Iron oxide labeling of human mesenchymal stem cells in collagen type I hydrogels for cellular MR imaging

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Introduction:

The non-invasive monitoring of cell behavior in vivo is still one major issue in cell-based therapies in orthopedic surgery. In particular, detailed information about the localization, proliferation, and differentiation of the transplanted cells in the target tissue is of utmost importance. In this study, magnetically labeled human mesenchymal stem cells (hMSCs) were embedded in collagen type I hydrogels and visualized in vitro using high-resolution magnetic resonance imaging (MRI).

Materials and Methods:

Very small superparamagnetic iron oxide nanoparticles (VSOPs) were used to label hMSCs. Particle incorporation was demonstrated using fluorescent dye-labeled VSOPs. Stability of labeling during expansion of cells was determined with iron specific histological staining (Prussian blue). To assess whether the iron oxide particles are incorporated into the cells or only attached to the cellular surface, transmission electron microscopy (TEM) was performed. The influence of VSOP-labeling on the differentiation ability of hMSCs was determined histologically and on the mRNA level. For in vitro MR imaging, different concentrations of both magnetically labeled and unlabeled hMSCs were embedded in collagen type I hydrogels (Arthro Kinetics AG, Esslingen). MRI was performed at different time points using a Bruker 11.7 T MR spectrometer.

Results:

After incubation of hMSCs with VSOPs, fluorescent dye-labeled particles could be detected within the cells. This was confirmed with iron specific Prussian blue staining and TEM. During expansion in monolayer culture, a distinct reduction of VSOP-labeling appeared after 5 to 9 cell divisions, based on the dilution of label upon cell division. Compared to unlabeled cells, no inhibition of adipogenic, osteogenic, and chondrogenic differentiation of magnetically labeled hMSCs could be detected. Both, VSOP-labeled and unlabeled cells showed a specific matrix production and similar expression levels of according genes. After embedding of magnetically labeled hMSCs in collagen type I hydrogels, where no proliferation takes place, the cells could be detected with a MR spectrometer over at least 20 weeks. Controls with unlabeled cells were also visible in the
MR images, but didn’t exhibit the typical signal intensity decrease conditioned by VSOP.

**Conclusion:**

The results of our study show that the incorporation of VSOPs in hMSCs leads to an efficient cellular label with no adverse effect on their stem cell function. VSOP-labeled hMSCs can be successfully detected in a three-dimensional construct in vitro using high-field MRI. Further investigations have to reveal how long labeled cells can be visualized and monitored reliably in vivo.