Vessel repair: do progenitor cells hitchhike a piggyback ride?

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Since the first observations that the numbers of circulating CD34+ progenitor cells are increased in patients with coronary artery disease and after myocardial ischaemia1,2 and are associated with a better cardiovascular outcome,3 a plethora of mechanisms have been proposed to explain their potential beneficial effects and investigate their therapeutic usage.4 Along with the rather improbable potential to transdifferentiate into cardiomyocytes and reduce tissue scar, CD34+ progenitors cells have been implicated in promoting pro-angiogenic reactions and regulating vascular repair—probably by a paracrine mechanism.5 CD34+ cells along other progenitors are mobilized during myocardial ischaemia and may home towards the ischaemic tissue, driven at least in part by the chemokine receptor CXCR4.6 The mechanism involving recruitment of progenitor cells and their homing towards ischaemic tissue is complex and involves chemoattraction, migration, adhesion, and tissue dissemination. However, it remains unclear how circulating progenitors are directed towards and colonize the injured tissue, after acute myocardial infarction. The signalling pathway that links endothelial lesions to recruitment of progenitor cells to the injured site may be driven by the (stromal cell-derived growth factor-1) SDF-1/CXCR4 pathway.7 Accordingly, low-level shear stress after injury induces the release of SDF-1 by damaged endothelium engaging the CXCR4 receptor on progenitor cells and favours attraction of mesenchymal stem cells to the lesion.8 However, adhesion of progenitor cells to extracellular matrix proteins does not seem to be a very efficient process, and it is unclear whether adhesion of progenitor cells to vascular lesions requires additional factors. There is evidence that platelet-derived SDF-1 which is the predominant chemokine for progenitor cells, increases after acute myocardial infarction.9,10 Therefore, it has been proposed that platelets may rescue and help in recruiting stem cells to sites of injury on blood vessels. Progenitor cells can tether to platelets and exchange signals that help them to adhere to the vascular wall and differentiate into endothelial cells, thereby promoting healing.11 According to this view, platelet adhesion would be essential to direct progenitor cells towards sites with endothelial lesions. Differentiation of progenitor cells is helped by both adhering platelets and platelet-derived factors. Recent evidence suggests that a direct interaction between platelets and CD34+ cells may be involved in their endothelial adherence.12 Stem cells may indeed hitchhike a piggyback ride on circulating platelets that would drive them to their new permanent domicile.

The study now published by Stellos et al.13 asks the question of whether platelets may form co-aggregates with circulating CD34+ progenitors in patients with acute coronary syndromes and thereby increase peripheral recruitment within the ischaemic microcirculatory district and promote adhesion to the vascular lesion, and thus increase healing. The major finding is that in patients with acute coronary syndrome, the levels of circulating platelet–CD34+ cell complexes increases (Figure 1). More importantly, the numbers of these cell complexes are the highest in a subset of patients with acute ST-elevation myocardial infarction as compared with patients with stable angina or non ST-elevation myocardial infarction. Notably, the authors found a positive correlation between the level of platelet-derived SDF-1 and the number of CD34+ cells and the improved haemodynamic function, measured as left ventricular ejection fraction, in patients with acute ST-elevation myocardial infarction. Moreover, the increased level of platelet–CD34+ complexes was associated with platelet activation, and patients with higher baseline levels of the platelet–CD34+ complex had a reduced myocardial infarction size at 3 months follow-up. This suggests a beneficial effect of the platelet–CD34+ interaction. Because platelet–CD34+ complexes show increased adhesion to both collagen and endothelial cells in vitro and in vivo, it is likely that formation of aggregates of these two cell types is important for homing and adhesion of CD34+ cells to damaged endothelium. Clearly the study poses a series of intriguing questions. The first relates to other studies in vitro and in vivo showing that CD34+ cells increase after acute myocardial infarction, but that simple endothelial

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lesions are also sufficient to drive progenitors to the injured area (shear stress). In addition it is clear that CD34+ cells are not the only progenitors to be mobilized. The more immature progenitors expressing the CD133+ marker are also mobilized after acute myocardial infarction, and the levels of both CD34+ and CD133+/CD34+ cells predict survival. Accordingly, transplantation of CD34+ or CD133+/CD34+ cells stimulates neovascularization and promotes functional recovery after myocardial infarction in vivo. The authors do observe an increase in the numbers of CD133+/CD34+/CD42b aggregates in patients with acute coronary syndromes, clearly suggesting that more than one progenitor cell type is involved in the ischaemic process. It remains to be established whether a similar mechanism of co-aggregate formation applies to CD133+/CD34+ progenitors and other progenitor cells. If so, treatment strategies to increase co-aggregate formation or ex vivo expansion of these complexes may provide interesting therapeutic tools. The study does not address the relative contribution of co-aggregation compared with other mechanisms of homing. It would be of relevance to compare the levels of SDF-1 with or without platelet activation and test adhesion and the number of cell–cell aggregates in CXCR4 knock-out mice or in the presence of small molecules that antagonize the SDF-1–CXCR4 interaction.

Notably, the fluctuations in circulating endothelial progenitor cell levels, including CD133(+), KDR(+), and CD34(+) cells, show significant pattern differences between acute ST-elevation myocardial infarction patients and patients with stable coronary artery disease or controls. The functional consequences of aggregate formation and whether this mechanism applies to other progenitor cells will need to be addressed by future work. The authors are to be congratulated for their meticulous work and for again stimulating progenitor cell research in cardiovascular science which seems to have lost some of the momentum of the last decade. Nevertheless, the findings are hypothesis-generating but do not provide causality and so far it has not been proven whether progenitors are significantly involved in human cardiovascular damage and ultimately repair or even regeneration.14 This may partly be related to the complexity of the underlying mechanisms. The proposed platelet progenitor interplay adds yet another preliminary piece in solving the puzzle. However, it remains to be determined where, in what quantity, and for how long these co-aggregates adhere in the human heart and what their

**Figure 1** Progenitor–platelet co-aggregates: following myocardial injury, CD34+ progenitor cells are mobilized from the bone marrow; they migrate and home to sites of damaged endothelium. The study by Stellos et al.13 identifies a new cell population, i.e. CD42b–CD34 cell co-aggregates, as being increased in patients with acute coronary syndromes. Progenitor cells form complexes with activated platelets, display better adherence to sites of endothelial injury, and may enhance vessel repair and reduce infarct size.
biological role may be. It cannot be excluded that these cells serve just as a measurable marker for yet another unknown additional process—which could still be of considerable clinical value.

In addition, the interaction with antiplatelet therapy needs further investigation. What is the impact of antiplatelet treatment on the formation of platelet–progenitor cell co-aggregation formation? Aggressive treatments against platelet aggregation are of current use in patients with acute coronary syndromes. Yet, antiplatelets seem to hamper the novel potentially beneficial roles of the co-aggregates. Additional investigations of these parameters in a longer time frame could shed some light in this potential contradiction.

Taken together, the study by Stellos et al. identifies progenitor–platelet co-aggregates as novel players in the myocardial ischaemia arena and opens new research avenues, both pre-clinical and clinical, to investigate the role and, more importantly, the mechanisms of action of these cell complexes. Considering that despite huge advances in therapies, cardiovascular mortality continues to pose an immense burden, new therapeutic strategies targeting myocardial regeneration following ischaemia are indeed needed.

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References