Pancreatic islet graft monitoring by magnetic resonance imaging in non-human primates

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Background

Islet transplantation emerges as the most promising treatment modality for type 1 diabetes. In spite of the success of the Edmonton protocol, however, significant graft loss occurs immediately after transplantation, often necessitating repeated infusions of additional islets. Therefore, there is a critical need for noninvasive longitudinal monitoring of transplanted islet fate. We have previously developed a method to detect transplanted islets non-invasively using magnetic resonance imaging (MRI) in mice (1,2). We have also demonstrated the feasibility of monitoring the survival of transplanted islets in a murine model of immune rejection (3). We report here the extension of this methodology for the long-term tracking of transplanted islet fate in a non-human primate model as a first step toward clinical applications.

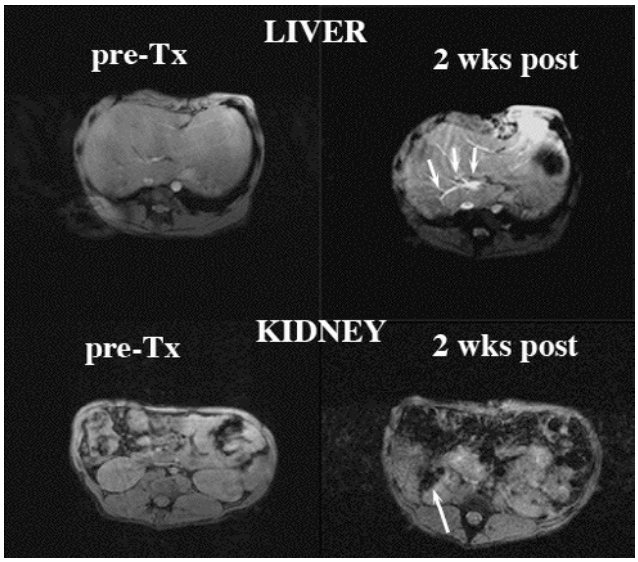
Methods and Materials

Islet labeling: Baboon islets were incubated overnight with the FDA-approved commercially available agent, Feridex, which is clinically used for liver imaging at a concentration of 200μg Fe/ml.

Islet transplantation: Autologous, Feridex-labeled baboon islets were transplanted underneath the left renal capsule (Case 1) and both into the liver, via intra-portal infusion, and underneath the left renal capsule (Case 2).

Imaging: In vivo MR imaging was performed before transplantation and weekly after transplantation using a 1.5T Siemens Trio magnet equipped with a 6 channel body matrix coil. Respiratory gating was employed in these studies. The imaging parameters were as follows:

Liver- TR/TE = 100/2.3-29.3 ms, slice thickness 3 mm, FoV = 200 x 200 mm^2, matrix size 192 x 192, flip angle = 25°, and in plane resolution 1 x 1 mm^2.



Kidney- TR/TE=200/2.3-29.3 ms, slice thickness 3 mm, FoV = 180 x 180 mm^2, matrix size 192 x 192, flip angle = 25°, and in plane resolution 0.9 x 0.9 mm^2.

Results MR imaging of transplanted autologous pancreatic islets revealed the presence of signal voids corresponding to labeled islets along the hepatic blood vessels. Islets in left kidney were detected as a noticeable drop in T2 signal, seen as a pocket of signal loss over the capsule (not seen in right kidney). Our longitudinal observations suggest that in the autologous non-human primate model, islets transplanted underneath the kidney capsule can be detected for at least 6 months after transplantation (Case 1). Islets transplanted both into the liver, via intra-portal infusion, and underneath the left renal capsule can be detected at least 40 days after transplantation (Case 2) (2 wks post-Tx shown, arrows).

Summary This study suggests the feasibility of longitudinal in vivo imaging of Feridex-labeled transplanted islets in a nonhuman, pre-clinical primate model, as a means of assessing long-term islet graft fate. This study will facilitate the transition of this approach to human clinical trials.

References

1. Evgenov N et al, Nat Med 2006;12:144-148.
2. Medarova Z et al, Nature Prot 2006;1:428-434.
3. Evgenov N et al, Diabetes 2006;55:2419-2428.