Monitoring the pancreatic islets implantation in the subcutaneous polymeric scaffolds by DCE-MRI and optical imaging

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

Purpose: Intraportal transplantation of pancreatic islets is an alternative treatment for type 1 diabetes, however its outcome is limited and new transplant sites are tested. Subcutaneously implanted polymeric scaffolds might serve as an experimental artificial site. The devices supported by mesenchymal stem cells showed improved vascularization[1]. In this study, isogeneic pancreatic islets were co-transplanted with isogeneic bioluminescent mesenchymal stem cells (MSC) into the scaffolds in the subcutis of diabetic rats. We suppose that due to the positive effect of stem cells on the scaffold vascularization a lower number of islets is needed to induce normoglycaemia. In order to assess the functionality of the model, anatomical MR, Dynamic Contrast Enhanced MR (DCE-MR) and optical imaging were used to monitor the blood perfusion and graft survival.

Methods: Two polymeric scaffolds (Ella-CS, Fig. 1E) with plugs were implanted into the subcutis of Streptozotocin-induced diabetic Lewis rats (n=4). One week later, the plugs were removed and adipose-derived mesenchymal stem cells expressing gene for Luciferase were injected into one of the chambers (15 mil.). Three days after, 1000 pancreatic islets were co-implanted. The second scaffold served as a control without cells. MRI was performed on a 4.7T MR scanner equipped with a resonator coil. Anatomical images were obtained by a gradient echo sequence (TR/TE=111ms/3.7ms). A 3D gradient sequence was used for DCE-MRI: TE/TR=3.1/10 ms, resolution 0.2x0.4x0.7 mm^3, evolution delay 5s, 32 slices and 24 repetitions. After the 8^{th} cycle, a contrast agent Gadofosveset (0.12mM) was injected intravenously. A difference between pre- and post-contrast mean MR signal intensity in the internal diameter of the artificial cavities normalized to kidney was calculated for each cycle. After MRI, bioluminiscent images were acquired by an optical imager before and after injection of Luciferin (Fig.1G). Average photon radiance emitted from each scaffold was calculated. Animal weight and blood glycaemia were measured 2-3 times per week. The animals were monitored for 2 months.

Results: MR images showed tissue changes inside the scaffolds in time (Fig.1A-D). At the day of islets implantation, a cavity was observed in the middle part of the chamber (Fig.1A,B,F). DCE-MRI showed no significant difference in perfusion between chambers before implantation of cells (p=0.86). After MSC implantation, the perfusion in the experimental scaffold increased and stayed significantly higher if compared to the control one during the whole examination (p=0.001). This MRI signal related to vascularization reached maximum 7-9 days after the MSC implantation (Fig.2B). A peak of the optical signal confirming the presence of MSC appeared 3-5 days after their implantation (Fig.2A) and then continuously declined down to approximately 15% of the peak value two months after. One animal reached normoglycaemia two weeks after islet transplantation; the rest remained hyperglycemic.

Discussion: MRI revealed that the cavity in the cell-supported scaffold was filled by a soft highly vascularized tissue enabling islet injection. The increased perfusion persisted until the end of the experiment. Optical imaging confirmed the presence of viable MSCs inside the chamber at least for two months. Normalization of blood glucose level in one animal using a transplantation of suboptimal number of islets suggests a positive effect of MSCs on blood supply and islets viability; however the number of islets should be higher for glycaemia normalization in all animals.

Conclusion: Our results suggest that diabetes treatment by pancreatic islet transplantation may benefit from mesenchymal stem cell co-transplantation. MSCs may improve vascularization, graft survival and normalization of glycaemia with lower number of islets.

References: 1. Fabryova E, et al. Transplantation Proceedings 2014; 46: 1963-1966

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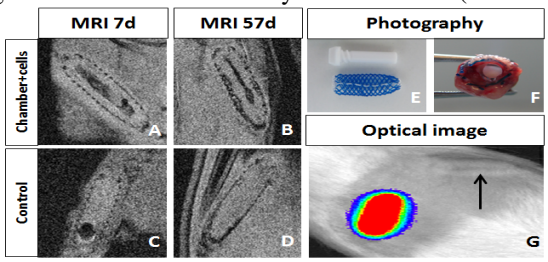

Fig.1 Illustrative MRI images of the experimental (A,B) and control (C,D) chambers. Scaffold photography before (E) and at the third day after MSC implantation (F). An optical image of the scaffolds, arrow points the control (G).

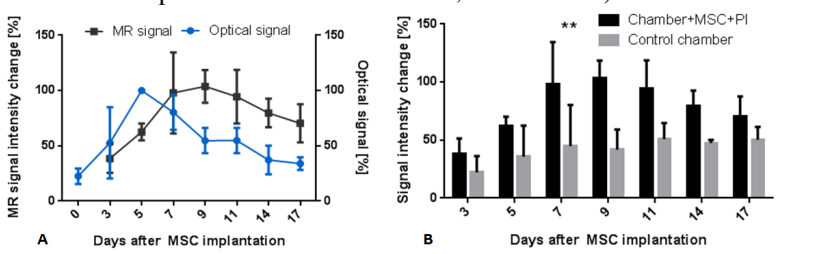

Fig. 2 Comparison of changes in optical and DCE-MRI signal intensity after stem cells implantation (A). Differences in perfusion between the scaffolds with MSCs and the controls during the first 17 days (B). Statistical analysis was performed by paired t-test with significance level **p<0.01.