

Stem Cell Therapy for Tissue Repair: The Stem Cell-Host Interaction

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INTRODUCTION: Mesenchymal stem cells (MSCs) reside within the stromal compartment of bone marrow and other tissues. These cells have generated a great deal of interest because of their potential use in regenerative medicine and tissue engineering. While the therapeutic testing of these cells has progressed well, there are still many questions to be addressed concerning the role of endogenous populations of stem cells in the adult and the function of various stem cell niches.

The purpose of this study was to evaluate the nature of the transplanted stem cell-host interaction that underlies the therapeutic mechanism of action. Three animal models of human disease were used, each of which allows an assessment of aspects of the host response. The disease models were (1) osteoarthritis (OA) of the knee, (2) myocardial infarction (MI) and (3) human breast cancer xenografts. Each of these models allows an assessment of the mode of action of the transplanted cells. The results of these studies lead to the conclusion that neither extensive engraftment nor differentiation of the transplanted cells are prerequisites for a useful therapeutic response.

METHODS: MSCs were isolated from bone marrow aspirates from multiple animal species, and characterised by measurement of cell surface antigens. OA was induced by complete medial meniscectomy in goats and MSCs expressing GFP were delivered by intraarticular injection. MI was induced by irreversible ligation of the LAD coronary artery in Fischer rats and PKH26-labelled MSCs were delivered by myocardial injection. Female athymic nude mice received a subcutaneous injection of 2×10^7 T47D cells. When tumors had reached a volume of $\geq 100 \text{ mm}^3$ the mice received a subcutaneous injection of 1×10^6 PKH26-labelled MSCs.

Animals were sacrificed at several time points post delivery of cells and the target tissue was harvested, processed and sectioned for histological evaluation. In the case of the infarcted rats the hearts were harvested, digested with a mixture of collagenase and

trypsin and the resulting cell suspension was separated by high speed cell sorting. The retrieved labelled MSCs were analysed for expression of tissue-specific and cell-specific markers and for differentiation potential.

RESULTS: In each disease model labelled transplanted cells were observed at the site of injury (Fig. 1). Levels of engraftment appeared low in the OA joints and in the infarcted hearts and higher in the xenograft tumours, even when they cells were delivered by IV infusion. Cells retrieved from the infarcted hearts up to 7 days after delivery showed no evidence of cardiomyocytic differentiation but appeared to retain the stem cell phenotype.

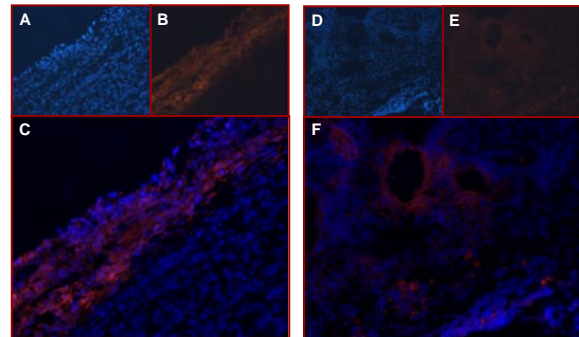


Fig. 1: In Vivo MSC engraftment in breast tumor tissue in tumor-bearing mice following injection adjacent to a T47D tumor (A-C) and intravenous injection (D-F).

DISCUSSION & CONCLUSIONS: MSCs delivered to the injured host have the capacity to migrate to the site of injury and engraft, although with low efficiency. Engrafted MSCs apparently do not differentiate in a tissue-specific manner, but certainly remain viable. It appears unlikely that the engrafted cells proliferate but this cannot be ruled out. These observations suggest that the therapeutic effect associated with MSC delivery is unrelated to their capacity to differentiate and more likely associated with their capacity to deliver soluble factors to the injured host.

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