Cardiovascular Molecular Imaging: Cell Therapy

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Introduction:

Cardiovascular cell therapy trials, which were initiated over a decade ago using skeletal myoblasts,[1] are primarily targeted at adult stem cell lines. Initial trials with a limited number of patients have shown the safety of various cell lines and delivery routes, but they have largely failed to demonstrate efficacy in rebuilding the failing heart. [2-7] In addition, trials using similar administration routes or cell lines have shown vastly different results. While preclinical studies in a variety of species have demonstrated dramatic improvements in cardiac function, clinical results have failed to replicate these findings. Stem cell labeling may offer a method to better understand from a mechanistic point-of-view the role that stem cells are playing in cardiac repair to help design better cell therapy products as well as clinical trials.

Labeling Techniques:

Stem cell labeling for non-invasive imaging can be largely divided into two basic techniques: direct cell labeling and reporter gene methods. There are advantages and disadvantages to each technique. Ideally, any labeling technique should be non-toxic, not alter the metabolism and physiology of the cell, and provide a high sensitivity using the desired imaging technique.

Direct Cell Labeling

Using direct cell labeling techniques, contrast agents are either altered,[8] combined with transfection agents,[9] or the cells electromechanically disrupted [10] to encourage uptake of the contrast agent into the cell. Direct labeling techniques are typically very inexpensive and easy to perform. Using these techniques contrast agents, such as superparamagnetic iron oxides (SPIOs), have been used to exogenously label cells prior to implantation and have been tracked using clinical MRI scanners in a variety of animal studies.[11] Recently, a few groups have shown the ability gadolinium-based direct cell labeling to have sufficient sensitivity as well.[12] Similarly, manganese has shown promise as a cellular labeling agent for MRI.[13] Due to the good biocompatibility profile of SPIOs [14-17], a few non-cardiac trials using SPIO-labeled stem cells have been performed.[18, 19] However, the recent withdrawal of commercially available SPIOs will probably thwart the adoption of SPIOs in cardiovascular clinic trials.

More recently, several groups have experimented with non-proton MRI contrast agents containing fluorine moieties.[20, 21] Specialized hardware is needed to perform fluorine MRI,

but FDA-approved perfluorocarbons could potentially be used to hasten clinical acceptance. A major concern about any direct labeling technique is the fate of the label if the stem cell dies. If the label becomes detached from the stem cell, then serially imaging will no longer provide a means of tracking stem cell viability and engraftment. Furthermore, should the cell rapidly divide, the sensitivity will be degraded as the label is diluted with each cell division.

Reporter Gene Methods

Reporter gene methods involve alterations to a cell to encourage the production of a protein, enzyme, or receptor that can either be imaged directly or imaged with the introduction of a reporter probe. One of the oldest know reporter gene methods was the induction of cells to produce green fluorescent protein (GFP) for tracking of cell fate histologically using fluorescent microscopy. Reporter gene methods have been extensively used in other forms of optical imaging,e.g., luciferase for bioluminescence imaging (BLI), and radionuclide imaging, e.g., 18F-FHBG for positron emission tomography (PET). MRI reporter gene methodologies are less ubiquitous. One of the earliest MR reporter genes caused the overexpression of the transferrin receptor (ETR).[22] A monocrystalline iron oxide (MION) conjugated to transferrin was used as a reporter probe to enable the detection of cells containing the reporter gene.[22] One advantage of reporter gene labeling is that for the most part, only viable cells will express the reporter gene product. Another potential advantage is that a few cells can be transfected with the reporter gene and then clonally expanded. However, this benefit can become disadvantageous for non-pleuripotent cell lines that cannot be expanded infinitely, such as mesenchymal stem cells. With the introduction of clinical PET-MRI scanners, it is likely that the more advanced reporter gene methods developed for PET imaging may be combined with conventional MRI for anatomical localization of stem cells.

Hybrid Techniques

In addition to hybrid imaging suites, such as PET-MRI, several groups have demonstrated multi-modality imaging agents. One example is combining radiopaque agents, e.g., gold, with conventional MR contrast agents, e.g., gadolinium, to provide a dual X-ray-MRI labeling agent.[23] Microencapsulation techniques, where the contrast agent is impregnated into a capsule surrounding the cell, have been developed using a wide assortment of contrast agents for multi-modality imaging.[24]

The poor temporal resolution and lack of high quality physiological monitoring with MRI makes the delivery of stem cells using MRI-guidance in cardiac patients unlikely in the near future. One technique to overcome this hurdle is to combine MRI anatomical and metabolic information with real-time X-ray fluoroscopic guidance. These X-ray fused with MRI (XFM) techniques will encourage the development of multi-modality labeling techniques that allow the visualization of stem cells using each imaging modality. Another possibility is to combine

anatomical localization during delivery using direct MRI labeling techniques and reporter gene techniques using other imaging modalities to follow cell fate.[25]

Perhaps the biggest hurdle for MRI delivery and tracking of labeled stem cells will be the incompatibility of many cardiac devices such as stents and pacemakers with the magnetic environment. As better MR-compatible devices are developed in concert with advanced real-time interfaces, it is likely that interventional MRI techniques that can lessen radiation exposure to patients and operators will gain more widespread adoption.

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