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Review

Platelet interaction with progenitor cells: vascular regeneration or injury?

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Abstract :
Increasing evidence supports the role of stem and progenitor cells in vascular regeneration or injury. Following tissue ischemia, progenitor cells are mobilized from their bone marrow or peripheral niches into circulation, adhere at sites of vascular lesion and differentiate into a variety of mature cell types according to their origin and the local environment. Impairment in this pathophysiological process due to either low numbers of circulating progenitor cells or dysfunctional progenitor cells leads to inadequate vascular repair and upon co-existence with different cardiovascular risk factors to vascular injury and atherosclerosis. Vascular repair is a complex process which includes mobilization, chemotaxis, adhesion, proliferation and differentiation of progenitor cells. The common cardiovascular risk factors can impair this process resulting into inhibition of vascular healing and enhancement of inflammatory pathways which ultimately leads to atherosclerosis. Although homing of progenitor cells into bone marrow has been extensively studied, domiciliation of precursor cells into peripheral tissues and differentiation into mature cells are poorly understood so far. Recently, the role of platelets in domiciliation and subsequent differentiation of progenitor cells has been highlighted. Adherent platelets recruit circulating progenitor cells *in vitro* and *in vivo* and induce differentiation of the latter into endothelial cells or macrophages and foam cells. Although further studies are needed to describe the mechanisms that lie underneath these observations, it seems that platelet interaction with progenitor cells is an essential step in both vascular regeneration and injury.

Key words:
progenitor cells, platelets, regeneration, atherosclerosis

Introduction

Progenitor cells are a population of immature tissue precursor cells capable of self-renewal and differentiation into many different cell types [12]. They participate in the regeneration of injured endothelium and of ischemic organs [26]. On the other hand, recent studies report that progenitor cells are critically involved in the development of atherosclerotic plaques elucidating this complex pathophysiological phenomenon [57].

It becomes increasingly evident that blood platelets do not only perform important functions in hemostasis and thrombus formation, but are also involved in vascular regeneration, inflammation and atherosclerosis [17]. Platelets are the first cells that adhere to sites of vascular lesion, there upon secrete many growth factors, chemokines and cytokines, and are capable of interacting either with the vascular wall or with other circulating blood cells and especially with progenitor cells [17]. On the other hand, activated platelets adhering to intact endothelial cells, lead to activation of the latter and cause subsequent inflammation and atheroprogression [31].

The goal of this review is to briefly summarize the role of platelets and progenitor cells in tissue regeneration and atherosclerosis and to present the current data describing the interaction between progenitor cells and platelets. Understanding the interaction between platelets and circulating progenitor cells is the key to the main mechanism that lies behind tissue regeneration or injury.

Platelets in vascular regeneration

Platelets are known for their role in hemostasis where they prevent blood loss at sites of vascular injury. Platelet adhesion, aggregation and formation of a procoagulant surface leads to thrombin generation and fibrin formation [17]. Moreover, circulating platelets release mediators and angiogenic factors, including the chemokine stromal cell-derived factor-1, the cytokines platelet factor 4 and CD40-ligand and the growth factors vascular endothelial growth factor, platelet-derived growth factor, transforming growth factor-β, epidermal growth factor, insulin-like growth factor, angiopoietin-related growth factor, promoting tissue repair [17, 38, 47]. Platelet-derived serotonin promotes tissue repair after normothermic hepatic ischemia in mice, while liver regeneration and repair are significantly reduced in platelet-depleted animals [29, 36]. Autologous platelets are used as a source of proteins for healing and tissue regeneration in dental implant surgery with guided bone regeneration [1]. In addition to proteins generated, activated and released during the activation of clotting cascades, platelet-derived lipid mediators, such as lysophosphatidate, phosphatic acid and sphingosine 1-phosphate, are known to play a crucial role in many aspects of angiogenic response including liberation of endothelial cells from established monolayers, chemotactic migration, proliferation and morphogenesis into capillary-like structures [13]. Moreover, platelets express a series of adhesion molecules including P-selectin, GPIIb/IIIa, GPIb, junctional adhesion molecules, β_3 integrins, which enable them to interact with endothelial cells [16, 32], leucocytes [41, 46, 58] and also with progenitor cells [9, 27, 34]. Since progenitor cells are the precursor cells of many different types of mature cells, their interaction with platelets is of utmost importance in understanding the complex phenomenon of tissue regeneration.

Platelets in vascular injury

On the other hand, increasing evidence supports the critical role of platelets in atherogenesis and atheroprogression. Activated platelets adhere to intact endothelial cells of the vascular wall, express P-selectin on their surface and release CD40-ligand and interleukin-1β, which stimulate endothelial cells to provide an inflammatory environment that supports proatherogenic alterations of endothelium [31, 52]. Adherent platelets on endothelial cells subsequently recruit monocytes through ligand/receptor interactions involving P-selectin and P-selectin glycoprotein ligand-1, Mac-1 and glycoprotein IIb-IIIa (and fibrinogen bridging) or glycoprotein Iba [17]. Thereby, platelets initiate monocyte secretion of chemokines, cytokines, and procoagulatory tissue factor, upregulate and activate adhesion receptors and proteases, and induce monocyte differentiation into macrophages [17]. Recently, we showed that platelets adhere to the vascular endothelium of the carotid artery in apoE-deficient mice before the development of manifest atherosclerotic lesions [31]. Platelet adhesion to injured or inflamed vessel *in vivo* is a critical step for the initiation of atherosclerotic lesion formation and subsequent atheroprogression [6, 22, 31, 33]. In accordance with these data, inhibition of cyclooxygenase-1 (COX-1), an enzyme that is exclusively presented in platelets, prevented lesion formation in apoE$^{-/-}$ mice [5]. Enhanced systemic platelet activation in humans has been described in a variety of atherosclerotic diseases, including coronary artery disease [56], transplant vasculopathy [14], and carotid artery disease [15]. Thus, platelets provide the inflammatory basis for plaque formation before they physically occlude the vessel though thrombosis upon plaque rupture.

Progenitor cells in vascular regeneration

The regenerative ability of progenitor cells following organ injury (e.g. vasculogenesis [2, 4, 24]) is well established. Bone marrow-derived, tissue resident and circulating stem and progenitor cells, including hematopoietic CD34$^+$ progenitor cells, can exhibit tremendous cellular differentiation in numerous organs. Progenitor cells promote structural and functional repair

in several organs such as heart, liver, kidney or brain [7, 11, 35, 45]. For instance, $CD34^+$ cells have been described to be recruited to the ischemic myocardium, differentiating into cardiac and vascular cells, and restoring cardiac function [12, 37].

Intracoronary or transcoronary transplantation of progenitor cells after myocardial infarction is associated with moderate but significant improvement in the left ventricular ejection fraction and also with a significant reduction of the occurrence of major adverse cardiovascular events after acute myocardial infarction (AMI) [3, 43]. Mobilization of stem cells into the peripheral circulation for myocardial regeneration using subcutaneous injections of granulocyte-colony-stimulating factor (G-CSF) has been tested in patients with AMI. G-CSF treatment seems to be safe and initial trials in patients with AMI were encouraging [25]. However, large double-blinded placebo-controlled trials have not been able to demonstrate effects of G-CSF treatment [39]. In patients with AMI or chronic ischemic heart disease, G-CSF mobilized stem cells of known importance for myocardial regeneration, but there seemed to be a general lack of homing of the stem cells into the ischemic myocardium [20, 39]. Given the limited recruitment of transplanted or mobilized progenitor cells at sites of vascular injury, elucidating the domiciliation mechanisms of progenitor cells after tissue lesion is of utmost importance.

Progenitor cells in vascular injury

Increasing data imply the involvement of progenitor cells in atherogenesis [57]. There are multiple ways describing that both the absence and presence of progenitor cells favour atheroprogression: (a) reduced number of progenitor cells results in a consequent delayed vascular repair allowing the recruitment of inflammatory cells and the infiltration of oxidized low density lipoprotein to sites of endothelial denudation or dysfunction [55]. In addition patients at risk for coronary artery disease have a decreased number of circulating progenitor cells with impaired activity [19, 44, 53]. (b) Cardiovascular risk factors such as diabetes and hyperlipidemia influence the functional capacity of progenitor cells decreasing their ability to migrate or to form endothelial colonies [54, 57]. (c) Circulating smooth muscle progenitor cells or hematopoietic progenitor cells could differentiate into smooth muscle cells or macrophages and foam cells, respectively, leading to the development of atherosclerotic plaque [9, 42]. Progenitor cells migrate to sites of vascular injury and differentiate not only to an endothelial phenotype [2] (vascular repair), but also to vascular smooth muscle cells (SMCs) [21] or foam cells [9] contributing therefore to neointimal formation [18] and finally to vascular disease. Circulating smooth muscle progenitor cells contribute to atherosclerosis *in vivo* [40]. Moreover, Tanaka and colleagues showed that bone marrow cells contribute to neointimal hyperplasia after mechanical vascular injuries [51]. However, it is poorly understood which factors influence the fate of progenitor cells in damaged tissues.

Platelet interaction with progenitor cells

The role of platelets in domiciliation of progenitor cells at sites of vascular lesions has recently been described [10, 23, 27, 34, 48–50]. While homing of hematopoietic progenitor cells to bone marrow has been extensively studied [28], the mechanisms of progenitor cell domiciliation to sites of tissue injury are poorly understood. Domiciliation is a multi-step cascade including the initial adhesion to activated endothelium or exposed matrix, transmigration through the endothelium, and finally migration and invasion to the target tissue.

Vascular injury due to systemic platelet activation and/or endothelial dysfunction is characterized with enhanced platelet adhesion either to the exposed subendothelium or to inflamed endothelium [8, 33]. We recently showed that platelet adhesion constitutes an essential step for the targeting of progenitor cells to sites of endothelial dysfunction [34, 50]. Platelets induce chemotaxis and migration of murine embryonic endothelial progenitor cells [27]. The combination of platelets and fibrin promoted $CD34^+$ cell migration even to a greater extent than vascular endothelial growth factor *in vitro* [10]. Moreover, the chemokine stromal cell-derived factor-1 (SDF-1) was found to be secreted by activated platelets, which supports chemotaxis and primary recruitment of progenitor cells on the surface of arterial thrombi *in vivo* [34]. Pretreatment of mice with a function-blocking monoclonal antibody to SDF-1, showed a significant at-

tenuation of progenitor cells accumulation within the growing platelet-rich thrombus *in vivo* [34]. Moreover, cytokine-mediated deployment of SDF-1 coming from activated platelets induces revascularization through mobilization of $CXCR4^+$ hemangiocytes [23].

Using real-time *in vivo* double fluorescence microscopy of the mouse carotid artery we demonstrated that $CD34^+$ and c-Kit^+ Sca-1^+ Lin-1^- (KSL) bone marrow-derived progenitor cells directly adhere to platelets after vascular injury in a process that involves platelet P-selectin and GPIIb integrin. Platelet-progenitor cell adhesion is an essential step for the recruitment of progenitor cells to vascular injury areas because progenitor cells do not directly adhere to subendothelial matrix proteins under high arterial shear. Flow cytometric experiments showed that progenitor cells do not express on their surface the respective adhesion receptors to collagen, fibronectin, fibrinogen and vitronectin, the main components of extracellular matrix (such as GPIb-V-IX and GPVI). Moreover platelet depletion through blocking monoclonal antibodies to GPIb and GPVI virtually completely blocked the recruitment of $CD34^+$ to sites of vascular injury *in vivo* [34].

Consistent with the findings in the mouse model, human $CD34^+$ cells adhere to immobilized human platelets but not to immobilized collagen type I alone, which represents the major extracellular matrix component of the injured arterial wall [9]. Adhesion of human $CD34^+$ cells to immobilized platelets is significantly attenuated in the presence of blocking mAbs anti-CD162 or anti-CD62P indicating that the platelet P-selectin interacts with the endothelial progenitor cells (EPCs) through interaction with P-selectin glycoprotein ligand-1 [9, 10, 30]. Moreover,

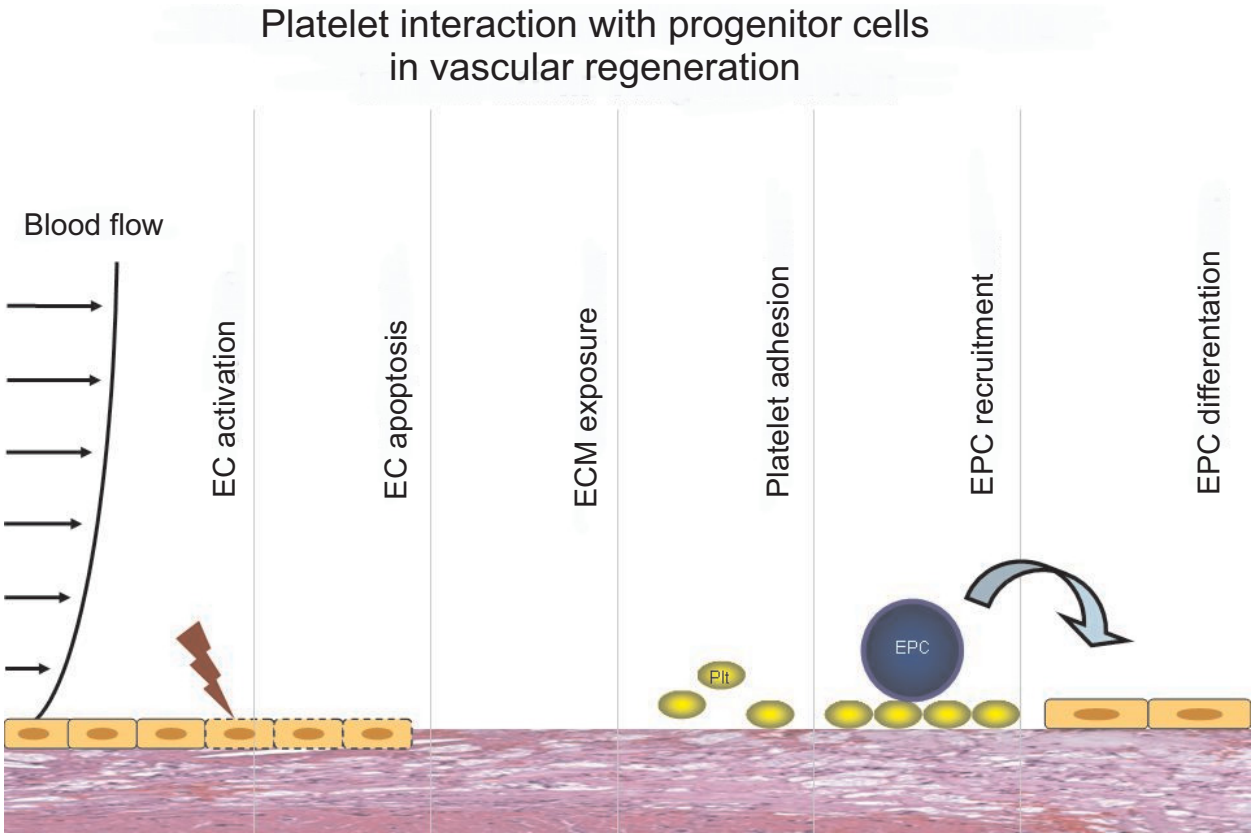

Fig. 1. Platelet interaction with progenitor cells in vascular regeneration. A variety of cardiovascular risk factors activate endothelial cells causing the apoptosis of the latter. Apoptotic endothelial cells are subsequently liberated to peripheral circulation leading to exposure of subendothelium, i.e. extra-cellular matrix (ECM), being mainly composed of collagen. Platelets express a variety of receptors which enable them to firmly adhere to ECM including the collagen receptor glycoprotein VI. Upon adhesion, platelets get activated and therefore express a plethora of adhesive receptors on their surface including P-selectin, stromal cell-derived factor-1 and activated form of the glycoprotein IIb-IIIa, facilitating the recruitment of endothelial progenitor cells (EPCs) to sites of vascular injury. Hereupon platelets induce the differentiation of progenitor cells to endothelial cells

both β_1- and β_2-integrins expressed on EPCs surface are involved in the adhesion process between immobilized platelets and human progenitor cells [9] (Fig. 1). Furthermore interestingly, the direct binding of $CD34^+$ cells to non-stimulated and even to stimulated endothelial cells was limited under flow, implicating that $CD34^+$ cells are inert to (dys)functional endothelial cells [9, 10]. After vascular injury, $CD34^+$ cells adhere to denuded mouse carotid arteries [10]. Therefore, platelets act as an intermediate mediator to tether progenitor cells, indicating that platelets are a prerequisite for the initial step of the homing process of $CD34^+$ cells to vascular injury.

Platelets play a critical part not only in the capture, but also in the subsequent differentiation of murine EPCs, inducing the differentiation of the latter into spindle-shaped cells which are positive for vWF [27]. Progenitor cells recruited to platelet aggregates give rise to neointimal cells, indicating that accumulation of progenitor cells in arterial thrombi may contribute to vascular repair and pathological remodelling *in vivo* [34]. In the human system, co-culture of platelets and $CD34^+$ cells results in decreased number of apoptotic progenitor cells indicating that platelets support the survival of the latter [10]. Furthermore, human $CD34^+$ progenitor cells can form colonies on immobilized platelets similar to immobilized fibronectin, and further differentiate into mature endothelial cells [9, 10, 50] (Fig. 1).

In vitro co-culture experiments for 1–2 weeks between platelets (2×10^8/ml) and human $CD34^+$ progenitor cells induce distinct morphological changes of the latter and differentiation into macrophages at an early phase and later on into foam cells (Fig. 2) [9]. These cells are positive for naphtyl-acetate-esterase and CD68 staining, indicating differentiation into the

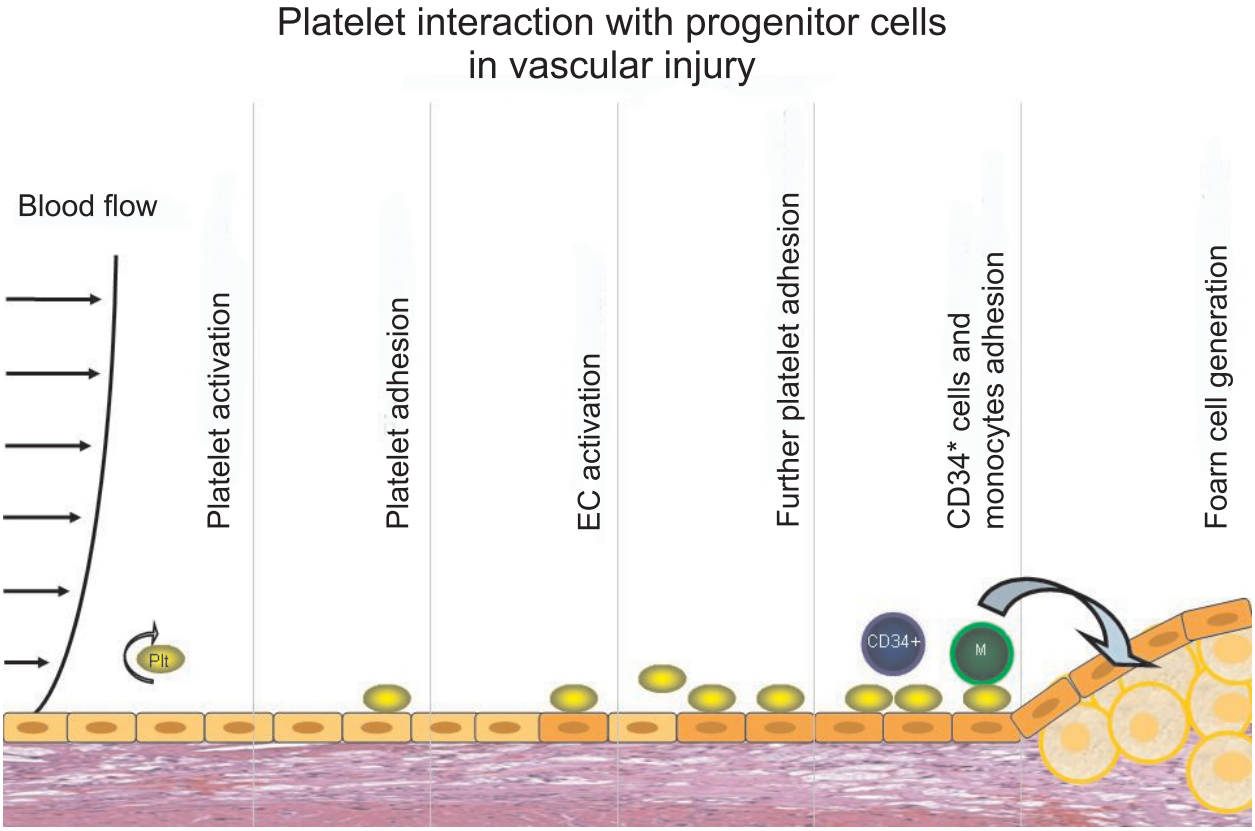

Fig. 2. Platelet interaction with progenitor cells in vascular injury. Systemic platelet activation has been documented in a variety of atherosclerotic and inflammatory diseases including coronary artery disease, ischemic stroke, vasculopathy, carotid stenosis, and various infections, autoimmune diseases, respectively. Upon activation platelets begin to roll over and finally firmly adhere on endothelial cells. Subsequent to adhesion, platelets secrete proinflammatory molecules such as CD40L and IL-1β activating the beneath endothelial cells. Activation of endothelial cells causes further platelet adhesion, secretion, surface expression of adhesion receptors and finally recruitment of monocytes and progenitor cells. Engulfment of platelets by leukocytes and progenitor cells leads to the differentiation of the latter to foam cells and to development of the atherosclerotic plaque

macrophage/monocytic lineage. By Sudan red III staining, we found out that a subpopulation of human $CD34^+$ cells transform into large granular and lipid-rich cells, a morphology typical for foam cells (Fig. 2) [9].

Phagocytosis of platelets is involved in foam cell generation derived from $CD34^+$ progenitor cells [9]. Phase contrast microscopy shows that these foam cells are surrounded by a platelet-free zone, indicating enhanced phagocytotic activity of these cells. Transmission electron microscopy of the foam cells revealed the presence of multiple vesicles with phagocytosed platelets or platelet fragments. We found that internalization of platelets occurred rapidly and after 24h a substantial number of platelets were internalized by foam cells [9].

Platelet interaction with progenitor cells: vascular regeneration or injury?

Recent studies provide evidence that platelets interact with progenitor cells regulating domiciliation and differentiation of the latter: (a) activated platelets support mobilization and chemotaxis of progenitor cells through release of the chemokine SDF-1, (b) adherent platelets support recruitment of progenitor cells *in vitro* and *in vivo*, (c) activated platelets support the survival of progenitor cells, (d) adherent platelets regulate differentiation of human progenitor cells into endothelial cells *in vitro* and (e) platelet phagocytosis by progenitor cells leads to the differentiation of the latter to macrophages and foam cells *in vitro*.

Although there is increasing evidence that bone-marrow-derived progenitor cells play a decisive role in vascular regeneration or injury, the mechanisms that lie behind are poorly understood so far. What determines their fate in peripheral tissues remains to be answered in future studies. Moreover, taking for granted the plasticity of progenitor cells, i.e their ability to differentiate into different cell types, the local environment at sites of vascular injury seems to play a decisive role, not only in the recruitment of progenitor cells, but also in their further differentiation. The recently described progenitor cell interaction with adherent platelets may potentially help us to understand the mechanisms regulating both, vascular regeneration and injury.

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