The stem cell army in heart failure: do we mobilize or pave the way home?

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This editorial refers to ‘Circulation of CD34+ progenitor cell populations in patients with idiopathic dilated and ischaemic cardiomyopathy (DCM and ICM)’ by H.D. Thiess et al., on page 1258

Pharmacological modulation of heart failure, although capable of substantially reducing morbidity and mortality, does not halt the relentless progression of adverse cardiac remodelling and failure. Hence, invoking the body’s own repair mechanisms embodied in its stem cell population present in the myocardium itself or mobilized from the bone marrow is an attractive therapeutic concept to combat heart failure. Pre-clinical studies have shown the promise of this therapy; however, much work needs to be done to address various questions that arise about bone marrow-derived stem cells in regard to mobilization, homing to the myocardium, their fate within the myocardium, and whether mechanism of benefit is due to regeneration of myocardial cells or other paracrine effects of stem cells. The study by Theiss et al. provides some important insights into the field of stem cell biology in heart failure.

In this study, the authors examined circulating stem cell populations, peripheral levels of haematopoietic growth factors and other cytokines, and the expression of homing factors in the myocardium of subjects with ischaemic cardiomyopathy (ICM), dilated cardiomyopathy (DCM), and normal subjects. Majority of the subjects was men in all three groups, and the mean age was elevated, although non-significantly, in the ICM population compared with DCM and controls. Therapeutic regimens were similar, except for a greater use of statins and aspirin in the ICM population, which did not significantly affect the results. Other clinical characteristics including left ventricular ejection fraction were also similar between the ICM and DCM groups. Circulating stem cell levels were analysed by flow cytometry, differentiating CD34+ haematopoietic stem cells into those expressing CD133 (endothelial progenitor cell marker), CD31 (mature endothelial cell marker), and CXCR4, which is the receptor for the powerful stem cell homing factor stromal-derived factor-1 (SDF-1). All three stem cell populations were increased in DCM subjects compared with ICM and control subjects. The levels of granulocyte-colony-stimulating factor (G-CSF) and stem cell factor (SCF), which are powerful mobilizers of bone marrow-derived cells, were similar to controls (or decreased in the case of SCF in DCM subjects). Since the levels of G-CSF and SDF-1 were similar between ICM and DCM and since SCF levels were lower in DCM subjects, it does not appear that a disparity in haematopoietic growth factors led to the observed difference in circulating stem cells between the two groups.

The authors examined the possibility that a difference in the degree of stem cell homing to the myocardium could be a factor in the observed difference in circulating stem cell number. The homing factor SDF-1 and its receptor on stem cells CXCR4 form an important axis in the mobilization of stem cells from the bone marrow and in their homing to tissue sites of injury. SDF-1 is expressed in the bone marrow and presumably holds stem cells captive in the bone marrow by binding to CXCR4 on the stem cell surface. In response to stem cell mobilizing factors such as G-CSF, SDF-1 is degraded by proteases, and a gradient is established between bone marrow and peripheral circulation that promotes stem cell migration into blood. The subsequent fate of circulating stem cells is determined by the presence of homing factors in tissue. The authors analysed mRNA expression utilizing real-time PCR for various putative homing factors in the left ventricular myocardium from the three groups. The striking finding was the marked elevation of SDF-1, SCF, hepatocyte growth factor, hypoxia inducible factor-1α, and vascular cell adhesion molecule in ICM hearts compared with DCM and control hearts (DCM and control hearts showed similar expression). Although the authors did not analyse protein expression, these results strongly suggest a marked upregulation of homing factor expression in ICM hearts compared with DCM hearts. Limitations of these results include the small number of subjects, the fact that heterogeneous myocardial tissue was homogenized for the analysis, and that protein expression was not measured. However, the several-fold increase in mRNA expression of all factors analysed in ICM hearts lend
credence to the possibility that ICM hearts upregulate homing factors, whereas DCM hearts do not. A recent study indicated that myocardial injury was necessary in addition to SDF-1 to induce stem cell homing; this study did not address the degree of ongoing myocardial injury in ICM hearts vs. DCM hearts. Stem cells expressing the SDF-1 receptor CXCR4 were increased in DCM subjects also; hence, suppression of homing receptor expression in circulating stem cells is unlikely to be a reason for decreased homing in DCM. It has been suggested that plasma SDF-1 levels may need to be low to permit 'release' from the peripheral circulation and homing to tissues. Since plasma SDF-1 levels were high in both DCM and ICM subjects, it is not clear whether homing would occur to the myocardium in ICM subjects even in the presence of high myocardial SDF-1 expression, since an appropriate gradient may not have existed between blood and the myocardial tissue.

Overall, this study raises the intriguing possibility that the expression of homing factors in the myocardium and subsequent ingress of cells feeds back on bone marrow mobilization. This would explain the inverse relation between increased circulating stem cell number and myocardial homing factor expression in DCM and ICM hearts. As the authors suggest, further pre-clinical studies are needed to understand the process of stem cell mobilization and homing and the regulation of these processes. It is possible, as the authors suggest, that focusing on increasing the expression of homing factors in DCM and on stem cell mobilization in ICM would be reasonable approaches to achieve the aim of improving myocardial remodelling. In this regard, a small pilot study from our group suggested that ICM subjects may respond better to stem cell mobilization with GCSF. We cannot discount the possibility that stem cells may act by endocrine or paracrine mechanisms as suggested by the pilot study, and that consequently stem cell mobilization strategies may be beneficial in DCM even in the absence of myocardial homing. Regardless, the present study shows that the biology of stem cells and stem cell-based therapies may be different in ICM and DCM. Hence, careful mechanistic clinical studies and pre-clinical studies are needed to understand the process of stem cell mobilization, homing factor expression, tissue fate of stem cells, and endocrine and paracrine effects of mobilized bone marrow-derived blood cells in addition to their specific myocardial effects, before clinical trials are initiated in chronic heart failure.

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References