Molecular Imaging & Contrast Agents - Sunrise Course

Preclinical & Clinical Applications of Metal Based Paramagnetic/Iron Contrast

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Introduction

Magnetic resonance imaging is a powerful tool for visualizing cellular/macrophage tracking and migration or inflammatory processes. MRI examinations can be performed longitudinally and non-invasively, at isotropic image resolutions approaching 50 microns within reasonable scan times in live animals.

Whereas vascular and interstitial compartments are investigated using Gadolinium-based contrast agents, specific molecular or cellular imaging can be obtained using metal-based contrast agent like Manganese (Mn) or iron oxide particles.

To provide enhanced contrast on an MR image, cells are loaded with an MRI contrast agent prior to or during imaging. Superparamagnetic iron oxide (SPIO) nanoparticles can be used to generate contrast based on magnetic susceptibility differences between the labeled cells and the surrounding tissue. Cellular detection is most often accomplished via T2 or T2* imaging (negative contrast) after incorporation of iron oxide either within or attached to the cell. Coupling of the particles with fluorophores allows correlation of in vivo and ex vivo MRI with optical imaging and histology. At sufficient iron concentration and high resolution, single cells can be detected, even in vivo. Methods to provide positive and/or quantifiable contrast from iron containing cells are currently important topics of research. On the other hand, the T1 paramagnetic effect of Mn gives directly a positive contrast effect that can be used to assess the intracellular distribution of this ion.

Preclinical applications

Cell tracking using iron oxide particles

Iron oxide labeling is used to provide contrast between cells or clusters of cells for monitoring the initial success and the progression over time of a graft. Natural contrast is often insufficient and the use of contrast agents allows very small structures to be distinguished and quantified. Nanoparticles cause susceptibility artifacts, which destroy local signal, producing dark regions on image that are larger than the actual region of iron. Problems with this include areas of low signal from other structures and difficulties in quantification. Positive contrast techniques are an important area of preclinical research for the applications described, among others, as quantifiable and unambiguous images are obtained. Techniques include the 'IRON' or 'off-resonance' methods to suppress everything except the susceptibility 'artifact', or excite just the signal from the affected protons; 'White-marker' which acts to recover the lost signal and 'dUTE' imaging showing positive signal from even the very short T2 protons near the particles, while suppressing signal from the surrounding tissues and background.

Islets of Langerhans

Treatment of type 1 diabetes by islet of Langerhans transplantation has given excellent short-term results, but long-term attrition occurs, with approximately 20% of patients free of insulin 5 years after transplantation (1). For efficient treatment regimes against islet rejection to allow intervention before any clinical symptoms manifest, in-vivo non-invasive

quantification and monitoring of preliminary reports suggest the potential of magnetic resonance (MR) imaging for non-invasive serial monitoring for islet cells (2, 3), including immune rejection (4).

Stem Cells
Another important application is the visualization of stem cells, to monitor their engraftment at the region of interest. Multiple applications of this method based on in vitro loading of the stem cells have been demonstrated in the brain (5) and heart (6) and other organs (7). However, it may be difficult to evaluated the fate of the iron loaded stem cells as iron released from dead cells and phagocyted by local macrophages may be indistinguishable from iron contained in living stem cells (8).

Plaque imaging
The composition and stage of atherosclerotic carotid plaques are of paramount importance to evaluate the stroke risk. USPIOs can accumulate in plaques containing a high density of high macrophage. In-vivo signal loss studies of atherosclerosis have been reported using iron oxides particles (9). Positive contrast (10, 11) here has particular advantages as signal loss sequence produce notches in a vessel wall already surrounded by hypointense signal, and therefore suppression of normal wall signal and enhancement of iron signal allows better visualization of the actual size of the region of uptake as well as its location.

Monocytes and inflammation
Injected iron oxide particles which are then taken up by macrophages and monocytes, can then be tracked to the site of inflammation as show in studies of myocardial infarction (12), antigen-induced arthritis (13), autoimmune brain disorders (14) and atherosclerosis (15). In most of the studies, SPIO are injected once the experimental injuries have been induced. It is possible to inject SPIO before any injury to load monocytes and to track these cells migrating toward an inflammatory site. The demonstration of this in vivo loading approach has already been performed with monocytes and a model of myocardial infarct in rats (16).

Calcium channel activation and manganese
The paramagnetic manganese ion Mn^{2+} is an analogue of calcium (Ca^{2+}) that can enter cells through the voltage dependant calcium channel. This property has been widely used to image the cerebral activity in rodent since Mn can enter synaptically activated neurons (17). Another successful field of application for Mn enhanced MRI (MEMRI) is related to heart imaging since Mn can enter into cardiomyocytes. Mn accumulates in mitochondria for hours allowing very long imaging window and high image resolution. Myocardial infarct and area at risk have been demonstrated in rats and mice using such an approach (18, 19).

Clinical applications

Interest in Mn chelates and iron oxide particles stems from their FDA approval for clinical use that has been in place for many years. Iron oxide particles have been used to improve the detection and characterization of liver hepatocarcinoma and metastasis (20) as well as hepatic hemangioma (21).
Ultrasmall SPIO (USPIO) can detect malignant involvement of lymph nodes that do not show any uptake of the contrast agent with an improved sensitivity and specificity

compared to non-enhanced images (22).
Limited clinical studies demonstrating the feasibility of in vivo cell tracking in patients have been reported so far (23). In the case of pancreatic islet transplant, iron loaded cells were successfully detected by MRI as dark spots in the liver parenchyma up to 6 months after the transplantation and all diabetic patients could stop treatment with insulin, attesting that the iron load did not alter the function of the pancreatic islet (24).

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