developed an effective intraportal transplantation protocol to extend survival time of transplanted cells.

Methods: 6weeks old male Nagase Analbuminemic rats (NAR) were injected subcutaneously every 3.5 days with CCl4 dissolved in equal volume of olive oil at a dose of 2.0 ml/kg body weight for 8weeks. Repeated intraportal infusion of 5 x 10(6) rat BMC isolated from 6weeks old female enhanced green fluorescent protein transgenic (EGFP-tg)rat twice a week for the last 4weeks via an indwelling catheter connected to a subcutaneous port. Another NAR underwent repeated intraportal infusion of Dulbecco's Modified Eagle's Medium (DMEM). For assessment of liver function, Body and liver weight was measured and blood was obtained for total bilirubin, albumin, PT, transaminase and ammonia. We also evaluated the improvement of fibrosis by histology and repopulating cells by immunohistochemistry.

Results: At 4 weeks after the start of BMC transplantation (BMT), we found no significant difference in their total body weight (BMT model: 170g, Control model: 166g). But their liver weight of BMT groups remarkably increased (BMT model: 14.7g, Control model: 11.2g). We also observed macroscopically different between them. Control group liver was white and atrophic, but the liver from BMT model was red and expanded. Microscopic studies revealed that the liver of rat receiving continuous BMT showed decreases in fibrosis, necrosis and inflammatory infiltration. And in the BMT rat, GFP positive cells were found around the portal vein. Prothrombin time(PT), total bilirubin, serum ammonia and transaminase were also significantly better in BMT model compared with control model.

Conclusions: Repeated bone marrow cell transplantation via a portal catheter can decrease liver fibrosis and improve liver function of rats with liver cirrhosis and may be useful in the treatment of cirrhosis in humans.

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IMPACT OF MICROGRAVITY CULTURE ON SURVIVAL OF ALLOGENEIC MOUSE PANCREATIC ISLET TRANSPLANTS

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Aims: Diabetes mellitus (Type 1) remains a major cause of morbidity and mortality despite significant advances in medical management. Clinical pancreatic islet allotransplantation is a low-risk alternative to whole pancreas transplantation, offering great promise in treating patients. Although an Edmonton therapeutic protocol has dramatically improved the survival of islet allografts, the majority of patients eventually develop impaired graft function and chronic rejection. Therefore, the ultimate goal—to radically improve islet graft survival—is to induce transplantation tolerance.

Methods/Results: We have developed a unique mouse model of tolerance to pancreatic islet allografts [C57BL10 ($H2^b$) to C3H ($H2^k$)] by culturing islets in microgravity conditions using rotating bioreactors. Islets cultured in bioreactors for 7 days displayed decreased immunogenicity (lack of dendritic cells), resulting in long-term allograft survival (>100 days; n = 18) with superior islet morphology and function. Indeed, transmission electron microscopy showed gradual loss of dendritic cells and scanning electron microscopy revealed development of multiple nutritional channels in islets cultured in the bioreactor. Similar results were obtained in C57BL10 to Balb/c ($H2^d$) donor/recipient combination. However, although a 7-day culture produced long-term survival (>100 days; n = 4; p = 0.001), a limited 3-day culture shortened the survival to a mean survival time (MST) of 21.6 ± 5.8 days (n = 5; p = 0.026); fresh allogeneic islets survived 13.8 ± 2.7 days (n = 5). Interestingly, the results were different in Stat6 or Stat4 knockout (KO) mice deficient for Th2 and Th1 cells, respectively. Diabetic Stat6 KO mice rejected fresh islet allografts at 12.1 ± 1.6 days (n = 8) and Stat4 KO mice at 13.3 ± 2.4 days. Islets cultured for 3 days in the bioreactor achieved long-term survivals in all Stat4 KO recipients (>100 days; n = 7; p = 0.001). In contrast, Stat6 KO recipients transplanted with 3-day bioreactor islets produced a mixed response with some long-term survivals (>100 days; n = 4; p=0.001) and some rejectors (22.0 ± 1.7 days; n = 3; p = 0.01.

Conclusions: Microgravity condition decreases immunogenicity of allogeneic islets. Furthermore, bioreactor-cultured islets induce stable long-term allograft survival by induction of IL-4/Stat6-dependent Th2reg cells.

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IMAGING OF EARLY POST-ISLET TRANSPLANT EVENTS BY POSITRON EMISSION TOMOGRAPHY (PET)

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Aims: Since the implementation of the Edmonton protocol, islet transplantation results have improved significantly. However, recipients achieve beta-cell functions of only 20% of that of healthy subjects, although most have received islets from more than one donor. This suboptimal function is the result of a loss of endocrine cells, which is thought to occur mainly as an early post-transplant event, as often reflected by a peak of C-peptide in the first hours after implantation. Imaging of the islets could be a powerful tool to assess their fate early after implantation.

Methods: Sprague-Dawley (SD) rat islets (300IEq) were incubated with fluoro-deoxy-glucose (FDG) in DMEM during various incubation times and with various concentrations of FDG or glucose. After washing, radioactivity included in the islets was measured in an activimeter. After incubation, islet viability was assessed by propidium iodide/fluorescein diacetate staining. In vivo: intraportal injections of FDG alone or of radiolabeled islets (2000IEq) with or without pre-treatment with heparin were performed in SD rats (3 per group). Positron emission tomographies were performed hourly during the first 6 hours after transplantation. Radioactivity uptake was measured in liver, lung, brain, kidneys, heart and bladder and was expressed as % of uptake (radioactivity in a specific organ/total injected radioactivity).

Results: In vitro: FDG uptake increased with incubation time or concentration of FDG before reaching a plateau at 60min incubation or 3MBq FDG. Uptake decreased with increasing concentrations of glucose, reflecting a competition for the same channel. Islet viability was unmodified by FDG. In vivo: after injection, all islets remained in the liver, with an uptake 4.35-fold higher compared to control injected with FDG alone (44.2% vs 10.1%). In the other organs, the uptake was similar to control. Heparin did not improve primary islet integration in the liver and did not modify the decrease of radioactivity during the 6 first hours after transplantation compared to untreated islet isotransplantations.

Conclusions: Ex-vivo radio-labeling of islets and study of post-islet transplant events by positron emission tomograghy imaging is feasible. This method allows follow-up of the islets and testing of various strategies or treatments in order to improve islet implantation and survival.

*** Indicates one of the top 200 scoring abstracts. The Congress Organizing Committee encourages you to attend these presentations.**