Quantitative in vivo 19F MRI of transplanted pancreatic islets using clinically applicable, non-emulsion nanoparticles

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Introduction

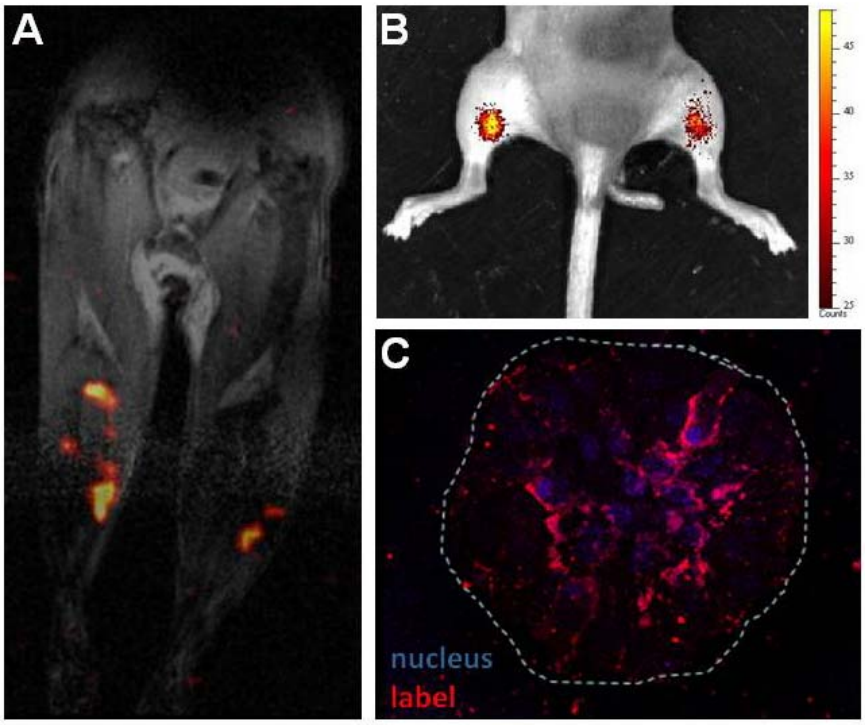
Pancreatic islet transplant is a promising therapy for type I diabetes patients, with over 100 ongoing clinical trials. However, the lack of an appropriate quantitative technique for tracking the islets after transplant has hindered development. Pancreatic islets are difficult to label for imaging, in part because they are non-phagocytic, fragile and surrounded by a membranous capsule. Islets have recently been ^{19}F-loaded using perfluorocarbon emulsions [1]. Here, we label primary murine pancreatic islets using a novel multimodal imaging probe that allows for quantitative ^{19}F MRI and fluorescence imaging. Importantly, the label nanoparticles can be formulated for clinical use, and are not emulsion-based, consisting instead of a fluorocarbon core with a fluorescent dye encapsulated within a polymer coat [2]. ^{19}F MRI allows for quantification directly from image data [3].

Methods

Murine pancreatic islets were isolated and labeled overnight. Viability, insulin secretion and ^{19}F loading were determined and optimized. Confocal microscopy was carried to localize the ^{19}F nanoparticles within the islets. For in vivo validation of the method, islets were isolated, labeled and transplanted in the left and right (100 and 600 islet isografts respectively) hind limb muscle of recipient mice. In vivo MRI and optical imaging were performed at various time points, up to two weeks after transplantation. MRI was carried out in a 7T horizontal bore system with a ^{1}H/^{19}F volume coil.

Results and Discussion

We found that labeling the islets required the use of a transfection agent to increase ^{19}F loading. Toxicity was minimal when the ratio of transfection agent to the particles was optimized. We imaged islets after transplantation in the quadriceps, and were able to detect them using both MRI and fluorescence in vivo (A and B respectively). This mouse received 600 islets in one side and 100 in the other. This difference in signal intensity is clearly visible in the images. Analyses performed on excised tissue confirmed that the transplanted islets produced insulin. Finally, we also carried out confocal microscopy to show that the imaging label is contained within transplanted islets (C; an intact islet with cell nuclei in blue and label particles in red). The islets remain detectable for at least two weeks post-transplant (data not shown). Thus, we describe the use of a novel imaging agent to allow quantitative in vivo imaging of transplanted islets without significant effects on their functionality or viability. Furthermore, the label is applicable to a cell type that is known to be difficult to label for in vivo imaging. Finally, the use of a non-emulsion based agent allows for greater stability and reproducibility of the agent.



Conclusion

Here we present a protocol for optimal islet labeling with ^{19}F/fluorescent nanoparticles. Cells are viable and functional after ^{19}F loading and detectable in vivo. Finally, the nanoparticles are taken up within the islets and are retained for at least two weeks post-transplant. The use of nanoparticles allows for greater stability of the constructs, which is necessary for long-term imaging of transplanted cells.

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