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MRI and Stem Cell Trafficking

Utilization of stem and progenitor cells for therapeutic purposes is a very attractive approach, however in most clinical applications this approach proved to be extremely challenging. To date the greatest success in cell-based therapy was achieved in hematology with bone marrow transplantation. This procedure is performed clinically since 1950s (1). In contrast, for non-regenerating organs e.g. central nervous system or heart, signaling directing stem cell differentiation is lost with completion of the development. For that reason in order to develop effective therapies for neurodegenerative diseases it will be necessary to instruct transplanted cells and guide their fate with exogenous migratory and differentiation signals. Such guiding needs to be performed in extremely precise manner and for that purpose cellular imaging technology seem to be ideally suited.

Technological advancements in recent years have introduced various in vivo imaging modalities, including those suitable for cellular imaging. Positron emission tomography (PET), bioluminescent imaging) (2), single photon emission tomography (SPECT) (3), and magnetic resonance imaging (MRI) (4) are all suitable to track labeled cells, with MRI having superior temporal and spatial resolution. Tracking cells using MRI relies either on labeling of cells with MR contrast agents or engineering the cells to express MR reporter gene. Number of techniques have been developed to magnetically label cells, most of them utilizing superparamagnetic iron oxide nanoparticles (SPIOs). Non-phagocytes for efficient labeling usually require use of transfection agent (5) or electroporation (6). Other MR contrast agents for cellular labeling include Gd chelates (7) or fluorine compounds (8). However, sensitivity of this agents is much lower as compared to ferumoxides (9).

Sensitivity of SPIO-based cellular MRI is very high and with higher field scanners it allows detection of nearly single cells in vitro and as little as 100 cells in vivo (10). Moreover the use of larger - micron size particles, allows imaging of single cells in vivo (11). Ferumoxides have been successfully used for cell tracking in numerous models of neurodegenerative diseases. Several groups were able to successfully perform longitudinal cellular MRI studies that visualized the distribution of cells over time (5,12). Another example of an application for MRI cell tracking and cell-based therapy is in multiple sclerosis (13). When MD-100-labeled neurospheres were transplanted into the ventricles of experimental allergic encephalomyelitis rats at the peak of their disease, migration into white matter structures could be observed on the MR images. A follow-up, in vivo longitudinal study in chronic experimental allergic encephalomyelitis mice demonstrated that the distance of cell migration correlated well with clinical severity of disease and with the number of microglia in white matter tracts, supporting the notion that inflammatory signals promote transplanted cell migration (14). In another study, in vivo MRI was used to demonstrate the extent of the distribution of neural-stem-cell-derived oligodendrocytes in a dysmyelinated rat model. Magnetodendrimer-labeled oligodendrocyte progenitors transplanted into the neonatal rat enabled in vivo detection for up to 6 weeks (15). Stroke is an example of another neurodegenerative brain disorder where restorative cell therapy may be even more challenging than in multiple sclerosis

and will likely require sophisticated monitoring methods, such as those provided by in vivo MRI cell tracking. Migration of superparamagnetic-iron-oxide-labeled embryonic stem cells toward the stroke lesion from one hemisphere to the other has been demonstrated on high-resolution MRI scans. The extensive migratory behavior was confirmed by conventional green fluorescent protein reporter gene fluorescent microscopy (16). MRI cell tracking was successfully used to monitor intracarotid delivery of mesenchymal stem cells and their targeting directly towards brain lesion (17). For spinal cord injury, the ability to follow the fate of transplanted cells has been tested in several studies. Monitoring the migration of olfactory ensheathing cells grafted into rat intact spinal cord has been demonstrated (18), however, when the spinal cords were transsected the interpretation of the olfactory ensheathing cell biodistribution was severely confounded by the presence of microhemorrhage.

Although the ability to observe single transplanted cells in the milieu of the living organism has been achieved with MRI, and there are reports about the successful application of this technology to monitor the migratory behavior of the cells in vivo, there are still unresolved issues and clear disadvantages inherent to the imaging of cells loaded with contrast agent. The disadvantages include dilution of the contrast agent during cell division (19) and lack of information about cell viability or function. Therefore, interpretation of the results can be difficult. The ideal solution to this problem would be an MR reporter gene that would demonstrate activity only in the viable cells. While there is significant effort to develop such reporter system (20-22), an MR reporter gene with a sensitivity sufficient for stem cell tracking is currently not available.

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