

Platelets: Inflammatory Firebugs of Vascular Walls

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Abstract—Atherosclerosis is an inflammatory disease. Platelets can “infect” the vascular wall by various mechanisms and thereby initiate and support the development of atherosclerosis. Platelet interaction with leukocytes, endothelial cells, and circulating progenitor cells triggers autocrine and paracrine activation processes, leading to inflammatory and atherogenic cascades at the vascular wall. This review highlights the molecular key components and pathways used by platelets to trigger and accelerate inflammation at the vascular wall and, thereby, atherosclerosis. (*Arterioscler Thromb Vasc Biol.* 2008;28:s5-s10)

Key Words: platelets ■ atherosclerosis ■ inflammation ■ vasculature ■ cardiovascular events

This article is part of a multi-part CME-certified activity titled Translational Therapeutics at the Platelet Vascular Interface. In order to achieve all of the activity's learning objectives, please read all of the components of the activity listed in the Table of Contents and follow the “Instructions for Participation and Obtaining CME Credit” outlined prior to the Introduction.

Atherosclerosis is a chronic inflammatory disease.¹ However, the contribution of platelets to the process of atherosclerosis was unclear until this millennium. Recently, we and others could provide conclusive evidence that platelets are crucially involved in atherogenesis.^{2,3} In apoE-deficient mice, platelets were found to adhere to the vascular endothelium of the carotid artery even before leukocyte invasion and before the development of manifest atherosclerotic lesions.² Platelet adhesion was found to be mainly mediated by both platelet glycoproteins (GP) Iba and $\alpha_{IIb}\beta_3$ and coincided with inflammatory gene expression.² Consequently, prolonged antibody blockade of platelet GP Iba prohibited leukocyte accumulation in the vascular wall and attenuated atherosclerotic lesion formation. Further, infused activated wild-type (but not P-selectin-deficient) platelets were found to promote the formation of atherosclerotic lesions in wild-type mice.³ In the meantime, we know that the interruption of platelet interaction with the vascular wall by any intervention, such as antibody inhibition or knockout of platelet adhesion receptors (eg, GP IIb, GP Iba, or P-selectin), substantially reduces the formation of atherosclerotic lesions in different mouse models.³⁻⁵

Interestingly, effective inhibition of downstream activation cascades (eg, CD40/CD40L) can also inhibit atherosclerosis. Although the specific platelet contribution has not been

proved in this context, disruption of CD40-CD40L in mouse models of atherosclerosis could attenuate plaque formation^{6,7} and could even stabilize and halt the progression of established lesions.⁸

Platelets Are Inflammatory Cells

A growing body of evidence indicates that platelets play a main part in inflammation.^{9,10} Activated platelets interact with various cell types at the vascular wall (Figure 1). During these cellular interactions, which involve direct receptor interactions as well as autocrine and paracrine pathways, platelets and their respective cellular counterpart activate each other in a mutual and vicious circle-like fashion¹¹ (see Figures 1 and 2). These processes lead to multiple inflammatory processes, including atherosclerosis, restenosis, thrombosis, and coagulation. Platelet activation is a common feature in inflammatory diseases and occurs in cardiovascular pathologies, such as unstable angina or acute myocardial infarction,¹²⁻¹⁷ but also in sepsis,¹⁸⁻²¹ inflammatory bowel disease,²² or arthritis.²³ In addition, platelets can actively initiate the development of severe cardiovascular complications, such as unstable angina, acute myocardial infarction, or stent thrombosis, and influence the outcome of cardiovascular interventions, such as percutaneous interventions or bypass surgery. Consequently, effective platelet inhibition reduces major adverse cardiovascular events in acute cardiovascular syndromes and cardiovascular interventions.^{24,25}

Despite being anucleate cells, platelets have the capacity to synthesize proteins by translational pathways.²⁶ In addition, platelets contain various compartments, such as 3 different granules (α -granules, lysosomes, dense core granules), and a complex membranous system that allows them to store and rapidly release a variety of factors, such as adhesion proteins

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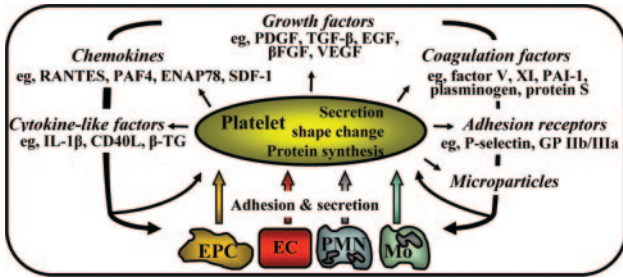


Figure 1. Inflammatory platelet response to cellular interactions. Platelet interactions with monocytes (Mo), neutrophils (PMN), endothelial cells (EC), or endothelial progenitor cells (EPC) can result in a variety of platelet reactions, including morphological shape changes, intracellular signaling with novel protein synthesis, and receptor upregulation and activation, as well as secretion of various soluble inflammatory factors as indicated. EPC indicates endothelial progenitor cell; EC, endothelial cell; PMN, polymorphonuclear neutrophil; Mo, monocyte/macrophage.

(eg, fibrinogen, fibronectin, von Willebrand factor [vWF], thrombospondin, vitronectin, P-selectin, and GP IIb/IIIa), growth factors (eg, PDGF, transforming growth factor [TGF]- β , EGF, bFGF), chemokines (RANTES, platelet factor 4 [PF4; CXC chemokine ligand 4, CXCL4], stromal cell-derived factor-1 [CXCL12, SDF-1], epithelial neutrophil-activating protein 78 [ENA-78; CXCL5]), cytokine-like factors (eg, IL-1 β , CD40L, β -thromboglobulin), and coagulation factors (eg, factors V, XI, plasminogen activator inhibitor [PAI]-1, plasminogen, protein S).¹⁰ These proteins act in a concerted and fine-regulated manner, influencing widely differing biologic functions, such as cell adhesion, cell aggregation, chemotaxis, cell survival and proliferation, coagulation, and proteolysis, all of which accelerate inflammatory processes and cell recruitment (Figure 2).

Under inflammatory conditions, platelets can physically interact with other circulating cells such as leukocytes or progenitor cells by coaggregation^{27–30} within the blood stream or when adherent to the vascular wall. Once recruited to the vascular wall, platelets can attract circulating leukocytes or endothelial progenitor cells (EPCs) through mediators such as platelet activating factor (PAF), macrophage inflammatory protein (MIP-1 α), RANTES, or SDF-1.^{10,31}

Platelet Interaction With Endothelium

Platelets usually do not interact with the intact vascular endothelium. Whereas the endothelium normally controls platelet reactivity through inhibitory and modulating mechanisms involving COX-2, PGI₂, or prostanoid synthetic systems, inflamed endothelial cells develop properties that render them adhesive for platelets. In vitro studies showed that platelets adhere to the intact but activated human endothelial monolayer.^{32,33} Platelet adhesion to activated human umbilical vein ECs (HUVECs) is mediated by a GP IIb/IIIa-dependent bridging mechanism involving platelet-bound fibrinogen, fibronectin, and vWF.^{32–34} Furthermore, the involvement of the EC receptors intercellular adhesion molecule-1 (ICAM-1), α v β 3 integrin, and GP Ib in the binding of activated platelets to HUVECs has been described

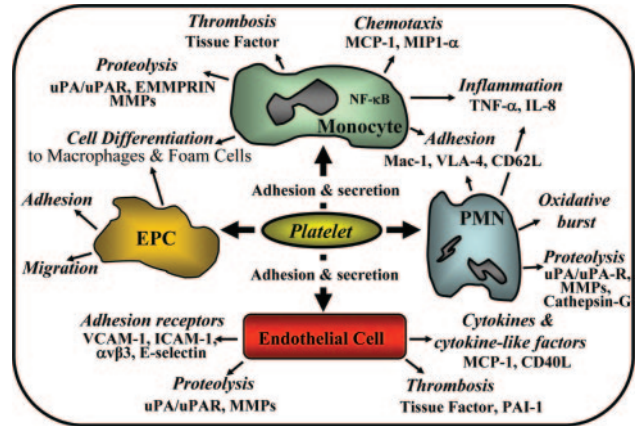


Figure 2. Platelets inflame their cellular interaction partners. Platelets can induce a variety of inflammatory responses in monocytes, neutrophils (PMN), endothelial cells, or endothelial progenitor cells (EPC), resulting in key inflammatory processes, such as adhesion, chemotaxis, migration, proteolysis, thrombosis, or even cell differentiation to macrophages or foam cells. These processes provide an atherogenic milieu at the vascular wall that supports plaque formation.

in vitro (for review, see references 9 and 35). During the adhesion process, platelets become activated and release an arsenal of potent inflammatory and mitogenic substances into the local microenvironment, thereby altering chemotactic, adhesive, and proteolytic properties of endothelial cells.^{9,26} For example, GP IIb/IIIa receptor engagement during platelet adhesion signals upregulation of CD62P and CD40L on platelets, resulting in CD40L-dependent endothelial activation.^{36,37}

Platelet Interaction With Leukocytes

Leukocyte recruitment requires multistep adhesive and signaling events, including selectin-mediated attachment and rolling, leukocyte activation, integrin-mediated firm adhesion, and diapedesis, which result in the infiltration of inflammatory cells into the blood vessel wall.³⁸ Activated platelets promote leukocyte arrest on the vascular endothelium, which is believed to be a key process in the development of atherosclerosis.^{1,9} Platelets physically interact with both leukocytes and with the vascular wall. This interaction can occur in variable sequences: first, platelets can coaggregate with leukocytes and thereby support leukocyte recruitment to the endothelium by activating leukocyte adhesion receptors, or by directly serving as bridging cells. For example, platelet-monocyte coaggregates can attach to the vascular endothelium by both platelet-endothelium or by monocyte-endothelium contacts. Second, when adhered to the endothelium, platelets can chemoattract leukocytes and then provide a sticky surface for their adhesion to the vascular wall. During these interactions involving platelets, leukocytes, and the endothelium, all cell types involved become activated in a cascade-like manner (see Figures 1 and 2). Whereas Figure 1 describes inflammatory platelet reactions on stimulation by interacting vascular cells, Figure 2 shows the inflammatory responses of vascular cells on interaction with platelets. These cellular interactions are part of a fine-regulated and orchestrated activation cascade involving autocrine and

paracrine pathways, as well as direct adhesion receptor interactions.

On adhesion or activation, platelets rapidly translocate P-selectin from α -granules to the plasma membrane. This allows leukocytes to tether to platelets via PSGL-1/P-selectin interaction. Subsequently, monocytes or polymorphonuclear cells firmly adhere to platelets in a Mac-1-dependent (CD11b/CD18, α M β 2) manner.³⁹ On platelets, various counterreceptors of Mac-1 have been identified: GP Ib α ,⁴⁰ junctional adhesion molecule-C (JAM-C, JAM-3),⁴¹ CD40L,⁴² ICAM-2,⁴³ as well as bridging proteins, such as fibrinogen (bound to GP IIb/IIIa)⁴⁴ or high molecular weight kininogen (bound to GP Ib α).⁴⁵ Nevertheless, the exact contribution of each receptor system awaits clarification.

During this adhesive process, receptor engagement of PSGL-1 and Mac-1, together with platelet-derived inflammatory compounds, induces complex activation cascades in monocytes.^{27,46,47} These activation processes involve the intracellular activation pathways, including NF κ B activation, and promote monocyte or neutrophil adhesion (up-regulation and activation of Mac-1 and VLA-4), thrombosis (monocyte secretion of tissue factor), monocytic chemokine and cytokine release (interleukin [IL]-1 β , IL-8, MCP-1, tumor necrosis factor [TNF]- α),^{27,47,48} or the oxidative burst of neutrophils.⁴⁹ In addition, engagement of PSGL-1 by P-selectin also drives translationally regulated expression of proteins, such as the urokinase receptor (uPAR), a critical surface protease receptor and regulator of integrin-mediated leukocyte adhesion *in vivo*.^{50–54} Additional adhesion receptor pairs appear to be involved and to signal inflammation. For example, we have recently identified the extracellular matrix metalloproteinase (MMP) inducer (EMMPRIN, CD147) as a monocyte receptor that induces MMP-9 synthesis and secretion on cellular interactions.^{55,56} The fact that these stimulatory effects can be mimicked by monocyte adhesion to immobilized recombinant EMMPRIN or EMMPRIN-transfected CHO cells suggests that homotypic EMMPRIN-EMMPRIN interactions account for these findings. One additional receptor pair, which contributes to neutrophil activation on platelet-neutrophil interactions, has recently been characterized: neutrophil surface TREM-1 and platelet surface TREM-1 ligand.⁵⁷ Although it is not required for platelet-neutrophil aggregate formation, cellular interactions involving this receptor pair induce respiratory burst activity and IL-8 secretion in neutrophils.⁵⁷

Platelet Interactions With Endothelial Progenitor Cells

Currently, one of the most challenging topics in atherosclerosis research is the investigation of the contribution of circulating endothelial progenitor cells. Although we are far from understanding stem cell biology in general, and the exact role of endothelial progenitor cells (EPCs) for atherosclerosis in particular, there is a consensus that circulating EPCs derive from bone marrow, typically surface express CD34 or CD133 and have the capability to differentiate to endothelial cells and, therefore, to repair vascular damage.^{58–61} A variety of factors have the potential to mobilize EPCs from bone marrow, including SDF-1, vascular endo-

thelial growth factor, erythropoietin, angiopoietin-1, granulocyte colony stimulating factor (CSF), and estrogen (for review see reference⁶²). Accordingly, a variety of physical or clinical conditions appear to influence the number and function of circulating EPCs, including exercise, statin use, age, smoking, diabetes, chronic heart failure, and acute coronary syndromes.^{63–66} Although EPCs can repair vascular damage by differentiation to an endothelial cell phenotype, they also may contribute to atheroprogession or restenosis, because they can also differentiate to smooth muscle cells or foam cells.^{67–70}

On vascular injury, extracellular matrix becomes exposed. However, EPCs do not surface express the respective adhesion receptors for collagen, fibronectin, fibrinogen, and vitronectin and do not directly adhere to these extracellular matrix proteins under arterial shear stress *in vitro*. Nevertheless, platelets appear to serve as “bridging” cells that both chemoattract EPCs and directly support their adhesion by providing a sticky surface. Platelets are the first cell type that attaches to the exposed subendothelium or altered endothelium.^{71,72} Recently, we have demonstrated that platelets can direct circulating EPCs to the site of arterial thrombi.³¹ Platelets were found to store SDF-1 in their alpha granules and to secrete this chemokine into the microenvironment on activation, which supports the recruitment of EPCs to surface of arterial thrombi *in vivo*.³¹ Antibody blockade of SDF-1 in mice attenuated EPC accumulation within the growing thrombus. The adhesion of CD34+ progenitor cells to immobilized platelets can be attenuated by blocking antibodies directed against PSGL-1, β 2-integrins, and β 1-integrins on EPCs as well as P-selectin on platelets.^{69,73,74} *In vivo*, antibodies against P-selectin and GP IIb inhibited the recruitment of CD34+ bone marrow-derived progenitor cells to intraarterial thrombi.³¹ Similar to platelet-leukocyte coaggregates (see above), platelets form coaggregates with circulating CD34+ progenitor cells.⁷⁵ We have recently demonstrated that patients with acute coronary syndromes do not only have an enhanced number of circulating EPCs, but also an enhanced proportion of platelet-EPC coaggregates. *In vitro*, platelet-EPC coaggregates show a dramatically increased adhesion to endothelial cells or immobilized collagen under arterial shear stress as compared with EPCs alone.⁷⁶

Platelets do not only recruit and bind EPCs to the altered vascular wall, but also support the differentiation process.^{77,78} On one hand, platelets can induce cell differentiation to cells with an endothelial phenotype and a typical surface receptor pattern.⁷⁷ On the other hand, coincubation of CD34+ progenitor cells with platelets for 5 to 10 days induces morphological changes in CD34+ cells toward macrophages and foam cells.⁶⁹ A key mechanism in this differentiation process is the phagocytosis of platelets within the first 24 hours. Surface-bound LDL on platelets appears to play a relevant role in this process.⁷⁹ Up to 30% of the original cells show a 3-fold increase in size (diameter approximately 25 μ m), round morphology, and high granularity.

However, these observations have been made *in vitro*. At present, we do not know under which conditions platelets drive CD34+ EPC differentiation toward endothelial cells or

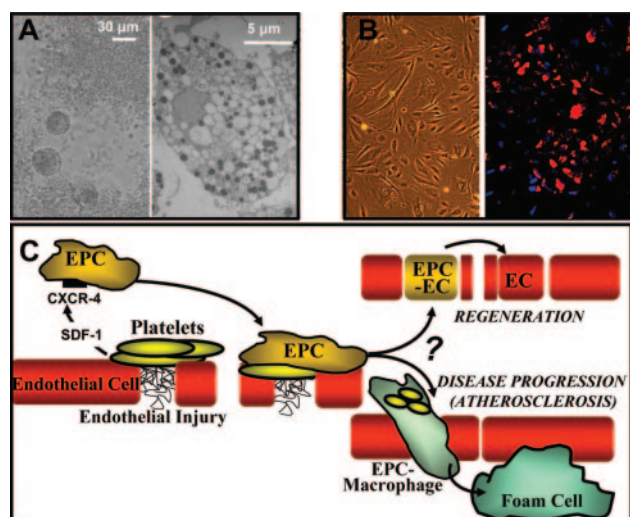


Figure 3. Platelets differentially differentiate endothelial progenitor cells. A, Coincubation of CD34⁺-progenitor cells with platelets for 8 to 10 days can lead to platelet phagocytosis, resulting in a morphological and functional transformation of endothelial progenitor cells to CD68-positive, lipid-laden foam cells.⁶⁹ B, Similarly, coincubation of CD34⁺-progenitor cells with platelets can result in differentiation to endothelial cells.⁷⁷ Left panel, Light microscopy shows typical endothelial-like cellular monolayers. Right panel, immunocytochemistry with Dapi (blue)- and phycoerythrin (red)-staining for nuclei and vWF, respectively. C, Model of platelet-directed differentiation of endothelial progenitor cells to either endothelial cells or foam cells. The key mechanism that flips the switch for regeneration vs disease progression remains unknown.

toward macrophages/foam cells or—in other words—toward vascular repair or damage (see Figure 3).

Conclusions

Platelets effectively inflame their (micro)environment. On adhesion to vascular endothelial cells, or on coaggregate formation with circulating leukocytes or progenitor cells, platelets stimulate, chemoattract, attach to, or even differentiate other cell types by a variety of mechanisms. Further work needs to be done before we fully understand the therapeutic antiinflammatory potential of this fascinating cell type.

Disclosures

None.

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