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COMMENTARY

Circulating endothelial cells and endothelial progenitor cells after angioplasty: news from the endothelial rescue squad

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In the 19th century, Friedrich von Recklinghausen discovered that blood vessels possess a lining [1]. It has been estimated that 1.2 trillion of these cells cover a surface of 400 m^2. They are not, as Recklinghausen had believed, a mere 'tapestry'. Instead, endothelial cells regulate vascular tone via nitric oxide, ensure the homoeostasis of coagulation, and participate in immune events via complex interactions with circulating cell subsets [2]. Endothelial dysfunction and damage have been the focus of investigators during the past decade and various approaches have been employed. Flow-mediated dilatation of the brachial artery has gained widespread use but the technique remains cumbersome. Endothelial damage can be assessed by soluble markers, such as thrombomodulin or von Willebrand factor, circulating endothelial cells (CECs) [3] and, more recently, endothelial microparticles [4]. Likewise, repair of endothelial damage has been studied ever since Jeffrey Isner and colleagues at Tufts University described bone marrow-derived endothelial progenitor cells (EPCs) [5]. Unfortunately, these cells still lack a clear-cut phenotype as reviewed elsewhere [6].

In this issue of the *Journal*, Bonello and colleagues from Marseille [7] report a remarkable study on CECs and EPCs in patients with stable coronary artery disease who underwent percutaneous catheter intervention (PCI). It was already known that numbers of CECs are elevated after myocardial infarction (MI) [8]. In fact such studies had already been done in the 1970s, albeit with primitive methodology [9]. Furthermore, EPCs have been demonstrated previously after MI [10]. What additional information does this study provide? Bonello and co-workers studied a cohort of patients with stable coronary artery disease and not with acute coronary syndromes. It is remarkable that elevated numbers of CECs are also found after angioplasty in stable coronary artery disease. These cells must derive from endothelial damage by the catheter procedure itself, as cell numbers had been normal at baseline. Immunomagnetic isolation is a very sensitive approach as the technique was originally devised to isolate circulating tumor cells. Flow cytometry may also have its advantages although a direct comparison between the two techniques is not available so far.

Mechanisms of endothelial cell detachment remain simple when mechanical force is the most likely cause, as in the present study. In contrast, we do not know the sequence of events in inflammatory disorders [11]. Factors that protect against endothelial detachment, such as cadherins, integrins and fibronectin, exist as well [11]. Little, if anything, is known about the kinetics of CEC clearance from peripheral blood. Bonello demonstrated a peak of CEC values after 6 h while cell numbers declined to baseline after 1 week. Such data need further corroboration, probably from animal models. Further studies should elucidate the fate of CECs, mechanisms of clearance and interactions with other cells [11]. Figure 1 summarizes the concept of endothelial cell detachment.

Bonello and co-workers next analyzed hematopoietic progenitor cells and EPCs, and found an increase in progenitor cells as early as at the end of the procedure. It is amazing to observe this very timely reaction of EPCs as an 'endothelial rescue squad'. Various mechanisms have been proposed to explain how EPCs are alerted to ongoing endothelial damage. At present, vascular endothelial growth factor (VEGF) is best characterized. Elevated serum levels of VEGF have been demonstrated as a sequel to ischemic injury and VEGF has been shown to mobilize EPCs from bone marrow [5]. More recently, the discovery that erythropoietin (EPO) regulates EPCs [12] has sparked considerable interest, not only among nephrologists who use this drug on a daily basis. These observations provided a tantalizing opportunity to manipulate the EPC system in vascular disease. Studies into the use of EPO in stroke and MI are currently under way. Administration of EPO would be much less cumbersome than the direct application of stem cells as described after MI [13]. More regulators of EPCs are currently emerging and others still await

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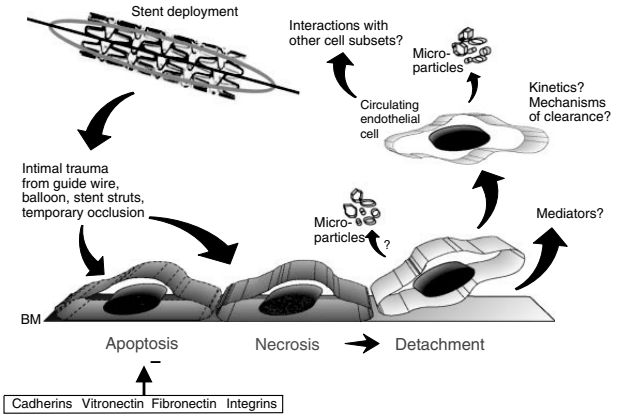

Fig. 1. Detachment of endothelial cells. BM denotes basement membrane.

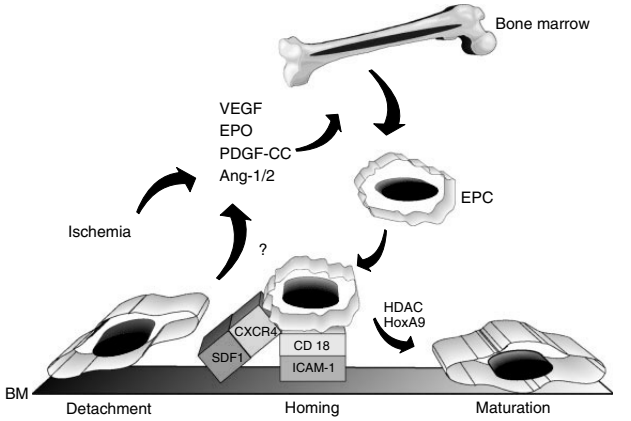

Fig. 2. Mechanisms of endothelial repair. BM, basement membrane; EPC, endothelial progenitor cell; ANG, angiopoetin; EPO, erythropoetin; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; SDF, stromal-cell derived factor; CXCR, chemokine motif receptor; HDAC, histone deacetylase activity; HoxA9, homoeobox transcription factor A9; CD, cluster of differentiation 18; ICAM, intercellular adhesion molecule.

discovery. Very recently, platelet-derived growth factor (PDGF-CC) has been shown to mobilize EPCs [14]. The Angiopoetins (Ang-1 and Ang-2) [15] and alpha-4 integrin [16] have been implicated as well. Much of the interest into these mechanisms stems from high hopes that their inhibition may halt tumor angiogenesis and thus improve anti-cancer treatment [17]. It is also tempting to speculate about mechanisms of EPC mobilization in the present study. Is it endothelial trauma or the brief period of ischemia during catheter occlusion of the diseased artery? At present, we do not know whether the detachment of endothelial cells directly mobilizes EPCs. Further studies should also investigate whether endothelial trauma without ischemia, for example, with a guidewire alone, is sufficient to mobilize EPCs. It is conceivable that interactions of CECs or microparticles with other cell subsets are involved in EPC mobilization, but can such interaction occur within 6 h? In addition, it would be interesting to see serial measurements of CECs, microparticles, VEGF and EPCs after a well-defined episode of vascular trauma. Mechanisms of EPC homing and maturation have been studied very recently. It has been shown that a chemokine, stromal-cell derived factor-1 (SDF-1), attracts EPCs through interaction with chemokine motif receptor 4 (CXCR4) [18]. Homing is then mediated, at least in part, via CD18/ICAM-1 interaction [19]. Commitment to an endothelial phenotype involves histone deacetylase activity (HDAC) and the homoeobox transcription factor (HoxA9) [20]. Figure 2 summarizes possible mechanisms of endothelial repair.

Finally, the authors noted an inverse correlation between CEC and EPC counts. The authors speculate that this finding supports the recent observation that CECs directly impede EPCs [21]. How can we understand these findings? If CECs would directly impair release of EPCs from bone marrow how could endothelial damage ever heal? At present, it seems difficult to reconcile these findings with current concepts of vascular healing and repair. Bonello and colleagues admit that EPCs may be no longer present in peripheral blood because they have already homed to sites of vascular trauma. Indeed, kinetics of EPC release and homing remain incompletely understood. For now, direct impairment of EPC function by CECs must be confirmed by further studies before it is accepted as a biological principle.

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