

Microfabrication of Multifunctional Alginate Capsule-in-Capsule (CIC) for Immunoprotected Cell Transplantation with MR, CT, and US Visibility

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Introduction

The clever combination of different nanoscale materials can lead to the development of multifunctional platforms for simultaneous imaging and therapy. To protect transplanted cells from immunorejection, immunoprotection of cells in semi-permeable alginate microcapsules has previously been employed. Superparamagnetic iron oxide nanoparticles (NPs) have been the dominant use of MR contrast agents for non-invasive MRI cell tracking including the use of magnetocapsules (B.P. Barnett, Nat. Med. 13, 986-991, 2007). However, other imaging modalities such as CT exist that are more developed for image-guided injection of cellular therapeutics. Gold NPs have recently been introduced as non-invasive computed tomography (CT) contrast agent. We have designed multifunctional alginate capsule-in-capsules (CICs) by combining Feridex and gold NPs for multimodal MRI, CT, and ultrasound tracking of transplanted human islets.

Methods

Feridex and gold NPs were first incorporated in core alginate microcapsules. The core microcapsules with contrast agent were then re-encapsulated with human islet cells in a second shell alginate microcapsule (Fig. 1) to produce CIC. To compare cell function, the glucose responsiveness and insulin secretion from unlabeled capsules, NP capsules, and CIC, all containing human islets, were measured using a human C-peptide ELISA kit. Mice injected with CICs in the peritoneal cavity were imaged in vivo using a 9.4 T MR, micro-CT, and 40 MHz ultrasound scanner.

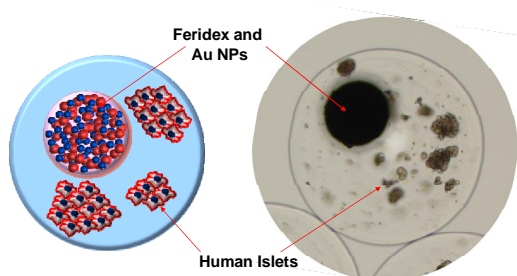


Figure 1. Schematic representation (left) and optical microscopic image (right) of CIC encapsulated with Feridex and gold NPs in the core capsule and with human islets in the secondary capsule.

Results

A comparison of the glucose responsiveness and insulin secretion for three different capsule groups showed that CIC can maintain a comparable human islet function as compared to unlabeled capsules (Fig. 2). In addition using CICs as compared to NP capsules with human islets appears beneficial for human islet viability and function (Fig. 2). By separating contrast agent and cells through reiterative encapsulation, we could avoid direct exposure of cells to contrast agent while providing a larger confinement space for transplanted cells. CICs encapsulated with human islets secreted insulin at least up to one month. The CICs injected in peritoneal cavity in live mice were easily visualized on MRI, CT, and ultrasound (Fig. 3).

Conclusions

A novel capsule-in-capsule (CIC) preparation was designed and microfabricated for immunoprotected cell transplantation with multimodal tracking capability including MRI, micro-CT, and ultrasound imaging. Using the dual capsule (CIC) approach for physical separation of cells from the NPs, a better viability and cell function can be retained as compared to single Feridex/Au NP capsules.

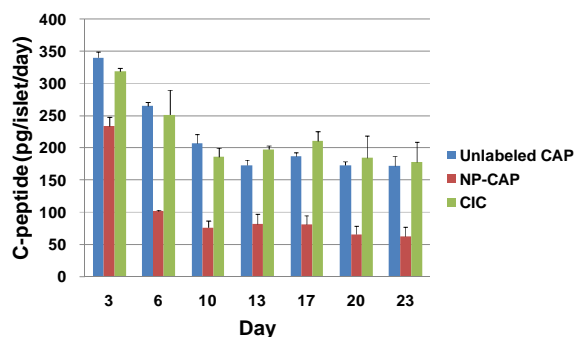


Figure 2. C-peptide secretion from unlabeled capsules, NP-capsules, and CIC encapsulated with human islets.

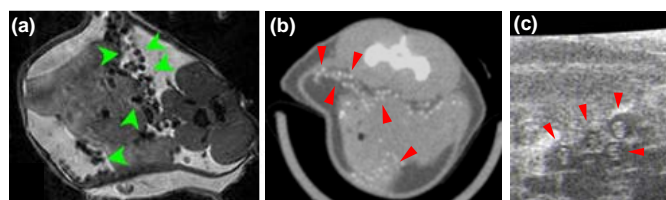


Figure 3. (a) *In vivo* T2-weighted MRI (b) micro-CT, and (c) ultrasound images of a mouse injected with CICs (arrow heads).