SDF-1 axis and myocardial repair

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THE ABILITY OF THE HEART to sustain hemodynamic demands is greatly challenged when cell loss or disruption of myocardial homeostasis occurs. Cell therapy using stem or progenitor cells is a promising option to restore the lost myocardium and normalize ventricular function. Initial clinical trials have documented the feasibility and safety of this therapeutic approach with an indication of the potential benefit for the diseased heart (2, 3, 11). While various cell types with cardiogenic potential have been identified, several aspects need to be refined and optimized in the setting of cell transplantation to successfully promote cell retention, survival, engraftment, and, ultimately, myocardial regeneration.

The heart presents a limited regenerative capacity, which is inadequate to replace the necrotic tissue after ischemic episodes (6). However, these adverse events trigger the recruitment of progenitor cells to the site of injury (4), indicating that homing signals activated during hypoxia may be exploited to target transplanted cells to the damaged myocardium. Among the molecules formed after ischemic insults, stromal cell-derived factor-1 (SDF-1) is transiently upregulated and acts as a stem cell homing agent by stimulating the CXCR4 receptor in these primitive cells (1, 7, 13). Thus the SDF-1/CXCR4 axis may offer potential advantages for cell treatment.

In this issue of the American Journal Physiology-Heart and Circulatory Physiology, Zhang and colleagues (14) demonstrate that an enhanced recruitment and penetration of exogenous mesenchymal stem cells (MSCs) in the ischemic myocardium can be achieved by combining tissue engineering with genetic and pharmacological interventions. Specifically, the authors employed MSC sheet grafts implanted in rats 7 days after myocardial infarction. Additionally, they potentiated the SDF-1α/CXCR4 axis by inhibiting the enzymatic degradation of the ligand and by overexpressing CXCR4 in MSCs.

The use of monolayered MSC sheets (9), rather than direct intramyocardial injections or intracoronary delivery, appears to be particularly suitable for the study of Zhang and colleagues. This approach promotes cell retention in the proximity of the area of damage and allows the evaluation of the invasive properties of MSCs in the infracted region. The effects of perturbations of the SDF-1α/CXCR4 system on MSC migration and homing were carefully dissected by comparing three cell types characterized by high, normal, or compromised CXCR4 expression. These different cell categories were transplanted in rats with physiological or pharmacologically elevated SDF-1 levels. The main finding of Zhang and colleagues is that CXCR4 overexpression alone enhanced the number of transplanted MSCs present within the infarcted myocardium, leading to increased capillary density, reduced fibrotic tissue, and amelioration in cardiac function. Importantly, these positive results were significantly improved when CXCR4 overexpression in MSCs was combined with elevated SDF-1 level. Of note, when MSCs with normal or compromised CXCR4 expression were employed, the inhibition of SDF-1 degradation appeared to have minimal impact on MSC recruitment, preserving a functional and anatomical benefit at the organ level. The latter result may arise from the reduced myocardial apoptosis reported by the authors or by a promotion of endogenous repair mechanisms.

Overall, these findings indicate that the regenerative capacity of MSCs can be substantially enhanced by exploiting the chemotactic properties of SDF-1. The overexpression of CXCR4 alone stimulates MSC mobilization to the injured myocardium, suggesting that receptor expression and function are suboptimal in this cell pool. When the function of the CXCR4 receptor was amplified, SDF-1 elevation significantly potentiated the repair capacity of MSCs.

In light of these results, new research directions may be aimed at the identification of a subpopulation of cells with high CXCR4 expression to be used for regenerative purposes. This cell population may present a superior response to the chemotactic action of SDF-1, promoting their migration and homing to the site of injury. The current findings, together with previous reports from the same and other laboratories, indicate that several possibilities exist for the improvement of cell therapy for the injured heart (1, 10, 12, 13). An implementation of strategies enhancing the SDF-1/CXCR4 system may represent a valid direction for future studies and a potential positive clinical outcome.

MSCs are currently being employed clinically in patients with myocardial infarction, and initial observations suggest that this cell class exerts a beneficial effect on ventricular remodeling and cardiac performance (5). However, other bone marrow-derived progenitor cells are given to patients with ischemic cardiomyopathy (2, 11) or refractory angina (8). Additionally, autologous adult cardiac stem cells have appeared on the clinical arena and are being administered to patients with old myocardial infarction and multivessel coronary artery disease. Therefore, it is puzzling whether any effort should be made to enhance the indirect impact of bone marrow-derived cells on endogenous reparative processes or any emphasis should be placed on the resident pool. This question cannot be answered at present but constitutes a major challenge for all of us to define the “best cell” for cardiac repair and the recovery of structure and function of the diseased heart.

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DISCLOSURES

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REFERENCES


