Editorial

Role of stromal cell derived factor-1 in myocardial healing—novel insights from comparative studies in the fetal and postnatal myocardium

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Comment on: Zgheib C, Hodges MM, Allukian MW, *et al.* Cardiac progenitor cell recruitment drives fetal cardiac regeneration by enhanced angiogenesis. Ann Thorac Surg 2017;104:1968-75.

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Myocardial infarction is the most important cause for chronic systolic heart failure in adults since the adult heart has negligible regenerative capacity implicating that every ischemic insult leads to loss of contractile tissue. On the other hand, chronic remodeling processes in the viable myocardium also contribute to the development of heart failure after myocardial infarction. All these processes are critically regulated by innate immune cells, especially monocytes and macrophages (1,2). These cells have recently been shown to respond differently to myocardial injury in adult and fetal or newborn hearts, which have an astonishing regenerative capacity (3,4). Of note, nearly complete and scarless regeneration of fetal and neonatal myocardium has been described not only in rodents (5) but also in newborn children (6).

Zgheib and coworkers (7) show that the fetal sheep heart regenerates from experimental infarction. This is accompanied by the restoration of the myocardial microvasculature. There were differences in the expression of M2-like macrophage genes (CD163, CD206) within the myocardium from injured fetal and adult hearts. Especially, within the infarct zone of the adult heart there was persistent upregulation of the aforementioned markers which could be indicative of both differences in macrophage differentiation over time and myeloid cell numbers, including recruited monocytes, within the myocardial tissue. Interestingly, inhibition of stromal cell derived factor-1 (SDF-1) reproduced the adult pattern of sustained M2-like marker expression in fetal hearts at 30 days after injury. The M2-like markers were upregulated but vascular endothelial growth factor (VEGF) expression was downregulated in SDF1 inhibitor treated fetal hearts at 30 days which nicely parallels the defective restoration of the microvasculature in anti-SDF-1 treated animals. Although the authors did not directly analyze the differentiation and activity of cardiac macrophages the data fit well into the concept mainly derived from mouse studies that cardiac macrophages are critical determinants of the heart's regenerative potential (8).

Under hypoxic conditions, the transcription factor HIF-1α is up-regulated. HIF-1α in turn up-regulates SDF-1 and its ligands, CXCR4 and CXCR7. By this mechanism SDF-1 facilitates stem cell homing to hypoxic tissues (9). Local hypoxia drives SDF-1α expression, which under steady state conditions results in the retention of stem cells in the bone marrow (10). SDF-1 is up-regulated in various experimental and clinical studies of acute myocardial infarction. The expression of SDF-1 in infarcted myocardium has been associated with recruitment, retention, survival, and proliferation of various stem/progenitor cell subsets (11-13).

Most of the abovementioned studies regarded SDF-1 as a factor attracting stem/progenitor cells to the injured myocardium leaving aside potential effects on embryonic tissue resident macrophages. As infiltration of circulating monocytes/macrophages is less prominent in neonatal

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hearts than in adult hearts after acute injury, regeneration is probably largely mediated by the embryonically-derived resident macrophage population which plays a crucial role in regenerative processes and is required for neonatal heart regeneration. Neonates depleted of macrophages were unable to regenerate and develop fibrotic scars, resulting in reduced cardiac function and angiogenesis (14). Immunophenotyping and gene expression profiling of cardiac macrophages from regenerating and non-regenerating hearts indicated that regenerative macrophages have a unique polarization phenotype and secrete numerous soluble factors that may facilitate the formation of new myocardium (14). On the other hand, the massive influx of pro-inflammatory monocytes in the post-natal injured myocardium together with a loss of resident embryonic macrophages likely precludes scarless healing and complete regeneration (15). Monocyte derived macrophages predominate in the adult myocardium after injury where they acquire a M2-like pro-fibrotic phenotype. Hence, besides its well described effects on stem cell attraction to injured issues one should consider a potential effect of SDF-1 on the maintenance of self-renewing tissue resident macrophages.

SDF-1 delivery to the myocardium was associated with improved angiogenesis and left ventricular function in different animal models and human studies (16). These promising data from animal models prompted a clinical phase 1 dose escalating study testing a DNA plasmid encoding human stromal cell-derived factor-1 in subjects with stable ischemic cardiomyopathy (17). The investigational intervention improved 6-minute walk distance and quality of life. Due to its open label design it needs further validation.

A potential drawback for the therapeutic use of SDF-1 early after infarction to modify cell recruitment to inflamed tissues is the relatively short half-life of SDF-1 due to myeloid cell secreted proteases (18). An interesting approach to prolong its half-life relates to a class of anti-diabetic drugs. Dipeptidylpeptidase-4 (DPP-4) inhibitors have been designed to prevent the breakdown of the incretin glucagon-like peptide 1 (GLP-1) by inhibiting the protease DPP-4 thereby increasing insulin secretion in the pancreas. Active SDF-1α is also cleaved by DPP-4 and thus DPP-4 inhibition increases the half-life of SDF-1α by preventing its degradation (19).

Several experimental studies have attempted to exploit this mechanism. Combined DPP-4 inhibition using Diprotin A with G-CSF-mediated stem cell mobilization in a murine model of myocardial infarction (19). The study found increased CXCR4+ progenitor cell homing, reduced cardiac remodeling and apoptosis, and improved ejection fraction and survival. An analogous approach was then clinically tested in a phase III trial using Sitagliptin (Safety and efficacy of Sitagliptin plus Granulocyte-colony-stimulating factor in patients suffering from Acute Myocardial Infarction, SITAGRAMI). The trial randomized patients to either G-CSF and Sitagliptin or placebo after acute myocardial infarction in a double-blind design. However, the study failed to show a beneficial effect on cardiac function and clinical events (20). The reasons for the failure in the clinical trial were not clear but indicate that we do not sufficiently understand the function of SDF-1 in adult myocardial healing yet. Therefore, further comparative studies like the study from Zgheib and coworkers (7) will bring the field forward towards a better understanding of the role of progenitor cell recruitment and local macrophage proliferation after acute myocardial infarction.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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