Human umbilical cord blood cells and myocardial infarction:
Novel ways to treat an old problem

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The report by Ma et al. [4] in the current issue of Cardiovascular Research provides encouraging new evidence concerning an alternative cellular source for cardiac repair following myocardial infarction. The authors transplanted human umbilical cord blood mononuclear cells containing 0.11 to 1.1% CD34-positive cells intravenously into immunocompetent NOD/SCID mice that had or had not previously undergone ligation of the left anterior descending coronary artery. At time points 24 h, 1 and 3 weeks, homing to bone marrow, spleen, liver, and heart was analyzed by immunostaining, and myocardial scar formation, capillary density, and stromal-derived factor-1 (SDF-1) expression were assessed. Transplanted human umbilical cord blood cells were found in bone marrow, spleen, and liver of both control animals and mice with myocardial infarction. In contrast to controls however, transplanted cells were only detected in hearts of mice with myocardial infarction (10 out of 19 cases). The hearts of these animals were characterized by a reduction in infarct size and collagen deposition, while capillary density in the infarct border zone and SDF-1 expression were increased. These results indicate that human umbilical cord blood mononuclear cells have the potential to selectively home to the heart under ischemic conditions, and may contribute to regeneration of infarcted myocardium by enhancing neoangiogenesis and cardiac remodelling.

This finding is of particular interest, as the number of stem cells detected in different compartments of the body is very low, and the use of cells from cord blood might offer a number of advantages compared to other cellular sources for cardiovascular regeneration. In that respect, the number of stem cells that can be derived from human cord

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blood seems to be much higher than from peripheral blood, and at least equal to or higher than from bone marrow [5]. Furthermore, cord blood contains different subpopulations of stem cells, including endothelial progenitor cells and mesenchymal stem cells [6]. Cord blood-derived stem cells possess a high potential for transdifferentiation into a variety of cell types, and seem to proliferate and differentiate at a faster rate than stem cells derived from other adult sources, possibly due to their neonatal origin [7,8]. From a functional perspective, transplanted umbilical cord blood CD34-positive stem cells have been shown to increase both neovascularization and perfusion in the ischemic hindlimb model [8], where umbilical cord blood-derived stem cells have been shown to exhibit myoendothelial differentiation [9]. Moreover, ex vivo differentiated endothelial and smooth muscle cells from human cord blood progenitors have been shown to home to the angiogenic tumour vasculature [10].

Positive results from experimental and clinical studies have raised hopes that cell-based strategies for cardiovascular regeneration will be of therapeutic value in the future [1,2]. However, there are still several unanswered questions that need to be addressed. First, studies comparing the different cellular sources for cardiac repair are warranted. These studies should determine the cell type or mixture of stem cell subpopulations with the highest regenerative capacity, the optimal number of cells to be transplanted, and the most efficacious route of delivery (i.e., intravenously, intracoronary, transendothelial, or intramyocardial). Similarly, as Ma et al. [4] have provided evidence for the cardiovascular repair potential of transplanted human cord blood cells, these will have to be subfractionated in future studies to characterize the functionally relevant stem cell or stem cell mixture. Secondly, the mechanisms of homing of the administered cells to the infarcted area of the myocardium need to be characterized (Fig. 1A). What are the chemokines, chemokine receptors,
endothelial adhesion molecules, and cellular integrins involved? In that respect, it is particularly interesting that Ma et al. [4] found a sevenfold upregulation of SDF-1 mRNA in the infarcts as compared to control. One could speculate that increased secretion of SDF-1 by the infarcted myocardium attracts circulating stem cells via the CXCR4 receptor, leading to activation of surface integrins and subsequent recruitment into the vasculature. Third, the mechanisms of action of transplanted stem cells need to be dissected (Fig. 1B). As only low numbers of administered stem cells are found within the area of damage but are sufficient to exert beneficial effects, do they act indirectly via secretion of cytokines or directly by transdifferentiation into various functionally active cell types? Interestingly, Ma et al. [4] did not observe any evidence for cardiomyocyte differentiation of transplanted cord blood cells. However, Ma et al. [4] did not analyze myocardial and peripheral blood cytokine profiles in recipient mice, and also failed to provide data on the functional consequences of cord blood cell transplantation such as left-ventricular ejection fraction. Possibly, a strategy combining cardiac cell therapy and therapeutic neoangiogenesis using angiogenic growth factors might yield the best results for cardiovascular regeneration [11]. Interestingly, our group has recently shown that physical training increases endothelial progenitor cells, inhibits neointima formation, and enhances angiogenesis [12]. Finally, large-scale, placebo-controlled, randomized clinical trials need to be performed to confirm results from early phase I clinical trials. While the report by Ma et al. [4] provides encouraging new evidence for an alternative cellular source for cardiac repair, there clearly is still a long way to go before such cell-based therapeutic strategies can be translated into the clinics.

References