

The effect of mesenchymal stem cells on vascularization of an artificial transplant cell site studied by DCE-MR and bioluminescence imaging

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Target audience: This information could be beneficial for the researchers focused on molecular imaging and cell transplantation.

Purpose: Artificial polymeric chambers have been tested as an alternative cell transplant site¹. Sufficient blood supply to the transplanted cells is crucial for their survival and can be enhanced by implantation of stem cells. Dynamic Contrast Enhancement Magnetic Resonance (DCE-MR) can assess perfusion inside of the cavity related to vascularization. Using stem cells with expression of gene for luciferase, we can monitor their presence by bioluminescence imaging. In the current study, we performed a long-term examination of the effect of genetically modified mesenchymal stem cells on vascularization of polymeric scaffolds intended for pancreatic islet transplantation by DCE-MR and optical imaging.

Methods: Two polymeric scaffolds (Ella-CS, CZ) were implanted into subcutis of Lewis rats (n=3). One week later, mesenchymal stem cells (MSC) expressing gene for Luciferase (11-15 mil.) were injected into one cavity. The second device served as a control chamber without addition of MSC. MRI examination was performed on a 4.7T Bruker MR scanner equipped with a resonator coil. A 3D gradient echo sequence for the DCE-MRI was used: TE/TR=3.1/10 ms, resolution 0.2x0.4x0.4 mm³, evolution delay 5s, 64 slices and 32 repetitions. After the 10th cycle, MR contrast agent (CA) Gadofoveset (60 μ L) was injected intravenously. Regions of interest (ROI) were outlined manually around kidney and both devices. The mean MR signal intensity was calculated for every cycle and difference between basal (before injection of CA) and contrast-enhanced signal intensity (after injection of CA) normalized to the kidney was calculated (Fig.1). After MRI examination, optical images were acquired by IVIS Lumina XR imager (Life Sciences) with 1 min exposure time before and after intravenous injection of D-Luciferin (50 mg/kg). Average radiance (photons/sec/cm²/sr) was calculated from ROIs selected around the each cavity. All rats were monitored for 2 weeks after cell implantation; one rat underwent a long-term examination for 2 months.

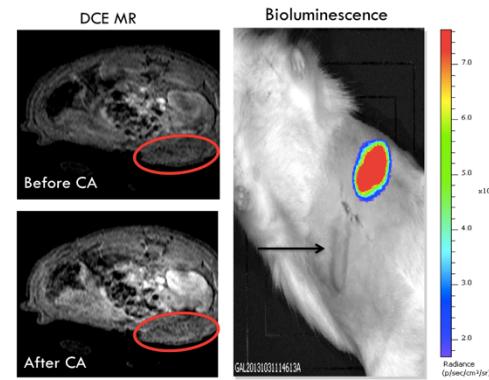


Fig. 1: DCE MR images before and after injection of the contrast agent (CA) (left). An optical image (overlaid on a photography) shows a strong signal originated from the chamber with MSC (right).

Results: Higher perfusion inside the chamber containing stem cells compared to the control chamber was observed for 15 days after their implantation (Fig.2). This MRI signal related to vascularization increased within one week, however the MRI signal from the control chamber starts to elevate at the end of the second post-transplant week. Optical signal confirming the presence of stem cells increased 2 days after implantation and then continuously declined. Long-term examination showed sufficient optical signal (>0.17 mil ph/sec/cm²/sr) and MRI signal above its pre-transplant level for 2 months following cell implantation (Fig.3). We found a correlation between optical and MRI signal during the first 20 days ($R^2=0.56$), however the peak of optical signal appeared in advance of MRI signal.

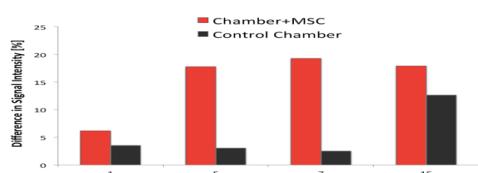


Fig.2: Changes in DCE-MRI signal intensity in the chamber with implanted MSC and the control within 15 days after cell implantation.

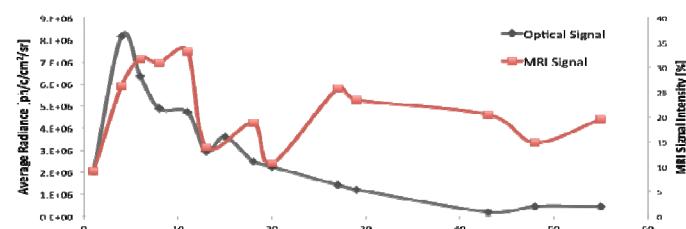


Fig.3: Long-term assessment of perfusion (MRI signal) and the presence of mesenchymal cells (optical signal).

Discussion: Optical signal confirmed the presence of the living stem cells inside the chambers immediately after their implantation and during the whole examination. The increase of MRI signal intensity originating from the chamber with stem cells suggests that there is an improvement in vascularization, which is established faster compared to control chamber without cells.

Conclusion: Our results suggest that stem cells implantation improves the vascularization of the artificial cell transplant site. Prolongation of cell survival due to higher blood supply ameliorates efficacy of transplantation outcome. Combination of optical imaging and DCE-MR can also assess the optimal time for cell implantation.

References: 1. Kriz J, Jirak D, et al. Vascularization of Artificial Beds for Pancreatic Islet Transplantation in a Rat Model, Transplantation Proceedings 2010; 42: 2097–2101

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