Stem Cell Tracking in Physiology and Pathology

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Synopsis

This presentation focusses on the potential of in vivo MR microscopy for the observation of stem cell dynamics in a host organ. For this purpose, the established immunohistochemical and microscopical approaches are discussed and compared with the strategies for the in vivo MRI detection of stem cells. Applications to ischemic heart muscle and cerebral ischemia will be demonstrated and used to discuss potential and limits of the in vivo MR approach. Finally, a subjective analysis of future potential and synergistic needs of the technique as a Molecular Imaging contribution will be given.

During the last few years, stem cell biology has experienced a rapid advancement, leading to rising hopes that stem cell, migrating towards the lesion target area, will contribute to functional improvement. Here, two basically different strategies have been considered: the first is taking advantage of the observation that even in adult animals (and humans) several locations have been found with continuous generation of adult stem cells, e.g. bone marrow derived stem cells, hematopoietic stem cells or also neural stem cells, generated in the subventricular zone (SVZ) or the subgranular zone (SGZ) of the dentate gyrus of the hippocampus. The second strategy aims at injecting (embryonic) stem cells in the vicinity of a lesion, in the hope of their integration into the lesioned tissue area, thus functioning as tissue replacement therapy.

Sofar, all these approaches have relied exclusively on invasive techniques to study the fate of these cells. For this purpose, exogenous stem cells were labeled with fluorescent dyes or transfected to express proteins like the green fluorescent protein (GFP) allowing the cells to be later retrieved on tissue sections. Endogenous cells were labeled during generation or proliferation, taking advantage of BrdU uptake into DNA during its synthesis. Extensive immunohistochemistry and microscopic techniques assured the observation of the stem cell fate at individual survival times on tissue sections.

Recently, the spatial resolution and the sensitivity of MR microscopy has been increased to a point where appropriately labeled cells may be detected again after their implantation in host tissue. (Stem) cells were labeled with T2*-sensitive iron oxide nanoparticles leading to a strong contrast against the host tissue, thus allowing the detection and longitudinal study of their dynamics *under true in vivo conditions*. A broad range of applications has been reported on already during the past two years, with of these studies having more a proof-of-principle character than a real application. This presentation will therefore focus on applications of in vivo MR microscopy of labeled stem cells to ischemia in two major organs: the brain and the heart. The feasibility to track labeled cells after implantation and to follow their fate in the host organ as well as the potential and limits of this approach will be discussed. The iron oxide nanoparticle based cell labeling will be critically evaluated and the potential of new labeling strategies will be considered. Finally, the future potential of MRI as a *Molecular Imaging* technique in the field of (stem) cell tracking will be analyzed in view of the needed synergies provided by the close marriage with contrast agent experts and molecular and cell biologists.