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CLINICAL IMPLICATIONS

The promise of stromal cell-derived factor-1 in novel heart disease treatments

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The stromal cell-derived factor 1 (SDF-1), also known as C-X-C motif chemokine 12 (CXCL12), is a chemokine that is ubiquitously expressed in many tissues and cell types [1]. Chemokines activate leukocytes and are induced by pro-inflammatory stimuli such as lipopolysaccharide, tumor necrosis factor-α (TNF-α), or interleukin-1 (IL-1). SDF-1 is important in hematopoietic stem cell homing to the bone marrow as well as in hematopoietic stem cell quiescence. The *CXCL12* gene encoding SDF-1 contains a single-nucleotide polymorphism (SNP) associated with coronary disease [2]. CXCR-4 is an alpha-chemokine receptor specific for SDF-1. The two molecules represent an axis that plays a role in stem cell homing during embryogenesis and in adulthood especially after tissues are exposed to ischemia [3]. Thus, the idea that SDF-1 could be relevant to human disease has great appeal.

Cardiovascular disease is the commonest cause of death worldwide, and ischemic heart disease with resultant ischemic cardiomyopathy and heart failure are major contributors to this grim statistic. Stem cell-based approaches to alleviate ischemic heart failure have generated much excitement; however, results to date are unconvincing and disappointing [4]. CD34-expressing bone marrow-derived cells seemed to improve cardiac function even in initial human trials, but subsequent more rigorous studies could not duplicate the initial results [5]. The original idea in these studies was the hope that bone marrow-derived cells would trans-differentiate into cardiomyocytes [6]. Insufficient homing and engraftment could have contributed to the eventual lack of success. Another approach could be recruitment of cells in cardiac tissue that specifically express the surface tyrosine receptor kinase, cKit. Mesenchymal stem cells (MSCs) enhance the efficacy of cardiac cKit+ cells. Hatzistergos et al. recently tested the hypothesis that MSCs stimulate endogenous cardiac cKit+ cells via the SDF-1/CXCR4 pathway [7].

The endothelial expression of SDF-1 acts as a signal indicating the presence of tissue ischemia. The hypoxia-inducible factor-1 (HIF-1) directly regulates SDF-1 expression [8]. Subsequent events, including proliferation, patterning, and assembly of recruited progenitors, are also influenced by tissue oxygen tension and hypoxia. Furthermore, both SDF-1 and hypoxia are present in the bone marrow niche. This finding suggests that hypoxia may be a fundamental requirement for progenitor cell trafficking and function. Thus, ischemic tissue may represent a conditional stem cell niche with the recruitment and retention of circulating progenitors regulated by hypoxia through differential expression of SDF-1.

In this issue of J Mol Med, Ghadge et al. took advantage of these interrelationships to address the issue of cardiac repair after experimental myocardial infarction [9]. They used transgenic CXCR4-EGFP reporter mice that contain a modified bacterial artificial chromosome (BAC) vector harboring an enhanced green fluorescent protein (EGFP) reporter gene. Mononuclear bone marrow-derived cells from these mice could be visually followed. Groups of mice were subjected to left anterior-descending (LAD) coronary artery ligation-induced myocardial infarction. Fluorescent antibody cell-sorting analysis of CXCR4-EGFP reporter mice display enhanced numbers of CD45+/CXCR4+/CD11b+ cells in the bone marrow and within the ischemic hearts. In the ischemic hearts, cells expressing CD4+,CD20+, and other markers including cKit+ were increased. In the bone marrow and heart, CXCR4-EGFP was predominantly expressed in CD45+/

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CD11b+ leukocytes, which significantly increased after myocardial ischemia.

The authors next aimed to augment CXCR4+ cell recruitment and myocardial repair by activating HIF-1α target genes, including SDF-1 and CXCR4. They administered dimethyloxalylglycine (DMOG), a compound inhibiting prolyl-hydroxylase (PH). DMOG treatment caused upregulation of HIF-1α. Furthermore, DMOG increased SDF-1 and CXCR4 mRNA expression time and dose dependently. SDF-1 was increased in both cytosol and nuclear fraction of non-infarcted and infarcted hearts. Other HIF-1α target genes such as vascular endothelial growth factor (VEGF), phosphoinositide-dependent kinase-1, and lactate dehydrogenase-A were also increased. Finally, reporter mice treated with DMOG showed a robust CXCR4-EGFP activity induction in coronary artery vessels and cardiac capillary networks. The authors also found that DMOG treatment decreased apoptosis and increased neovascularization in the heart. But more impressively, DMOG reduced myocardial scar size and improved cardiac function.

For the functional studies, mice were anesthetized with thiopental, intubated, and ventilated. A Millar Instruments catheter was introduced via the right carotid artery. Stroke volume was reduced from 15 to 6 μL with LAD ligation. In DMOG-treated mice, this reduction was lowered to 9 μL. Similarly, cardiac output fell about 60% with LAD ligation, while in DMOG-treated mice, that value was reduced to about 40%. Further, ejection fraction was largely preserved and the value for Tau, representing the time constant for isovolumetric relaxation, was reduced. These are impressive hemodynamic results. The data largely go along with an earlier report from the same investigators [10]. In that study, they applied the dipeptidylpeptidase (DPP)-IV inhibitor that minimizes degradation of SDF-1.

SDF-1 as a stem cell homing and tissue regeneration strategy was employed earlier in a rat study [11]. In that study, SDF-1 was sufficient to induce therapeutic stem cell homing to injured myocardium. The results suggested a strategy for directed stem cell engraftment into injured tissues.

SDF-1 has also been investigated in patients after myocardial infarction. Uematsu et al. reported that the production of SDF-1 in infarcted myocardium in the chronic phase of myocardial infarction was associated with adverse left ventricular remodeling and progressive dysfunction in acute myocardial infarction survivors [12]. Who knows, perhaps the sick ones were working the hardest. A therapeutic intervention trial has also been reported. The SDF-1 plasmid treatment for patients with ischemic heart failure (STOP-HF) trial was a phase II, double-blind, randomized, placebo-controlled trial to evaluate the safety and efficacy of a single treatment of plasmid SDF-1 delivered via endomyocardial injection to patients with ischemic heart failure [13]. The STOP-HF trial demonstrated the safety of a single endocardial administration of SDF-1 but failed to demonstrate the primary endpoint of an improved heart failure composite score. Thus, there was not just jubilation in paradise. However, when the going gets tough—the tough get going!

DMOG would not appear to be ready for prime time in a human study (Fig. 1). However, other HIF-specific prolyl hydroxylases (e.g., FG4952) are currently tested in phase III clinical trials for treatment in anemia. So inhibition of prolyl hydroxylases could be a clinically relevant approach in promoting cardiac repair via recruitment of reparative CXCR4+/CD11b+ cells to the ischemic heart. Furthermore, DPP-IV inhibitors such as the "gliptins" are on the market in the treatment of type-2 diabetes mellitus, a high-risk heart disease group. According to Zaruba et al., we would expect DPP-IV inhibitors to be cardioprotective [10]. However, the opposite appears to be the case. There are data from studies using

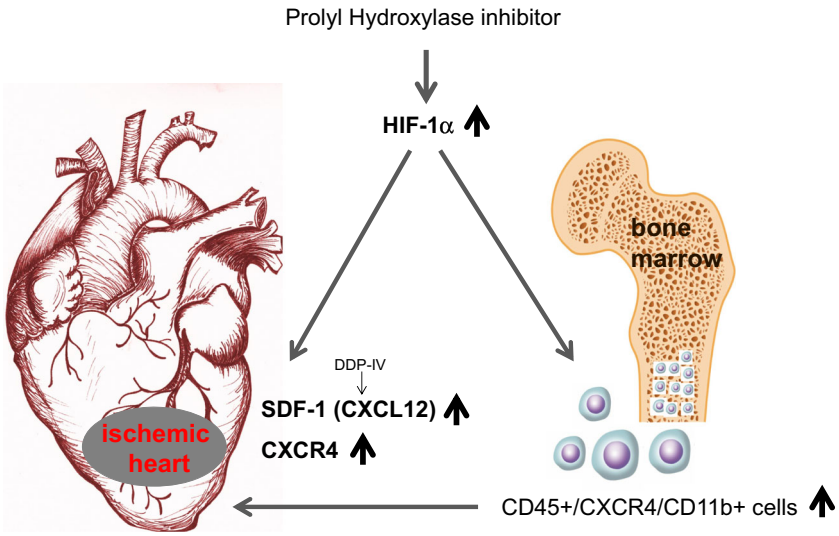

Fig. 1 SDF-1 is shown as a "mister-fix-it" molecule. Myocardial ischemia causes release of SDF-1 and upregulates the receptor CXCR4. Signaling to the bone marrow stem cell niche mobilizes CD45+/CXCR4/CD11b+ cells. The pathway is upregulated by HIF-1α. SDF-1 catabolism could be inhibited by blocking SDF-1 degradation with dipeptidylpeptidase inhibitor DPP-IV. Figure is adapted from Ghadge et al. [9]

sitagliptin, saxagliptin, and alogliptin, showing that these agents may increase the risk of hospitalization for heart failure [14]. However, these oversimplifications are unfair since SDF-1 was not investigated in these studies and DPP-IV effects involve numerous peptides. In support of the current study is a recent publication demonstrating that the deficiency of CXCR4 in cardiomyocytes prevents the beneficial effects of DMOG on cardiac repair after myocardial infarction by preventing cardiac progenitor cell recruitment. These data suggest that the engagement of the SDF-1/CXCR4 axis through the early upregulation of CXCR4 in cardiomyocytes is a strategy for improving cardiac repair after MI [15].

The HIFs are key oxygen sensors that mediate the ability of the cell to cope with decreased oxygen tension. These transcription factors regulate cellular adaptation to hypoxia and protect cells by responding acutely and inducing the production of endogenous metabolites and proteins to promptly regulate metabolic pathways. Recently, West reviewed the physiological effects of chronic hypoxia [16]. He drew attention to the health or lack thereof in communities that reside above 5000 m. Perhaps our attention directed at populations at risk to answer these questions should be a focus. But then again, an animal study in this direction was recently reported [17]. Furthermore, the cardiac robustness of the hypoxia-champion in the rodent world is the naked mole rat [18]. Surely, we should scrutinize this model.

Respectfully,

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