platelet fraction was also observed in blood samples of patients suffering from acute MI. Moreover, platelets from patients

* Corresponding author. Tel. +31-43-3883390, Email: r.koenen@maastrichtuniversity.nl

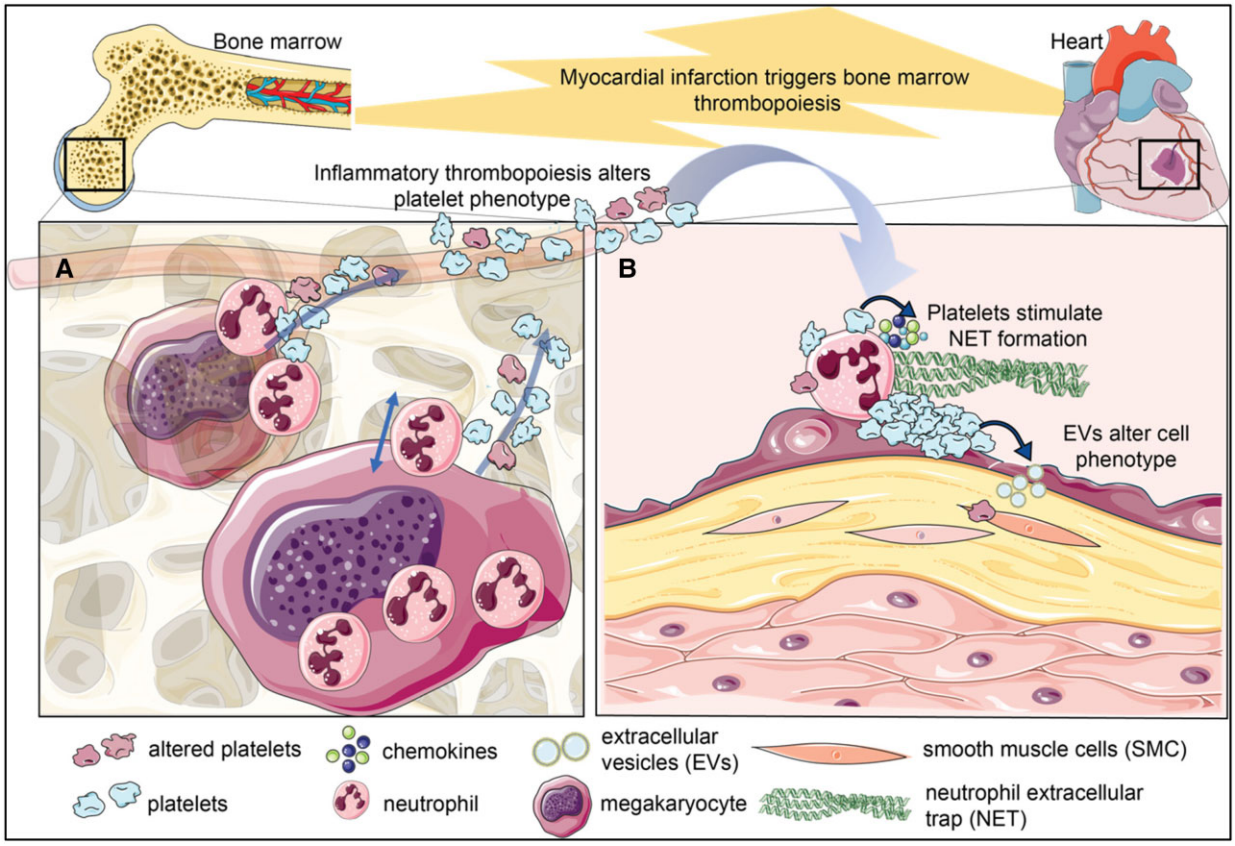

Figure 1 Platelet–neutrophil conduits during acute coronary syndromes. Myocardial infarction triggers a pro-inflammatory state, leading to an increased platelet production through the action of bone marrow neutrophils through 'plucking', emperipolesis, or uptake of neutrophil factors (*A*). This leads to an altered platelet phenotype that might be more reactive. Activated platelets can shed chemokines and bind to neutrophils, thereby inducing neutrophil extracellular traps (*B*). Platelets and their extracellular vesicles (EVs) can transfer molecular information to other cells, e.g. smooth muscle cell (*B*).

with MI were found to be more reactive than those from controls.[6] Further evidence from inflammation-related platelet alterations comes from a recent study that found that the neutrophil protein S100A8/A9 (calprotectin) was significantly elevated during MI.[8] Interestingly, platelets were shown to take up neutrophil-derived S100A8/A9, which might be an explanation for the correlation found between plasma S100A8/A9 levels and platelet aggregation observed in a community-based cohort.[8] The above examples demonstrate that neutrophils can not only modulate the production but also influence the cargo of circulating platelets during inflammation. The resulting platelets may have a net increased RNA content and an adapted proteome, leading to functional alterations (*Figure 1*).

But what might be the meaning of altered platelet contents? Although this question has not been fully addressed, there is increasing evidence pointing towards platelets as carriers of molecular information, depending on the pathophysiologic context. This is exemplified by the actions of platelets, and platelet-derived extracellular vesicles on smooth muscle cells (SMCs). In a mouse model of arterial injury, horizontal transfer of the microRNA micro RNA (mIR)-223 by internalization of platelets by SMC led to an enhanced resolution of arterial injury by switching the SMC to a quiescent phenotype.[9] Interestingly, this effect was attenuated in diabetic mice, possibly due to reduced levels of mIR-223 in platelets. A role of disease context was also suggested by the observation that isolated extracellular vesicles from platelets promoted the switching of cultured VSMC towards a proinflammatory and synthetic phenotype,[10] hinting towards currently uncharacterized stimuli skewing platelet functions towards promoting vascular repair or dysfunction (*Figure 1*).

Taken together, the view on platelets as (hemo-)static cell fragments is changing towards one of versatile and dynamic actors in inflammation and vascular (dys-)function. This new awareness might inspire research on innovative drugs that could interfere with harmful neutrophil-platelet conduits and reduce pro-inflammatory platelet functions while keeping hemostasis intact.

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Figure 1 was generated using elements from Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

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Data availability

All data pertaining to this article are available from the author upon reasonable request.

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