Stem cell highways: signalling beats trafficking?

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This editorial refers to ‘Migratory activity of circulating progenitor cells and serum SDF-1a predict adverse events in patients with myocardial infarction’ by O. Fortunato et al., pp. 192–200, this issue.

After the oocyte is fertilized, the resulting one-cell zygote gives rise to all stem cell progenies. During the developmental process, these cells are necessary to generate all specialized tissues. However, some of them elude the specification cues and remain quiescent in the adult tissue, as long as the organism does not suffer from injury, illness, or specific cell-type depletion. Most adult stem cells are quiescent, others, such as the intestinal stem cells, are very active and feature intense self-renewal kinetics.2 Nevertheless, when these adult stem cells are awakened by an injury or alerted upon the body’s request, they need to move on and reach the damaged area using special routes known as cellular highways (Figure 1). The more advanced the illness, the less the number of stem cells remaining in stock. Their ability to migrate effectively into damaged or diseased tissues makes the stem cells promising candidates for cell therapy. Unfortunately, cellular highways can also be used by cancer (stem-) cells during metastasis. As cellular highways also play a central role in tissue homeostasis, exposure to 100 ng/mL SDF-1α for 30 min induced a proangiogenic phenotype in CD34CXCR4+ circulating progenitor cells (PCs),8 resulting in cell migration and differentiation into vascular cords. The more advanced the illness, the less the number of stem cells remaining in stock. Their ability to migrate effectively into damaged or diseased tissues makes the stem cells promising candidates for cell therapy.

Fortunato et al.4 explore the SDF-1α/CXCR4 cellular highway in the context of cardiac damage, highlighting the correlation between SDF-1α plasma concentration and the migration ability of CXCR4+ circulating progenitor cells. In a prospective observational study in 172 consecutive patients with an acute coronary syndrome, of which the majority (83%) presented with ST-elevation myocardial infarction (MI), the authors correlate functional characteristics of circulating progenitor cells, antigenically defined as CD34/CD45/CD133/CXCR4pos, cells with a clinical outcome up to 1 year. When categorizing the study population into patients who developed a combined event (death, recurrent MI, or new-onset heart failure) during the 1-year follow-up and those without an event, the authors observed reduced spontaneous motility of these progenitor cells in an in vitro migration assay. Moreover, they report somewhat higher serum SDF-1α levels in patients with a subsequent event, although the significance of the latter is uncertain in view of the substantial variability in serum levels and the low number of these patients (n = 30/172 or 13.4%).

Stem cells home towards acutely damaged myocardium following systemic injection, although the molecular mechanism of this process is largely unknown. Migration towards damaged tissue is the first step in stem cell engagement during tissue regeneration. Chemokines and their receptors dramatically influence the pool of circulating and resident cardiac progenitor cells, which in turn promote tissue regeneration and recovery after MI. Stromal cell-derived factor-1α (SDF-1α), stem cell factor (SCF), hepatocyte growth factor (HGF), and leukaemia inhibitory factor (LIF) are primarily involved in the mobilization and homing of the circulating progenitor cells towards the infarcted heart.5 Several authors, including Fortunato et al., have confirmed the importance of the chemokine—chemokine receptor axis SDF-1α/CXCR4 (reviewed in Cencioni et al.6), which is stimulated during acute cardiac damage. In fact, many circulating progenitors highly express the chemokine receptors CXCR4, besides c-Met, CD117 (SCF receptor), and leukaemia inhibitory factor receptor. Local injection of SCF improves myocardial homing of systemically delivered progenitor cells.7 Since tissue or systemic injection of these potent chemokines could determine a dramatic change on the tissue homeostasis, ex vivo priming of progenitor cells with SDF-1α before transplantation has been challenged by several independent groups. Exposure to 100 ng/mL SDF-1α for 30 min induced a proangiogenic phenotype in CD34CXCR4+ circulating progenitor cells (PCs),8 resulting in cell migration and differentiation into vascular cords. Exposure of cardiac mesangioblasts, vessel-associated stem cells expressing CD31, CD34, CD44, CD117, and CD146, but not CD45 and CD133, to SDF-1α improves up to five-fold their homing to the infarcted heart free wall. The authors also showed that this treatment improves cardiac regeneration and the recovery of the left ventricular (LV) wall motion.9 In summary, SDF-1α pre-conditioning enhances cell survival and differentiation of stem cells during transplantation into infarcted myocardium.6,10

CXCR7 also shows high-affinity binding to SDF-1α and has a more restricted surface expression, mainly in tumour cells and endothelial progenitors.11 Although its role in calcium mobilization and chemotaxis is still controversial, it seems that CXCR7 is required for mesenchymal stem cell (MSC) migration and adhesion, whereas CXCR7 is responsible for MSC adhesion and survival.12 The fact that CXCR7 function depends on the cell type, is evident in the migration ability of renal progenitor cells. Although this phenomenon required the presence of both CXCR4 and CXCR7, only CXCR7 seems to be essential in renal progenitors in order to adhere to the endothelial cells.13 It is interesting to note that CXCR7 has been shown to internalize and degrade SDF-1 as a ligand scavenger,14 which could modulate the functioning of CXCR4 in PCs of Fortunato et al. clinical study.

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In this study, Fortunato et al. have performed a careful and detailed analysis of the migratory response of circulating progenitor cells to the SDF-1α gradient. Similar to the colony-forming capacity of mononuclear bone marrow cells, migratory capacity of circulation PC has been recognized as one of the key factors that may modulate the positive or negative effects of cell-based therapies for acute MI (AMI). However, the relevance of SDF-1α to cell migration can be indicated from a different angle as pointed out by Fortunato et al., discovering an intriguing aspect concerning the SDF-1α/CXCR4 axis. In fact, they hypothesize that an impaired functionality of CD34/CD45/CD133/CXCR4pos PCs might directly reflect a reduced cardiac reparative response in AMI patients. The foundation of the authors’ hypothesis is to establish a link between functionally impaired circulating stem cells and adverse events in AMI patients. They first determined whether abundance and migratory activity of PCs’ prognosticate re-infarction, new-onset heart failure, and all-cause mortality in patients with AML. Then they evaluated the association between cytokines and clinical outcomes, focusing in particular on the serum levels of SDF-1α, b-FGF, IGF, VEGF-A, PDGF-BB, troponin I, and CPK-MB. Their concept, however, has broad implications as a potential intermediate step between a clinical observation and future therapeutic approaches to modulate the amount of circulating cytokines and PCs. Recently, the role of SDF-1α in mobilizing stem cells in combination with endothelial progenitor cell (EPC) transplantation has been investigated in a regenerative strategy for MI therapy in a murine ischaemia–reperfusion model. Bone marrow was destroyed and restored with the use of green fluorescent protein (GFP)-labelled donor cells, before inducing myocardial ischaemia. After reperfusion, EPCs were injected directly into the border zones of the infarcted areas and challenged with anti-SDF-1α antibodies. Histological analysis revealed that EPC and anti-SDF-1α administration...
diminished the amount of GFP-positive bone marrow cells in the heart. The authors of this study concluded that transplanted EPCs, as well as SDF-1αx, are key factors in guiding endogenous bone marrow cells into the infarcted myocardium. Anti-SDF-1αx treatment results in a significant decreased left ventricular function, but does not alter the neovascularization of infarcted areas. This preclinical study clearly indicates that SDF-1αx and EPCs are strictly connected to the homeostasis of bone marrow cells and their perturbation implicates important changes in cell mobilization and clinical outcomes. Intriguingly, Fortunato et al. found that AMI patients that underwent percutaneous coronary intervention (PCI) present circulating PCs that are insensitive to SDF-1αx stimulation, as documented by in vitro migration assay. This reduced sensitivity to SDF-1αx may reflect an impaired recruitment of curative cells to the infarcted heart, leading to a defective recovery and a higher risk of late complications.

To translate these novel mechanistic insights into innovative therapeutic strategies, JVS-100, a DNA plasmid encoding human SDF-1αx, has been recently tested in a phase 1, dose-escalation study with 12-month follow-up in subjects with ischaemic cardiomyopathy.16 This promising study suggests that the overexpression of SDF-1αx improves heart failure symptoms in patients with ischaemic cardiomyopathy. Thus, the potential regenerative/regenerative mechanism of activated SDF-1αx/CXCR4 axis is not limited in stem-cell mobilization, but it could be related to other biological phenomena, i.e. neovascularization, cardio-protection, cardiomyocyte cell cycle induction.

One of the significant merits of the present study by Fortunato et al. is the recognition of this pathway as a putative predictor of adverse events in AMI patients at 1-year follow-up.

The role of SDF-1αx in stem-cell migration seems now well established, emphasizing the pivotal role of homeostatic CXCR4 receptors in this process. However, in view of the relatively small sample size and the low event rate in this low-risk AMI population receiving contemporary state-of-the-art reperfusion therapy, additional data are required in large-size follow-up studies. Obviously, we need to better understand the molecular mechanisms of homeostatic chemokines on stem-cell migration and other cell functions before we will be able to prevent fatal accidents on these cellular highways. In this regard, it has been recently shown that eNOS inhibition enhances cardiac fibrosis by activating SDF-1αx/CXCR4 axis in cardiac fibroblasts.17 On the other hand, ongoing strategies to enhance NO bioavailability in other PCs have augmented their repair potential.18 Moreover, chemokines are also likely to directly determine the viability and growth of stem cells, extending their mode of action beyond drivers of stem cell traffic on cellular highways. It is very likely that chemokine-receptor axes play a prominent role in the molecular signature of stem cells and exert significant prognostic information.

Taken together, this is an exciting area of translational science in need of additional learning. Novel predictors of early adverse events are of great value in our efforts to develop better therapies for high-risk patients, and may eventually become useful biomarkers to lead the way towards innovative treatments. The time is now right for larger cohort studies to assess the predictive value of these intriguing biological biomarkers and pave the way for future targeted cell-based intervention studies.

References