MR Tracking of Stem Cells Following Magnetofection

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There is now considerable evidence that the administration of stem cells and progenitors, by either local grafting or systemic injection, can result in amelioration or even cure of a variety of diseases in animal models. Most experimental studies have been aimed at disorders of the central nervous system (CNS) and the infarcted myocardium, using (ES-derived) neural stem cells and bone marrow stem cells, respectively. The encouraging outcome of these studies has raised the prospect of applying stem cell therapy in humans. Central to the future success of cell transplantation in the clinical setting is the ability of transferred cells to migrate from the site of transplantation or injection to relevant foci of disease, and to survive for prolonged periods of time, both of which are necessary for the cells to exhibit their regenerative properties. In animals, the fate and biodistribution of stem cells is currently being assessed by histology using fluorescent dyes or other reporter genes/molecules, which requires removal of living tissue and makes this technique unsuitable for clinical follow-up in humans. Several image modalities now fulfill the requirement of noninvasive and repetitive imaging of the in vivo biodynamics of administered stem cells. Compared to single photon emission computed tomography (SPECT), positron emission tomography (PET), and bioluminescence imaging, only MR imaging offers near-cellular resolution. In fact, recent work has shown that it is possible to image single cells at clinical field strengths using dedicated gradient coil inserts.

For stem cells to be visualized by MRI, they must be magnetically labeled in order to be discriminated from the surrounding native tissue. Because of their biocompatibility and strong effects on T2(*) relaxation, superparamagnetic iron oxide (SPIO) particles are currently the preferred magnetic label. The field of cellular MR imaging initially faced the challenge of developing methods and protocols that could achieve a sufficiently high intracellular magnetic labeling of stem cells, which are non-phagocytic cells. It appears that this issue has now largely been resolved due to the introduction of “magnetofection” as the most commonly used labeling procedure. In this procedure, SPIO particles are transfected across the cell membrane by coating them with dedicated agents developed for DNA transfection. One of the advantages is that commercially available materials can be used, including the FDA-approved SPIOs, Feridex® or Endorem®, although cells must be labeled in culture for extended periods. Larger, micron-sized SPIO particles that are not used clinically can be used in animal studies with higher sensitivity because of their larger size. Further refinement of magnetic labeling strategies is an ongoing process, which will ideally lead to instant clinical labeling of cells with the press of a button. A new technique called “magnetoelectroporation” (MEP), appears to be able to fulfill this requirement.

This presentation will include various examples of stem cell tracking following magnetofection in myelin diseases, stroke, brain tumors, and diabetes. The following lecture by Dr. Lederman will address the application of this technique in the infarcted myocardium. At the time that this abstract was prepared, clinical trials of MR tracking of Feridex/Endorem-labeled cells had already started in Europe; regulatory approval of future studies will likely be directed toward the biological properties of the stem cells themselves rather than the biocompatibility and biodegradation of the SPIO label. It should be noted that, to date, most stem cell MR tracking studies have been of the mere “proof-of-principle” type; that is, we can detect cells noninvasively in vivo with proper histological validation. Further use of the MR tracking technique should be aimed at obtaining a deeper insight into the spatial and temporal dynamics of in vivo stem cell-tissue interactions, so that we can optimize and fine-tune further therapies.

New emerging technologies in MR stem cell tracking include the development of new pulse sequences that render a positive cellular SPIO contrast rather than the visualization of “black holes,” and the pursuit of cellular MR reporter genes that can be visualized without the need for exogenous substrates or labels. Efforts toward noninvasive quantification of the cell density (n of cells per ml tissue) are also warranted, although this may turn out to be very challenging. The field of MR (stem) cell tracking is clearly still in a developmental stage; however, continuous improvements and innovations may make this technology eventually become part of diagnostic radiology practice.