

ENGINEERING OF A MESENCHYMAL STEM CELL HOMING RESPONSE

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Introduction: One of the greatest challenges in cell therapy is to minimally invasively deliver a large quantity of viable cells to a tissue of interest with high engraftment efficiency. Mesenchymal stem cells (MSCs) lack relevant adhesion molecules on their surface to promote a robust homing response. The central hypothesis of our work is that MSCs can be engineered to possess leukocyte-like adhesion properties, without otherwise altering function, to promote more effective rolling, adhesion and ultimately *in vivo* homing.

Methods: The sialyl Lewis^x (SLe^x) moiety, found on the surfaces of leukocytes representing the active site of the P-selectin glycoprotein ligand (PSGL-1), was covalently immobilized on the cell surface by biotin-streptavidin conjugation to improve the homing response. Specifically, the MSC surface was biotinylated with N-hydroxy succinimide ester of biotin followed by streptavidin and biotinylated SLe^x. The adhesive interactions of SLe^x modified MSCs were investigated under dynamic shear stress conditions on P-selectin coated substrate. The homing efficiency of systemically infused SLe^x modified MSCs was examined in LPS induced mouse ear inflammation model with a real time scanning confocal microscope designed specifically for live animal imaging. In addition, the phenotype of SLe^x modified MSC was characterized using a panel of standard assays.

Results: SLe^x modified MSCs exhibited velocities of 2 $\mu\text{m}/\text{sec}$ up to a wall shear stress of 1.89 dynes/cm² compared to 70 $\mu\text{m}/\text{sec}$ for the unmodified MSCs on P-selectin surface in a parallel plate flow chamber assay. The *in vivo* experiment showed a 67% increase in the number of SLe^x modified MSCs within the inflamed ear at 24hr compared to the unmodified MSCs. The lower rolling velocity and increased engraftment efficiency indicates that it is possible to direct systemically infused MSCs to specific sites through chemical engineering of the MSC surface. Moreover, the MSCs' native phenotype including multi-lineage differentiation potential, secretion of paracrine factors and transendothelial migration were not affected by the cell surface modification.

Conclusions: MSCs covalently conjugated with SLe^x may potentially be targeted to inflammatory sites without compromising the MSC phenotype. The approach described here offers a simple method to potentially target any cell type to specific tissues following systemic infusion.