High Resolution MRI of Arterially Delivered Mesoangioblasts

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Introduction

With new potential therapies on the horizon for muscular dystrophy, there is an urgent need for noninvasive imaging to study muscle and cardiac function. Gene and/or stem cell transfer, two therapeutic strategies that have tremendous potential, currently rely heavily on invasive techniques to evaluate the effectiveness of the intervention. Cell based therapies represent a greater challenge for noninvasive monitoring due to the variability in stem cell incorporation that occurs in the presence of massive cell death(1). In this work MR based strategies have been developed to track the arterial migration/integration of stem cells into skeletal muscles and the bone marrow of dystrophic mice.

Experimental

Animals and in vivo migration assays: Ten, 4-8wk old female mdx mice received femoral artery injections, as previously described(4). SPIO labeling (Feridex™) was optimized on muscle stem cells (mesoangioblasts). 100,000-500,000 SPIO labeled mesoangioblasts were injected and MR imaged between 1hr to 30 days post injection. After the final imaging session, hindlimbs were extracted and underwent high-resolution MRI and histological verification. MRI: Mice were imaged at 4.7 and 11.1T using Paravision® software (PV3.02;Bruker Medical). The animals were anesthetized using 2% Isofluorane in oxygen. The hindlimbs were placed inside a 1cm transmit-receive solenoid (4.7T) or loop-gap coil (11.1T) and imaged with a 3D-FLASH scan sequence at 4.7 (TR/TE=100/7.5&9,BW=100kHz,NEX=1,flip=30º, FOV=0.8×0.8×2.0cm³, matrix=384×192×128) and at 11.1T(TR/TE=100/2.9&9,BW=100kHz,NEX=1,flip=30º, FOV=0.8×0.8×2.0cm³, matrix=384×192×128). Mice hindlimbs were also imaged using 3D-RARE at 4.7T (TR/TE=2000/45, RARE factor=8, BW=75kHz, FOV=0.8x0.8x1.8cm³, Matrix=128x96x256,NEX=1) and at 11.1T (TR/TE=1000/22, RARE factor=4, BW=75kHz, FOV=0.8x0.8x1.8cm³, Matrix=128x96x256,NEX=1). Isolated muscles were imaged at 17.6T in perfluorocarbon at 12°C with a 5mm i.d coil (PV4;Bruker Medical) using 3D-FLASH(TR/TE=150/3.4, BW=100 kHz, Flip=30º, FOV=1.6×0.4×0.2cm³,matrix=512×128×64, NEX=4). Images were analyzed with OsiriX and IDL (ITT) software.

Results and Discussion

At both 4.7 and 11.1T, areas devoid of signal on both FLASH and RARE images could be readily detected throughout the leg muscles and bone marrow following femoral artery delivery of as few cells as 100,000 between one and 24 hrs post cell delivery. The majority of the cells could be visualized in muscles surrounding the injection site in upper limb muscles (quadriceps/hamstrings), but cells were also visualized along the entire length of the lower limb muscles and bone marrow (Fig 1). Prussian blue staining revealed cells with iron within the vasculature and within the muscles. Unlike intramuscular delivery, there was a dramatic loss of muscle MR contrast as early as 12hr post delivery. Whereas 3D-FLASH images resulted in higher signal to noise and better contrast and cell detection at 11.1T compared to 4.7T, the 3D-RARE images at 4.7T highlighted areas of tissue damage to a greater extent than at 11.1T.

Conclusions

The initial tracking of mesoangioblasts through muscle can be followed in vivo following the arterial delivery of SPIO labeled cells. It is this initial binding and transmigration of cells during the first 6-24hrs that is thought to be the most therapeutically relevant for vascular cell delivery therapies and MRI is ideally suited to follow these initial events. Noninvasive and longitudinal tracking will provide valuable feedback to cell biologist for enhancing cell delivery and tissue regeneration.

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References