Platelet interaction with progenitor cells: Potential implications for regenerative medicine

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Summary
Circulating endothelial progenitor cells have been shown to instigate new vessel formation via angiogenesis and neovascularisation and to induce ongoing vascular and tissue repair by domiciliation to sites of vascular or tissue damage. However, the mechanisms that recruit circulating endothelial progenitor cells towards vascular lesions and regulate repair mechanisms of ischemic peripheral organs are poorly described. Domiciliation of endothelial progenitor cells in peripheral tissue is a multi-step cascade including initial adhesion to subendothelial matrix or endothelium, transmigration and invasion of the target tissue. Platelets are the first circulating blood cells that interact with the injured vessel wall. They contain a number of growth factors, chemokines, cytokines and adhesive proteins that are released or surface-expressed upon platelet activation including adhesion. Recent studies suggest that platelet interaction with endothelial progenitor cells influences chemotaxis, adhesion, activation and differentiation of progenitor cells. Release of the chemokine SDF-1 from platelets enhances neovascularization through mobilization of progenitor cells. Adherent platelets recruit bone marrow-derived progenitor cells to arterial thrombi in vitro and in vivo and induce their subsequent differentiation towards an endothelial phenotype. Moreover, platelet accumulation in a co-culture system with CD34+ progenitor cells results in the differentiation of the latter to macrophages in vitro. Although further studies are needed to elucidate the mechanisms that platelets determine the fate of endothelial progenitor cells into vascular lesions, platelet interaction with progenitor cells seems to play a decisive role in vascular and tissue regeneration.

Keywords
Endothelial progenitor cells, platelets, vascular adhesion, endothelial injury

Stem and progenitor cells in regenerative medicine

By definition, stem cells are capable of both self-renewal and differentiation into at least one mature cell type. Stem cells are subclassified on their species of origin, tissue of origin and potential to differentiate into one or more specific types of mature cells (1). In the past few years a number of studies have shown that stem cells can be found in virtually every organ of the adult organism. Stem and progenitor cells can be found in bone marrow, in peripheral circulation, especially after their mobilization following organ injury, and in peripheral organs including liver, heart, kidney and brain (2–4). Bone marrow contains a complex assortment of progenitor cells including hematopoietic stem cells, which differentiate into every type of mature blood cells, endothelial progenitor cells, multipotent adult progenitor cells, marrow stromal cells or mesenchymal stem cells, which are proposed to give rise to the majority of marrow stromal cell lineages including chondrocytes, osteoblasts, fibroblasts, adipocytes, cardiomyocytes, neurons, endothelial cells and monocytes (1, 5–7). Apart from bone marrow, mesenchymal stem cells are located in other tissues such as adipose tissue, peripheral blood, cord blood, nervous system, liver and fetal tissues (7, 8). The functional capability of pluripotent bone marrow-derived, circulating or resident stem and progenitor cells to regenerate tissues includes liver, heart/cardiac muscle, skeletal muscle, central nervous system, kidney, pancreas, lung, skin and gastrointestinal tract (1, 2, 9–12).

Progenitor cells are defined as precursor cells of many different mature cells and they originate from pluripotent stem cells, including hematopoietic, mesenchymal and tissue resident stem cells. According to the last product of differentiation or their location in peripheral organs, progenitor cells are characterised as...
endothelial progenitor cells (13, 14), smooth muscle progenitor cells (15) or cardiac progenitor cells (6), hepatic progenitor cells (16), respectively. More and more studies describe the contribution of progenitor cells in tissue regeneration or remodelling. For instance, 25% of microvascular endothelium in transplanted hearts originates from extracardiac sources (17). Fifty-eight to 88% of neointimal smooth muscle cells originate from bone-marrow progenitor cells (15). Recent pre- and clinical studies using stem and progenitor cell transplantation for organ revascularization and regeneration have shown that introduction of bone marrow-derived hematopoietic and endothelial progenitor cells can restore tissue vascularization after ischemic events in limbs, retina and myocardium, as thoroughly reviewed by Rafii et al. (18) and by Dimmeler et al. (6). Endothelial progenitor cells are the mostly researched progenitor cells due to their capability to differentiate to endothelial cells and to rescue vascular and tissue injury contributing to regeneration and angiogenesis (6, 13, 14, 19–21).

Since the interaction between platelets and precursor cells has been mainly studied on endothelial progenitor cells (22–25), this commentary will focus on the role of platelets on endothelial progenitor cell recruitment, survival and differentiation and its potential implications for regenerative medicine.

Endothelial progenitor cells in tissue regeneration

Asahara et al. reported for the first time in 1997 that purified CD34+ progenitor cells from adults can differentiate ex vivo to an endothelial phenotype (13). These cells were named "endothelial progenitor cells", they expressed various endothelial markers and they incorporated into vessels at sites of ischemia. One year later Rafii et al. published the existence of circulating bone marrow-derived hematopoietic and endothelial progenitor cell in the adult (26). In a similar manner, a subset of CD34+ progenitor cells was shown to differentiate to endothelial cells (26). Moreover, bone marrow-transplanted genetically modified tagged cells were found in implanted grafts (26). Although currently there is a lack of definition of endothelial progenitor cells (14, 20, 27, 28), there is a consensus that they can derive from bone marrow and that CD34 or CD133 positive cells represent a population with endothelial progenitor cell capacity (13, 20, 21, 29, 30). Mobilization of progenitor cells from bone marrow to peripheral circulation takes place under a multifactorial cascade including vascular endothelial growth factor, stromal cell-derived factor-1, erythropoietin, angiopoietin-1, granulocyte colony-stimulating factor, exercise, estrogen and use of statins, as recently reviewed by Aicher et al. (31).

The regenerative ability of endothelial progenitor cells following organ injury (e.g. vasculogenesis [13, 32, 33]) is well established. CD34+ cells have been described to be recruited to the ischemic myocardium, differentiating into cardiac and vascular cells, and restoring cardiac function (6, 34). However, various studies have demonstrated that both in mice and in humans, cardiovascular risk factors, including diabetes and hypercholesterolemia, impair the number and function of endothelial progenitor cells (27, 35). A decrease in the number of circulating endothelial progenitor cells leads not only to impaired angiogenesis but also to the progression of atherosclerosis (36). Patients at risk for coronary artery disease have a decreased number of circulating progenitor cells with impaired activity (37–39). Furthermore, a reduced number of circulating endothelial progenitor cells predicts future cardiovascular events (37). Therefore it is not a surprise that recently there have been studies evaluating the clinical significance of progenitor cell transplantation or mobilization into patients with myocardial infarction (40–44). Intra-coronary or transcortynary 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) (40, 45). 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 (42). However, large double-blinded placebo-controlled trials have not been able to demonstrate effect of G-CSF treatment (43). In patients with AMI or chronic ischemic heart disease, G-CSF did mobilize stem cells of known importance for myocardial regeneration, but there seemed to be a general lack of domiciliation of the stem cells into the ischemic myocardium (43, 44). A molecular dissection is essential to define the multiple steps of progenitor cell homing to and invasion of the myocardium, especially for those cells in current use for clinical cardiac repair (6). Therefore, clinical trials dealing with stem cell transplantation or mobilization highlight the importance of understanding the domiciliation mechanisms of progenitor cells on vascular wall (1, 6, 17, 18, 46, 47).

Platelets beyond thrombosis and haemostasis

Accumulating evidence suggest that platelets play an important role not only in haemostasis, but also in inflammation and tissue repair through paracrine ways or direct cell-cell interactions (48). For instance, platelet-derived products released from activated human platelets increase reactive oxygen species production, resulting in the induction of tissue factor expression in vascular smooth muscle cells (49). Moreover, platelet-derived vascular endothelial growth factor was identified as predominant activator of angiogenesis, particularly of microvascular endothelial cell proliferation and migration (50). Platelets contain a number of growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), angiopoietin-related growth factor (AGF), which are released upon activation and influence the microenvironment and mediate tissue repair (48, 51, 52). Activated platelets release fibroblast growth factor-2 and vascular endothelial growth factor promoting survival and proliferation of endothelial cells and angiogenesis (53, 54). Chemokines (e.g. RANTES, CXC chemokine ligand 4 and 5), and newly synthesised active cytokine-like factors (e.g. IL-1β, CD40 ligand, β-thromboglobulin) are released upon platelet activation (48). Platelet-derived serotonin promotes tissue repair after normothermic hepatic ischemia in mice, while liver regeneration...
and repair are significantly impaired in platelet-depleted animals (55, 56). The fact that platelets secrete growth factors and active metabolites influences clinical situations requiring rapid healing and tissue regeneration (57). Dental implant surgery with guided bone regeneration is one situation where an autologous platelet-rich clot clearly accelerates ossification after tooth extraction and reduces the time for implant stabilization (57). Orthopedic surgery, muscle and tendon repair, reversal of skin ulcers, hole repair in eye surgery and cosmetic surgery are other situations where autologous platelets accelerate healing as thoroughly reviewed by Anitua et al. (57).

Moreover, platelets express a series of adhesion molecules including P-selectin, glycoproteins Ibα-IIIa and Ibβ, junctional adhesion molecules, β3 integrins, which enable them to interact with endothelial cells (58, 59), leukocytes (60–62) and also with endothelial progenitor cells (22, 23, 63). Transient interaction of activated platelets with endothelial cells induces expression of monocyte chemoattractant protein-1 (MCP-1) and matrix degradation by endothelial cells (64–66). Platelets induce alterations of chemotactic and adhesive properties of endothelial cells mediated through an interleukin-1-dependent mechanism (67). Since endothelial progenitor cells are the precursor cells of many different types of mature cells (endothelial cells, macrophages and foam cells), their interaction with adherent/activated platelets may be of utmost importance in understanding the complex phenomenon of tissue regeneration (22–25, 63, 68–70).

It becomes increasingly evident that blood platelets do not only exert important functions in haemostasis and thrombus formation, but are also involved in vascular or tissue regeneration (23, 48, 68). Platelets are the first cells that adhere to sites of vascular lesion, 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 endothelial progenitor cells. Recently, it was found that adherent/activated platelets induce also differentiation of endothelial progenitor cells to endothelial cells or macrophages which could play a pivotal role in tissue regeneration (22–25, 63, 68–70). Elucidating the interaction between progenitor cells and platelets may help us understand the mechanisms that lie underneath tissue regeneration.

Platelet interaction with endothelial progenitor cells: the missing link in tissue regeneration

While homing of hematopoietic stem cells to bone marrow has been extensively studied (71), the mechanisms of endothelial 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. The first response to vascular injury is platelet adhesion either to the exposed sub-endothelium or to inflamed endothelium (72, 73). We recently showed that platelet adhesion not only triggers vascular atherothrombosis but also represents the essential step for the targeting of endothelial progenitor cells to sites of endothelial disruption (23). The role of platelets in chemotaxis, migration, adhesion and differenti-
Adherent platelets recruit endothelial progenitor cells at sites of vascular injury

Platelets play a critical role in the recruitment and adhesion of circulating leukocytes to the vascular wall (77). Recent studies evaluated whether endothelial progenitor cells bind to platelets (22–25). Murine embryonic endothelial progenitor cells adhere to immobilized platelets via P-selectin glycoprotein ligand-1 and very late antigen-4 under high shear conditions in a flow chamber in vitro (22). 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 glycoprotein Ibβ integrin (Fig. 1). Platelet-endothelial 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+ progenitor cells to sites of vascular injury in vivo (23).

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 (63).

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 binds to P-selectin glycoprotein ligand-1 expressed on endothelial progenitor cells (24, 25, 63). Moreover, both β1- and β3-integrins located on endothelial progenitor cells surface are involved in the adhesion process between immobilized platelets and human endothelial progenitor cells (63) (Fig. 1). Furthermore, interestingly direct binding of CD34+ cells to non-stimulated and even stimulated endothelial cells was limited under flow, implying that CD34+ cells are inert to (dys)functional endothelial cells (24, 63). After vascular injury, human CD34+ cells adhere to denuded mouse carotid arteries (24). Therefore, platelets act as an intermediate mediator to tether progenitor cells, indicating that platelets may be a prerequisite for the initial step of the domiciliation process of CD34+ cells to vascular injury.

Adherent platelets induce differentiation of endothelial progenitor cells

Platelets play a critical role not only in capture, but also in subsequent differentiation of endothelial progenitor cells to mature endothelial cells or macrophages and foam cells (22–25, 63, 68–70, 78). Murine embryonic endothelial progenitor cells co-cultured with platelets in vitro revealed a typical endothelial cell-like cytoskeleton and were positive for von Willebrand factor (vWF), as verified by staining with phallolidin or vWF, respectively, and presented with Weibel-Palade bodies similar to mature endothelial cells as verified by transmission electron microscopy (22). Further characterization of the murine embryonic endothelial progenitor cell-derived endothelial cells with RT-PCR revealed expression of the endothelial cell marker CD31 (PECAM-1), flk-1 (vascular endothelial growth factor receptor), vascular endothelial cadherin and thrombomodulin, while the stem cell marker c-kit was decreased (22). Endothelial progenitor cells recruited to platelet aggregates in vivo give rise to neointimal cells, indicating that accumulation of progenitor cells in arterial thrombi may contribute to vascular repair and pathological remodelling (23).

In the human system, co-culture of platelets and CD34+ cells results in a decreased number of apoptotic progenitor cells indicating that platelets support the survival of the latter, as verified with flow cytometry by annexin-V binding (24). Consistent with the findings in the mouse model, human CD34+ progenitor cells can form colonies on immobilized platelets similar to immobilized fibronectin, and further differentiate into mature endothelial cells (24, 63) (Fig. 2). The differentiation of human CD34+ progenitor cells to endothelial cells was usually verified with immunofluorescence microscopy for vWF staining and flow cytometry for expression of the endothelial markers CD146, CD31 and CD144 (24, 25, 63). Furthermore, we could recently show that platelet-derived stromal cell-derived factor-1 (SDF-1) was found to regulate the differentiation of progenitor cells to endothelial cells (78).

On the other hand, in-vitro co-culture experiments for 1–2 weeks between platelets (2x10^6/ml) and human CD34+ progenitor cells induce distinct morphological changes (63). About one

Figure 2: Platelets induce differentiation of human progenitor cells to endothelial cells or to macrophages/foam cells. Human progenitor cells can differentiate in the presence of platelets whether to endothelial cells or to macrophages/foam cells.
third of cells showed a three-fold increase in size with round morphology, high granularity, and a diameter of approximately 25µm (63). These cells were positive for naphthyl acetate esterase (NSE) and CD68, indicating differentiation into the macrophage/monocytic lineage (63). To further characterize the intracellular granules, Sudan red III staining was performed which was found to be positive for these large cells (63). This indicates that a subpopulation of human CD34+ cells transform into large granular and lipid-rich cells, a morphology typical for foam cells (Fig. 2). Phagocytosis of platelets is involved in foam cell generation derived from CD34+ progenitor cells (63). We found that internalization of platelets occurred rapidly and after 24 hours a substantial number of platelets were internalized by foam cells in vitro (63). Phase contrast microscopy shows that these foam cells are surrounded by a platelet-free zone, indicating enhanced phagocytic activity of these cells(63). Transmission electron microscopy of the foam cells revealed the presence of multiple vesicles with phagocytosed platelets or platelet fragments (63). Further studies are needed to explore the biological significance of platelet phagocytosis from endothelial progenitor cells and the subsequent differentiation to macrophages and foam cells.

Antiplatelet medication and platelet function

An absolute prerequisite of all the effects that were described in the means of platelet interaction with endothelial progenitor cells was platelet activation/adhesion. The question that rises automatically is whether antiplatelet medication influences or inhibits the platelet-induced recruitment and differentiation of endothelial progenitor cells. Since platelet interaction with endothelial progenitor cells has been only recently studied, the effect of antiplatelet drugs on this interaction has not been described yet. On the other hand, there are plenty of studies evaluating either the expression and release of specific platelet activation markers or the effectiveness of antiplatelet therapy in patients with various ischemic diseases including acute myocardial infarction and stroke (79–85). These studies could provide us with a hint of how antiplatelet medication could influence platelet interaction with endothelial progenitor cells or with any other blood cells.

Accumulating evidence suggests that antiplatelet therapy can significantly decrease platelet activation or aggregation, but it is not sufficient to inhibit platelet secretion or even to adequately inhibit platelet aggregation in all patients (86–92). For instance, clopidogrel attenuated platelet aggregation to ADP by 22%, P-selectin expression by 16%, plasma levels of CD40L were reduced by 27% and soluble P-selectin by 15% compared to placebo (93). Moreover, variable platelet response among patients and presence of other diseases, like diabetes, influence the efficiency of antiplatelet therapy (90).

Several studies report that although patients with acute ischemic diseases, like acute myocardial infarction or stroke, receive antiplatelet therapy, they present with increased expression or release of platelet activation biomarkers (like P-selectin and CD40L) or increased platelet binding to circulating monocytes (79–85). Platelet activation, determined by surface expression of platelet-derived P-selectin, persists despite antithrombotic therapy in patients with unstable angina and non-Q-wave myocardial infarction (94). Moreover, platelet activation, measured as a combination of P-selectin expression, conformational expression of glycoprotein Ib/IIa, formation of platelet-leukocyte complexes, evaluation of plasma soluble P-selectin is evident in patients with acute pulmonary embolism or atrial fibrillation (95, 96). CD40 ligand (CD40L) is expressed on platelets and released from them upon activation (84, 85). Both platelet-bound CD40L and soluble CD40L are increased in patients with acute coronary syndromes, although most of the patients were under antiplatelet medication (84, 85).

Furthermore, we could recently show that the expression of platelet collagen receptor glycoprotein VI (GPVI) was constitutively expressed on circulating platelets in patients with stable coronary artery disease and it was significantly increased in patients with acute coronary syndromes, independent of antiplatelet therapy or any other medication (97). Collagen binding to GPVI not only activates platelets but also mediates their adhesion on subendothelium (72). Therefore, in case of endothelial denudation at sites of vascular injury, the subendothelial matrix (collagen, fibronectin, laminin, thrombospondin and vWF) is exposed to blood flow attracting resting platelets through interaction with specific receptors on the platelet surface (glycoproteins IIa, IV, VI and Ib/IX/V) (48, 98). Following adhesion, platelet activation can be initiated by several extracellular stimuli (98). Among these stimuli are the exposed collagen, the locally generated thrombin and the ADP released from damaged cells (98). Agonist-stimulated platelets change shape, secrete more platelet agonists (ADP, thromboxane A2, platelet activation factor and others) that recruit and activate additional platelets and transform the glycoprotein Ib/IIa into an active form leading to platelet aggregation (99). Adherent platelets on subendothelium facilitate the further recruitment and differentiation of endothelial progenitor cells as described above.

It is not surprising that a sole or a combination of current antiplatelet drugs is not able to completely inhibit platelet activation
and in specific granule secretion since platelets can be activated through multiple ways. Taking into consideration the beneficial effects of platelet adhesion and platelet interaction with progenitor cells, a complete abolishment of platelet activation/adhesion seems to be unlikely with the current antiplatelet drugs.

Platelets: the key players in tissue regeneration?

Recent studies provide evidence that murine and human platelets interact with murine and human progenitor cells, respectively, in multiple ways involving the following: i) activated platelets support mobilization and chemotaxis of endothelial progenitor cells, partially through release of the chemokine SDF-1, ii) adhesion of endothelial progenitor cells to vascular wall is abolished by platelet depletion in vivo, iii) human progenitor CD34 cells directly adhere to immobilized platelets in vitro and to denuded mouse carotid arteries in vivo, iv) platelets induce differentiation of endothelial progenitor cells to mature endothelial cells in vitro or give rise to neointimal cells in vivo, and v) platelets regulate differentiation of human progenitor cells either to a endothelial or to a macrophage/foam cell phenotype in vitro.

In conclusion, endothelial progenitor cells normally circulate within blood in small numbers, encountering only brief contacts with the vascular endothelium. In case of tissue ischemia or injury, endothelial progenitor cells are mobilized in the peripheral circulation and participate in the regeneration process. Activated circulating or adherent platelets can interact with endothelial progenitor cells promoting their recruitment and differentiation. Therefore, platelet interaction with endothelial progenitor cells could potentially play a central role in tissue renewal or repair (Fig. 3). Platelet adhesion to the vascular wall seems to be the first step for further interaction between platelets and progenitor cells (Fig. 3). Further studies are required to investigate the underlying molecular determinants of the platelet interaction with progenitor cells, which may offer new strategies to support vascular repair and tissue regeneration of ischemic organs. Moreover, the interaction of platelets and other progenitor cells or stem cells remains to be investigated in future studies since hematopoietic stem cells, mesenchymal stem cells, resident stem and progenitor cells actively participate in tissue regeneration. Moreover, identification of cellular mediators and tissue-specific chemokines, which facilitate selective recruitment of bone marrow-derived stem and progenitor cells to specific organs, will open new avenues of research to accelerate organ vascularization and regeneration (18). In addition, identification of factors that promote differentiation of progenitor cells will permit functional incorporation into neo-veins of specific tissues while diminishing potential toxicity to other organs (18).

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