STEM CELLS

Mesenchymal stem cells from adipose tissue could be used to deliver gene therapy to the liver

Mesenchymal stem cells derived from adipose tissue (AT-MSCs) offer unique advantages for the application of gene-based therapies: they are abundant, easily harvested, replenishable and home to damaged tissues undergoing regeneration. "These unique features of AT-MSCs led us to explore the feasibility of using them for gene delivery to the liver," explains Sihong Song, corresponding author of this report, which appeared in the *Journal of Hepatology*. "Our ultimate goal is to develop a liver regenerative therapy for α1-antitrypsin deficiency that is practicable for use in humans," he states.

The researchers infected mouse AT-MSCs with a recombinant vector derived from adeno-associated virus serotype 1 that resulted in expression of human α1-antitrypsin. Transplantation of these modified AT-MSCs into the mouse spleen (a commonly used hepatic delivery route that limits the adverse effects of cell transfer) resulted in long-term transgene expression in the liver and consistent, albeit low (average 100–200 ng/ml), serum levels of human α1-antitrypsin.

> "Transplantation of these modified AT-MSCs ... resulted in long-term transgene expression in the liver..."

"We need to … improve expression levels of human α1-antitrypsin in recipients," cautions Song, since these levels are too low to prevent the deleterious effects of α1-antitrypsin deficiency—patients who have serum levels of α1-antitrypsin <600 μg/ml can still develop emphysema. Crucially, however, no antibodies to this foreign protein were detected and the livers of recipient animals did not show any signs of lymphocyte infiltration. Song and colleagues hypothesize that a foreign gene product produced by a host cell is not immunogenic, and plan further studies to elucidate the mechanism underlying this immune tolerance.

Homing of the altered AT-MSCs to the liver was promoted by partial hepatectomy and administration of monocrotaline. These treatments create a demand for liver regeneration while efficiently suppressing proliferation of endogenous hepatocytes. As expected—since AT-MSCs strongly resemble bone-marrow-derived MSCs—a few transplanted cells were detected in bones and some were retained in the spleen. Surprisingly, however, they were also detected in the lung. The researchers speculate that monocrotaline might have caused an injury that created a demand for regeneration of lung tissue.

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Original article Li, H. *et al*. Adipose tissue-derived mesenchymal stem cell-based liver gene delivery. *J. Hepatol*. doi:10.1016/j.jhep.2010.07.051