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Magnetic Resonance Imaging of Transplanted Mouse Islets Labeled With Chitosan-Coated Superparamagnetic Iron Oxide Nanoparticles

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ABSTRACT

Although only 10% of islet recipients maintain insulin independence, 80% of them are C-peptide positive at 5 years after transplantation. To better understand the fate of transplanted islets, a magnetic resonance imaging (MRI) technique has been used to detect Feridex-labeled islet grafts in rodents. In this study, we used a novel MRI contrast agent, chitosan-coated superparamagnetic iron oxide (CSPIO) nanoparticles, to monitor mouse islet grafts. Male inbred C57BL/6 mice were used as donors and recipients of islet transplantation. The islet cytotoxicity was evaluated by fluorescein diacetate and propidium iodide staining for RAW cells incubated with CSPIO. After being incubated overnight with and without CSPIO (10 mg/mL), 300 islets were transplanted under the left kidney capsule of each mouse. After transplantation, 3.0-Tesla MRI of the recipients was performed biweekly until 19 weeks. At the end of study, the islet graft was removed for insulin and Prussian blue staining. The cell death rates in RAW cells did not increase with increasing CSPIO concentrations or incubation time. The grafts of CSPIO-labeled islets were visualized on MRI scans as distinct hypointense spots homogeneously located at the upper pole of left kidney. Their MRI signal was 30%–50% that of control islets and was maintained throughout the follow-up period. At 18 weeks, the histology of CSPIO-labeled islet graft revealed the insulin- and iron-stained areas to be almost identical. Our results indicate that isolated mouse islets labeled with CSPIO nanoparticles can be effectively and safely imaged by using MRI as long as 18 weeks after transplantation.

Recently, the Edmonton Protocol has markedly improved the success rate of human islet transplantation.[1] However, ≥2 pancreases are usually required to achieve normoglycemia. Moreover, long-term function of the transplanted islets has been disappointing.[2,3] Allograft failure may be due to nonimmunologic (eg, insufficient β-cell mass and islet engraftment problems) as well as immunologic (eg, immune rejection, toxicity of immunosuppressants and autoimmune recurrence) factors.[4] Although only 10% of recipients maintain insulin independence, 80% of them are C-peptide positive at 5 years after islet transplantation.[2] To better understand the fate of transplanted islets, a magnetic resonance imaging (MRI) technique has been used to detect Feridex (dextran-coated superparamagnetic iron oxide [SPIO])–labeled rat, porcine, and human islets transplanted into rodents.[5–7] In the present study, we used a novel MRI contrast agent, chitosan-coated SPIO (CSPIO) nanoparticles,[8] to monitor mouse islet grafts.

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MATERIALS AND METHODS

Animals

Male inbred C57BL/6 mice, aged 8–12 weeks, were used as donors and recipients of islet transplantation.[9] The animal experiments were approved by the Animal Ethics Committee of Chang Gung Memorial Hospital.

Islet Isolation

Under anesthesia with sodium amobarbital, pancreases were distended with 2.5 mL RPMI-1640 medium (Gibco, Grand Island, NY, USA) containing 1.5 mg/mL collagenase (collagenase from *Clostridium histolyticum,* type XI; Sigma Immunochemicals, St Louis, Mo), excised and incubated in a water bath at 37°C.[9] The islets were separated by a density gradient (Histopaque-1077; Sigma Immunochemicals), and purified islets were then hand-picked under a dissecting microscope.

Islet Labeling

Isolated islets were overnight incubated with CSPIO (10 mg/mL) in culture medium.[8] After incubation, islets were washed with culture medium and used for in vitro studies or islet transplantation.

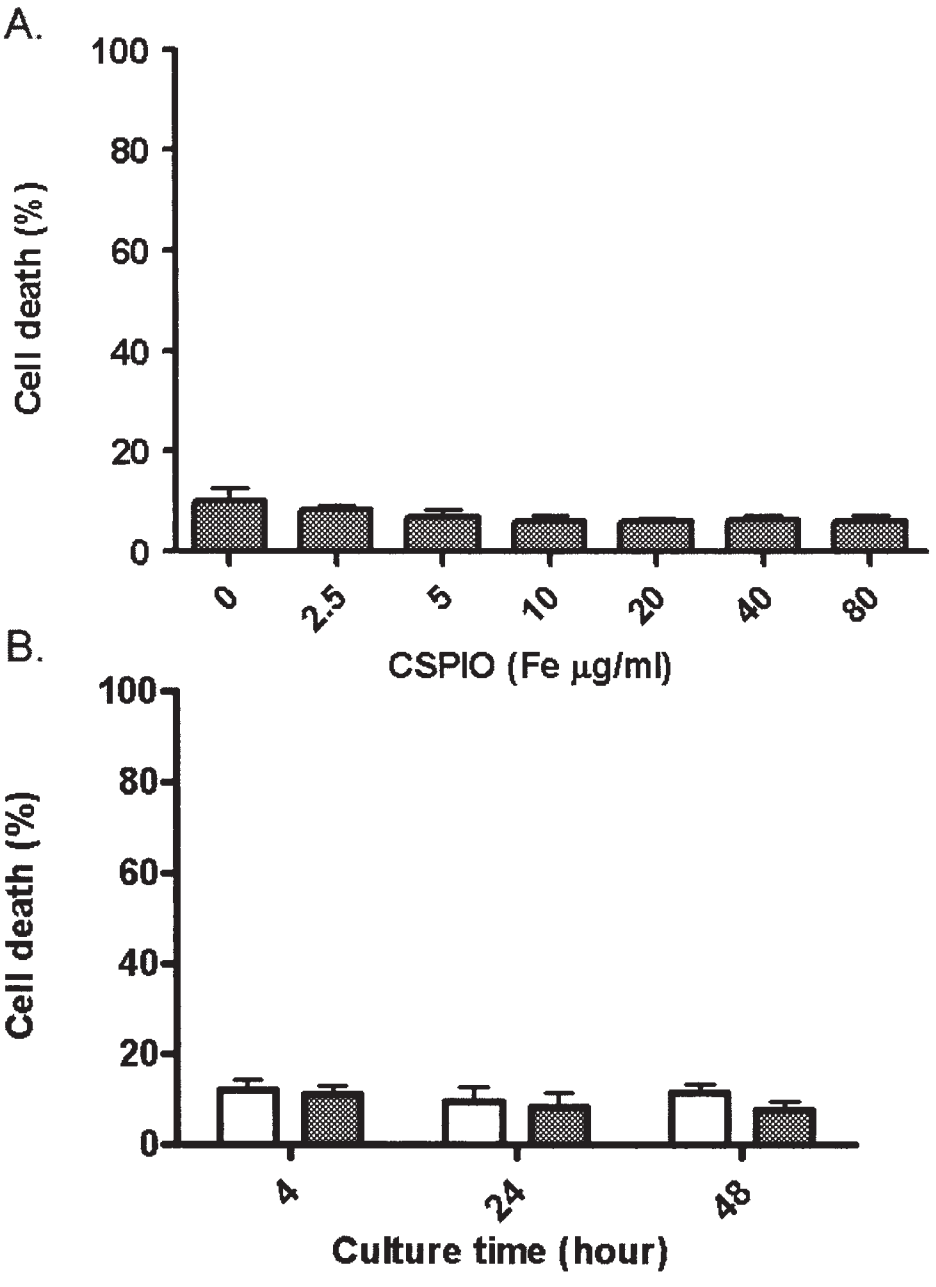

Fig 1. Cytotoxicity of chitosan-coated superparamagnetic iron oxide (CSPIO) on RAW cells. RAW cells were incubated with CSPIO of different concentrations **(A)** and different time periods **(B**; *open columns:* control; *shaded columns:* Fe 20 μg/mL) and then stained with fluorescein diacetate and propidium iodide. Cell death rates were assayed by flow cytometry analysis.