Mesenchymal stem cells for cardiac repair: Is the placenta the answer?

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Mesenchymal stem cells (MSCs) have been used extensively for the study of myocardial regeneration after an acute myocardial infarction. MSCs are especially attractive for cell regeneration therapy because they are easily isolated, expand in culture, can be transplanted across major histocompatibility complex barriers without the need for immunosuppression, and are not subject to ethical considerations associated with embryonic stem cells. Bone marrow has been the traditional and most commonly used source of MSCs for clinical trials; however, human bone marrow–derived MSCs (hBM-MSCs) cannot be harvested in large volumes, and bone marrow donation remains an invasive procedure that involves significant discomfort for the donor. Furthermore, the use of hBM-MSCs in clinical trials involving patients with a myocardial infarction has shown limited success because of low cellular retention, short-term homing, and decreased functional activity. In view of these limitations of hBM-MSCs, other tissues have been investigated as sources of MSCs.

In this issue of the *Journal*, Li and coworkers¹ report their results with human placenta–derived MSCs (hPD-MSCs) compared with hBM-MSCs in an in vitro model involving periods of hypoxia. Because the placenta is crucial for fetomaternal tolerance during pregnancy, placental cells must have some degree of immunomodularity. Furthermore, because placental cells are derived from early stages of embryologic development, they are capable of differentiating into multiple cell types. Placental tissue is available in large supply, and recovery of placental cells does not involve any invasive procedures for the donor or pose any ethical problems, because it is normally disposed of after delivery of the baby. Techniques have been developed to harvest hPD-MSCs for clinical trials.² Previous studies have shown that hPD-MSCs are similar to hBM-MSCs in terms of morphology, cell surface phenotype, chemokine receptor display, mesodermal differentiation, and cell immunosuppression capacity.³ Experiments in neonatal rat hearts have shown that hPD-MSCs can be integrated into cardiac tissues, where they differentiate into cardiomyocytes that can survive for 2 months when transplanted into areas of myocardial infarction.⁴ Isolated hPD-MSCs have also been shown

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Central Message

The placenta is a new source for mesenchymal stem cells for cardiac regeneration.

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to differentiate into cardiomyocytes and survive for as long as 80 days in an in vivo model.⁵

In their in vitro model, Li and coworkers¹ sought to determine the effects of hPD-MSCs and hBM-MSCs on the expression of C-X-C motif chemokine receptor 4 (CXCR4) under hypoxic conditions. CXCR4 is critical in regulating cell migration, homing, and engraftment, all of which are important in determining whether MSCs can reach the site of the infarcted myocardium. Hypoxia increased the expression of CXCR4 10-fold in hPD-MSCs, in contrast to an only 2-fold increase for hBM-MSCs. The CXCR4/MEK/ERK signaling pathway was predominately activated in hPD-MSCs, as opposed to the hBM-MSCs, in which the CXCR4/P13K/Akt pathway was dominant. Although these results suggest that hPD-MSCs may be a viable alternative to hBM-MSCs, there are several limitations to this study. These results were obtained in an in vitro model and will need further testing in in vivo models and clinical trials, which will need to include data on cell retention and survival. In addition, spatial arrangements in lattice formation, necessary for integration with myocardial tissue, as well as routes of administration for hPD-MSCs will also need to be determined from clinical data.

Although the results of this study by Li and coworkers¹ are preliminary, they are hypothesis generating and

contribute to a growing interest in the use of hPD-MSCs for myocardial regeneration. Further in vivo studies and human clinical trials will be necessary to determine whether the placenta will be the answer to the use of MSCs for the repair of infarcted myocardium.

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