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

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See also Bonello L, Basire A, Sabatier F, Paganelli F, Dignat-George F. Endothelial injury induced by coronary angioplasty triggers mobilization of endothelial progenitor cells in patients with stable coronary artery disease. This issue, pp 979–81.

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 m². 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
The discovery of circulating endothelial cells (CECs) has led to a significant advancement in our understanding of vascular biology. Recent studies have shown that CECs can be mobilized in response to endothelial trauma, which is crucial for vascular healing and repair. The mechanisms underlying CEC mobilization and their role in vascular biology are still being explored.

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

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

CECs must be confirmed by further studies before it is accepted as a biological principle.

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**References**