The Role of CXCR4 Overexpression in Mesenchymal Stem Cells and the Induction of Angiogenesis

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Introduction: Ischemic heart disease is a leading cause of death worldwide. Adult cardiomycoytes are considered terminally differentiated cells; thus, injury during an ischemic event such as myocardial infarction (MI) produces irreversible damage that leads to tissue remodeling, scar formation, and impairment of contractility. While current clinical approaches focus on the maintenance of remaining heart function, recent studies demonstrate ways in which the proliferative potential of cardiac tissue can be induced for repair. Mesenchymal stem cells (MSCs) have shown promise in differentiating into endothelial cells and cardiomyocytes following MI under proper conditions. The SDF-1α/CXCR4 signaling axis is crucial to this process, promoting progenitor cell migration and homing to the damaged tissue and upregulating expression of protective paracrine factors. However, the exact role of CXCR4 in inducing repair processes and subsequent cellular processes remains unknown. This study explores the relationship between MSC overexpression of CXCR4 and the process of angiogenesis, a key process in cardiac tissue repair following ischemia.

Methods: MSCs were genetically engineered with adenoviral transduction to overexpress CXCR4/green fluorescent protein (GFP) (MSC^{CXCR4}) or just GFP(MSC^{Null}).Three groups of MSCs (MSC^{parent}, MSC^{null}, MSC^{CXCR4}) were studied, under both hypoxic and normoxic conditions. To evaluate the role of CXCR4 expression in angiogenesis, tube formation assays were conducted to measure each group's capacity to develop capillary tubes, as observed with light microscopy. These groups were also tested for the uptake of DiI-Ac-LDL, an endothelial cell membrane marker. Differentiated cells were quantified with fluorescence microscopy.

Results: Under hypoxic conditions, MSC^{CXCR4} demonstrated greater formation of capillary branch point compared to the MSC^{parent} group ($p < .01$). However, this difference was not statistically significant in the normoxic group ($p = .366$). In DiI-Ac-LDL uptake, MSC^{CXCR4} showed greater LDL uptake than both the MSC^{parent} and MSC^{Null} groups ($p < .01$).

Conclusion: Our findings suggest that the overexpression of CXCR4 confers an advantage to MSCs for differentiation into endothelial cells, likely in both normoxic and hypoxic conditions, most probably due to the activation of certain signaling cascades that promote angiogenesis. Further experiments are needed to confirm these preliminary results, in addition to exploring the cellular mechanisms and signaling molecules involved.