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Prevention of Early Islet Graft Loss in Association with Engraftment in the Liver of Mice by Targeting IL-6/IL-6 Receptor Signaling

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Abstract：Currently, the low success rate in achieving insulin independence in patients with IDDM after islet transplantation from a single donor has been a major obstacle facing clinical islet transplantation. We herein determined whether this could be overcome by targeting IL-6/IL-6R signaling, facilitating to prevent early loss of transplanted islets in association with engraftment in the liver of mice.

Hyperglycemia of streptozotocin-induced diabetic mice was not ameliorated after transplantation of 200 syngenic islets, the number of islets from a single mouse pancreas, into the liver due to early loss of islet grafts. The serum IL-6 concentration was elevated in recipient mice with the peak at 6 hours after islet transplantation with accumulation of IFN-γ- and TNF-α-producing Gr-1$^+$CD11b$^+$ cells in the liver. The treatment with anti-IL-6 antibody or gp130-Fc targeting IL-6/IL-6R signaling produced normoglycemia in diabetic mice receiving 200 islets. FACS analysis revealed that each treatment not only reduced Gr-1$^+$CD11b$^+$ cells（neutrophils）in number but also prevented their IFN-γ and TNF-α production in the liver receiving islets. These findings indicate that IL-6/IL-6R signaling plays a crucial role in early loss of islet grafts, suggesting that it could be a target for intervention to improve the efficiency of islet transplantation.

Key words：**Islet transplantation, IL-6/IL-6R signaling, Early loss of transplanted islets**

Introduction

Pancreatic islet transplantation has now become an attractive procedure of choice for the treatment of insulin-dependent diabetes mellitus（IDDM）(1, 2). Currently, however, this procedure has only experienced limited success in achieving insulin independence of IDDM patients after islet transplantation from a single donor, and therefore sequential transplantations of islets with the use of 2-3 donor pancreases are required for the treatment of a single IDDM recipient (1, 2). Thus, the limitation of producing successful islet transplantation from one donor to one recipient has been a major obstacle facing clinical islet transplantation.

Ryan et al. recently reported that islet graft mass in diabetic patients receiving sequential islet transplantation is approximately 36% of that of normal individuals, even though these patients received almost the equivalent number of islets as normal individuals (3). The finding indicates that islet grafts are lost after transplantation, and therefore, sequential islet transplantation with the use of 2-3 donor pancreases are needed to make diabetic patients free of insulin treatments after transplantation.

One of major factors responsible for the islet graft loss after transplantation may relate to innate immune

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responses such as inflammatory insult to islet grafts soon after transplantation in association with engraftment as follows. Currently, the liver is a site of choice for clinical islet transplantation and donor islets are grafted into the liver via the portal vein of recipients under the local anesthesia (1). When islets are grafted into the liver, islets become lodged in the periphery of the portal vein resulting in ischemic degeneration of the corresponding area of the liver, which may trigger innate immune responses, leading to produce factor(s) having deleterious effects on islet grafts. In fact, previously we have shown in mice that Gr-1$^+$CD11b$^+$ cells (neutrophils) become accumulated into the liver receiving islets soon after transplantation and that their IFN-γ production, which is essentially mediated by natural killer T (NKT) cells, is responsible for islet graft loss in association with engraftments (4). Furthermore, the treatment targeting not only IFN-γ but also TNF-α and IL-1β was found to have a beneficial effect on preventing islet graft loss facilitating to produce successful islet transplantation from one donor even to two recipients in mice (5). Thus, our previous studies indicate that pro-inflammatory cytokines may serve as effecter and/or regulatory molecules responsible for islet graft loss in the liver in association with engraftments.

In the present study, we focus on IL-6/IL-6R signaling since IL-6 is another pro-inflammatory cytokine and has been reported to be involved in various inflammatory diseases (6-8). Regarding IL-6/IL-6R signaling, signal transduction in response to IL-6 requires binding of IL-6 to membrane bound IL-6R (mIL-6R) with subsequent homodimerization of gp130 (6-8). On cells that do not express IL-6R, complex formation of IL-6 with soluble IL-6R triggers dimerization of gp130 on cells to induce responses (6-8). Therefore, IL-6/IL-6R signal transduction can be inhibited by targeting IL-6R, IL-6 and gp130 with the use of anti-IL-6R antibody (9), anti-IL-6 antibody (10) or gp130-Fc (11), respectively.

Thus, the aim of the present study is to determine whether the procedures targeting IL-6/IL-6R signaling have any beneficial effect on prevention of early islet graft loss soon after transplantation. The present study demonstrates that the treatment with anti-IL-6 antibody or gp130-Fc prevented early loss of islet grafts mediated by Gr-1$^+$CD11b$^+$ cells in the liver of mice receiving islets enabling to achieve successful islet transplantation from one donor to one recipient in mice.

Materials and methods

Animals.

Male BALB/c (H-2d) and C57BL/6 (H-2b) mice were purchased from Charles River Japan (Kanagawa, Japan) and used for the experiments. Mice weighing 23-25g were used as recipients and those weighing 25-30g served as donors. Diabetes was induced in the recipients by the intravenous injection of STZ (180mg/kg) (Sigma, St. Louis, MO). The plasma glucose levels of the mice exceeded 400mg/dl at 2-3 days after the STZ injection and the mice remained hyperglycemic at the time of islet transplantation. The experiments were approved by the Institutional Animal Care and Use Committee.

Islet isolation and transplantation.

Islets were isolated by the static digestion method using collagenase (12) and then separated by centrifugation on Ficoll-Conray gradients (13). Islets of 150 to 250 μm in diameter were hand-selected using Pasteur pipette with the aid of a dissecting microscope, since it was critical to minimize the size variation of individual islets to compare the effects of the difference in the number of donor islets. The size of individual islets in each islet isolation procedure was confirmed by using a phase-contrast microscope equipped with a scale in the eyepiece. Hand-picked islets were transplanted into the liver via the recipient's portal vein (14) at 3 days after the induction of diabetes with STZ injection.

Monitoring plasma glucose and body weight.

The non-fasting plasma glucose levels and body weight were monitored three times a week in all the recipients for 60 days after islet transplantation. The plasma glucose was measured using a Beckman glucose analyzer (Beckman Japan, Tokyo, Japan). Normoglycemia after transplantation was defined as two consecutive plasma glucose levels reading below 200mg/dl.

Treatment with monoclonal antibodies.

Anti-IL-6 mAb (200 μg/injection/mouse, MP5-20F3, rat IgG1) and gp130-Fc (50 μg/injection/mouse, human IgG1) were purchased by BD Biosciences (San Jose, CA) and R&D (Minneapolis, MN). Anti-IL-6 antibody and gp130-Fc were administered IP once at the time of islet transplantation. Rat IgG (Chemicon International, Temecula, CA) and human IgG (Jackson ImmunoResearch Laboratories, West Grove, PA) were

used as corresponding controls.

Assay of serum IL-6 levels in mice receiving islets before and after transplantation.

Blood samples were obtained from the orbital sinus of naïve mice and of diabetic mice before and after islet transplantation of 400 syngenic islets into the liver. After centrifugation, serum was collected and stored at -80℃ until assay. IL-6 levels were determined by ELISA kit (BD Biosciences, San Jose, CA).

Morphological study.

The livers bearing islet grafts and pancreas were examined morphologically at 60 days after transplantation in appropriate groups of mice. The liver and pancreas were fixed with Bouin's solution, processed, and embedded in paraffin. The sections were prepared for light microscopy and stained with hematoxylin and eosin (HE), and aldehyde and fuchsin (AF).

Preparation of hepatic mononuclear cells.

Hepatic mononuclear cells (HMNCs) were prepared as described previously (15). Briefly, an excised liver was pressed through a stainless steel mesh, and the resulting dissociated liver tissue were suspended in Dulbecco's modified Eagle medium (D-MEM/F-12, Life Technologies, Tokyo, Japan) and washed twice. The mixture was re-suspended in an isotonic 33% Percoll solution containing heparin (67U/ml), and centrifuged 2,000 x g at 4℃ for 15 min. The resulting pellet was suspended in a 0.83% ammonium chloride solution to lyse erythrocytes. After counting, these HMNCs were washed twice in PBS and used for further analysis.

Flow cytometry analysis.

The following mAbs were used: anti-mouse FcR_III/II (2.4G2), FITC-conjugated anti-CD3 ε (145-2C11), FITC- or PE-conjugated anti-CD11b (M1/70), allophycocyanin-conjugated anti-IFN-γ (XMG1.2), anti-TNF-α (MP6-XT22), PerCP-conjugated anti-Gr-1 (Rb6-8c5), and isotype control (clone R3-34, Rat IgG1) were purchased from BD Biosciences (San Jose, CA). Allophycocyanin-conjugated anti-CD126 (IL-6R α chain) (D7715A7) was purchased from Bio Legend (San Diego, CA). PE-α-galactosylceramide (α-GalCer)-CD1d tetramers were prepared as previously described (16). For intracellular staining, cells were incubated with anti-FcR_III/II (BD Biosciences, San Jose, CA), surface stained, fixed, permeabilized, stained with mAbs, and analyzed on a flow cytometer (FACS Calibur, Becton Dickinson, San Jose, CA). 10,000 viable cells were analyzed.

Statistical analysis.

The statistical significance with respect to the rate of euglycemia in streptozotocin-induced diabetic mice after islet transplantation and that of plasma glucose levels during IPGTT was determined by Fisher's exact test and Student's *t* test, respectively. Differences were considered significant when the p values were less than 0.05.

Results

Elevation of serum IL-6 levels in mice receiving islets after transplantation.

First, we determined whether IL-6/IL-6R signaling is actually involved in early loss of islet grafts by measuring serum IL-6 levels in mice before and after islet transplantation. Previously, we have shown that the rate of normoglycemia in STZ-induced diabetic C57BL/6 mice receiving 400 and 200 syngenic islets, the number of islets from a single mouse pancreas, after transplantation into the liver was 100 or 0%, respectively (4). The serum concentration of IL-6 in diabetic mice receiving 400 islets was determined to avoid the potential effects of hyperglycemia in recipient mice on the serum levels of IL-6. The serum concentration of IL-6 in naïve mice and

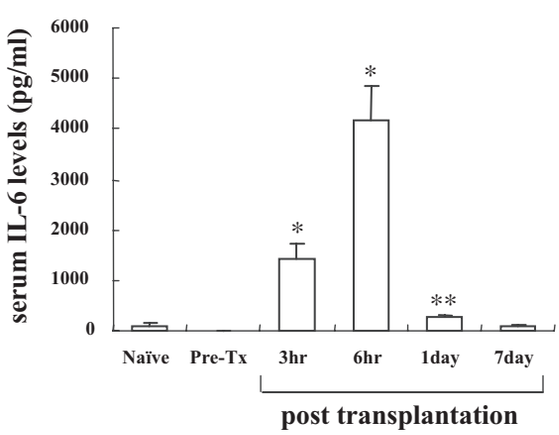

Figure 1. Serum IL-6 levels in mice before and after islets transplantation.
The serum concentration of IL-6 was determined in naïve mice and in diabetic recipient mice before and 3hr, 6hr, 1day and 7days after transplantation of 400 syngenic islets into the liver. * $p<0.01$, ** $p<0.05$ vs naïve.

diabetic recipient mice at the time of islet transplantation was 79.8 ± 60.4 pg/ml (n=5, mean ± SEM) and 0 (n=5), respectively, and those in mice at 3 hours, 6 hours, 1 day and 7 days after islet transplantation was 1426.3 ± 292.7 pg/ml (n=6), 4183.2 ± 672.3 pg/ml (n=5), 268.7 ± 48.6 pg/ml (n=7) and 74.0 ± 40.0 pg/ml (n=8), respectively (Figure 1). Thus, the serum concentration of IL-6 was found to be elevated with the peak at 6 hours after islet transplantation.

Beneficial effects of targeting IL-6/IL-6R signaling on prevention of early islet graft loss.

Next, we determined whether procedures targeting IL-6/IL-6R signaling with anti-IL-6 antibody or gp130-Fc have any beneficial effects on prevention of early islet graft loss after transplantation resulting in ameliorating hyperglycemia of diabetic mice receiving 200 islets, the number of islets from a single donor, into the liver. Diabetic mice receiving 200 syngenic islets with (n=5) and without the treatment (n=5) of control antibody remained hyperglycemic after transplantation (Figure 2, II and I), as reported previously. In marked contrast, hyperglycemia of diabetic mice receiving 200 islets and treated either with anti-IL-6 antibody (n=5) (Figure 2, III) or gp130-Fc (n=4) (Figure 2, IV) was ameliorated after the transplantation, but mice receiving the similar number of islets and treated with the control IgG (n=4) remained hyperglycemic after transplantation (Figure 2, V). Morphologically, de-granulated and well-granulated β cells of islet graft were seen in the liver of hyperglycemic and normoglycemic mice, respectively, at 60 days after transplantation (histology not shown). The difference in the euglycemic rates between diabetic mice receiving 200 islets and treated with control antibody and those receiving the same number of islets and treated with anti-IL-6 antibody was statistically significant ($p<0.05$). Similary, the euglycemic rate between diabetic mice receiving 200 islets and treated with gp130-Fc and those receiving 200 islets and treated with control IgG was statistically significant ($p<0.05$).

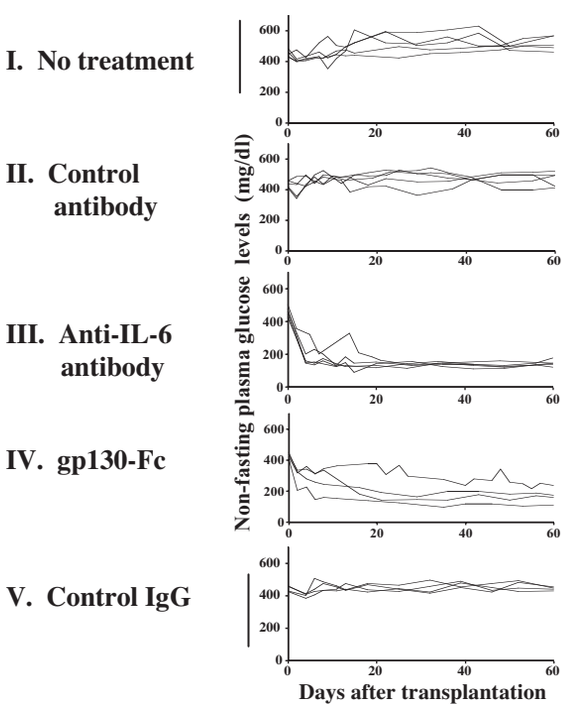

Figure 2. Plasma glucose levels of diabetic mice receiving 200 syngenic islets from a single donor.
Two hundred syngenic islets were grafted into the liver of diabetic mice without treatment (I) or treated with control antibody (II), anti-IL-6 antibody (III), gp130-Fc (IV) and control IgG (V). Anti-IL-6 antibody (200 μg/injection/mouse) or gp130-Fc (50 μg/injection/mouse) was administered IP once at the time of the islet transplantation. Individual lines represent the non-fasting plasma glucose levels of each animal.

IFN-γ and TNF-α production of Gr-1$^+$CD11b$^+$ cells accumulated in the liver of mice receiving islets are down-regulated by targeting IL-6/IL-6R signaling.

To dissect the beneficial effects of the treatment targeting IL-6/IL-6R signaling on prevention of early loss of islet grafts, mononuclear cells in the liver of mice receiving 200 syngenic islets and treated with anti-IL-6 antibody or gp130-Fc were isolated and examined by flow cytometry. As reported previously (4), Gr-1$^+$CD11b$^+$ cells (neutrophils) was found to become accumulated in the liver of diabetic mice receiving 200 islets with the peak at 6 hours after islet transplantation and that their production of IFN-γ and TNF-α was up-regulated. The treatment with control antibody or control IgG did not affect the accumulation as well as the IFN-γ and TNF-α production of Gr-1$^+$CD11b$^+$ cells in the liver of mice receiving islets (Figure 3, II and V). In the diabetic mice receiving 200 islets and treated with anti-IL-6 antibody, the accumulation of Gr-1$^+$CD11b$^+$ cells in the liver after islet transplantation also occurred, and however, the IFN-γ and TNF-α production of Gr-1$^+$CD11b$^+$ cells was down-regulated (Figure 3, III). The similar flow cytometry findings of mononuclear cells with respect to the accumulation of Gr-1$^+$CD11b$^+$ cells with down-regulation of IFN-γ and TNF-α

production were seen in the liver of mice receiving islets and treated with gp130-Fc（Figure 3, IV）to those of mice treated with anti-IL-6 antibody.

Expression of IL-6R on MNC in the liver of mice before and after islet transplantation.

Next, we determined the expression of IL-6R on MNC in the liver of mice before and after islet transplantation. In the liver of naïve mouse, IL-6R is expressed on all cells examined including NKT cells（Figure 4, a）, T cells（Figure 4, b）, Gr-1$^+$CD11b$^+$ cells（neutrophils, Figure 4, e）, NK cells, B cells, CD11c$^+$ cells（dendritic cells）（no shown）. Interestingly, IL-6R is found to be constitutively expressed on α-GalCer CD1d-tetramer$^+$CD3$^+$NKT cells（Figure 4, b）. In the liver of mice rejecting islet isografts, IL-6R$^+$Gr-1$^+$CD11b$^+$ cells became increased in number（Figure 4, f）, while in contrast, there was no change in number of IL-6R$^+$cells in other cell populations including NKT cells（Figure 4, c）and T cells（Figure 4,d）.

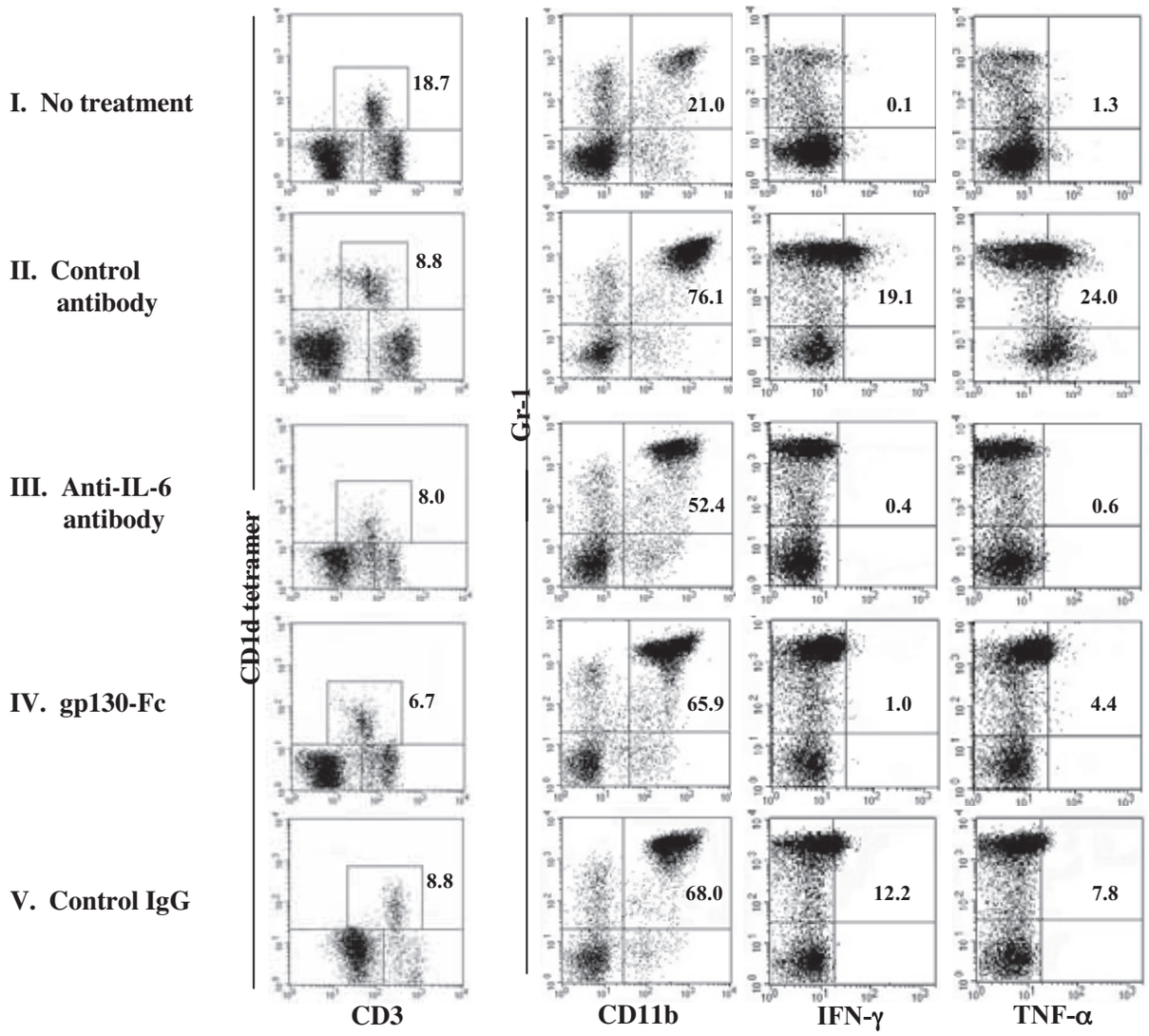

Figure 3. FACS profiles and IFN- γ and TNF-α production of mononuclear cells in the liver of mice before and after islet transplantation into the liver.

Mononuclear cells were isolated from the liver of naïve mice（I）and of diabetic mice receiving 200 syngenic islets and treated with control rat IgG（II）, anti-IL-6 antibody（III）, gp130-Fc（IV）or control human IgG（V）at 6 hours after transplantation. The figures in the boxes show the percentage of the cells in the corresponding area. Representative data of two to three experiments is shown.

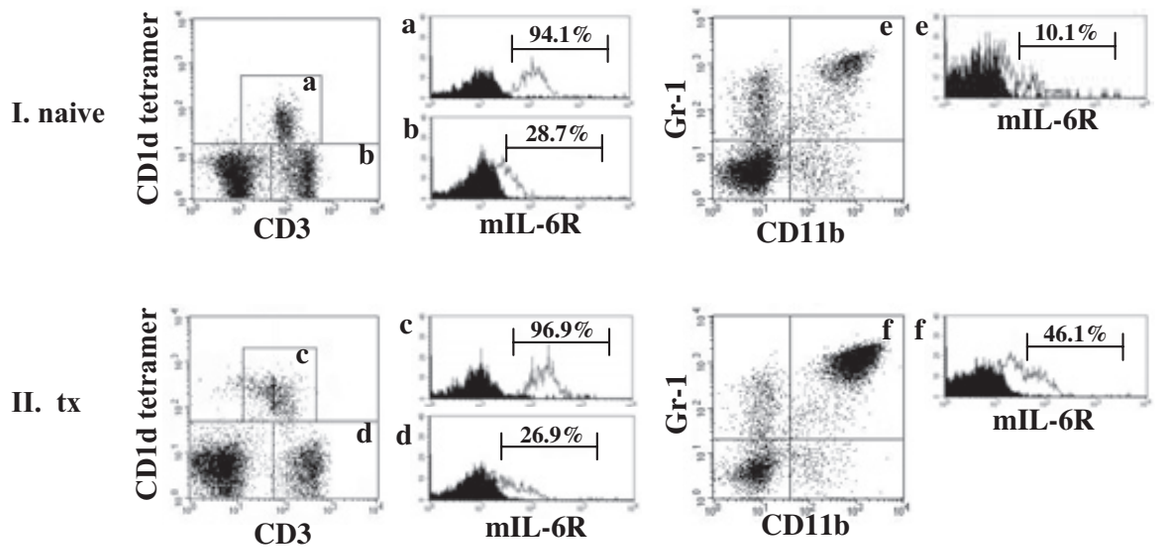

Figure 4. Expression of IL-6R on MNC in the liver of mice before and after islet transplantation.
Mononuclear cells in the liver of naïve mice (I) and those of diabetic mice at 6 hours after transplantation of 200 syngenic islets (II) were isolated and examined by flow cytometry. The figures in the boxes show the percentage of the cells in the corresponding area. Representative data of two to three experiments is shown.

Glucose tolerance in mice receiving 200 islets and treated with anti-IL-6R antibody.

To evaluate the functional mass of islet grafts in the livers of recipient mice, an intraperitoneal glucose tolerance test (IPGTT) was performed. The plasma glucose levels of naïve untreated C57BL/6 mice (n=4) were 59.5 ± 3.1 (mean ± SD), 249.8 ± 5.6 and 133.3 ± 4.8 mg/dl at 0, 30 and 120 minutes, respectively, after the IP injection of 1.0 g/kg glucose (Figure 5), and those of diabetic mice (n=3) without islet transplantation at 60 days after the injection of STZ were 460.0 ± 57.0, 658.3 ± 16.6, 561.3 ± 44.2 mg/dl, respectively (no shown).

The plasma glucose levels of the diabetic mice (n=6) receiving 400 were 66.5 ± 4.0, 395.0 ± 18.8 and 266.0 ± 22.7 mg/dl at 0, 30 and 120 minutes, respectively (Figure 5). The plasma glucose levels of diabetic mice (n=3) receiving 200 islets and treated with anti-IL-6 antibody were 83.6 ± 6.4, 303.0 ± 22.6 and 204.0 ± 19.6 mg/dl and those of mice (n=5) treated with control antibody were 366.7 ± 89.2, 671.0 ± 121.1 and 547.0 ± 106.2 mg/dl at 0, 30 and 120 minutes, respectively, after the injection of glucose (Figure 5). The difference in the plasma glucose levels at 30 and 120 minutes between the mice with 200 islets and treated with anti-IL-6 antibody and those with 200 islets without the treatment was statistically significant ($P<0.05$ by Student's t test).

Discussion

These findings clearly show that the treatment targeting IL-6/IL-6R signaling has beneficial effects

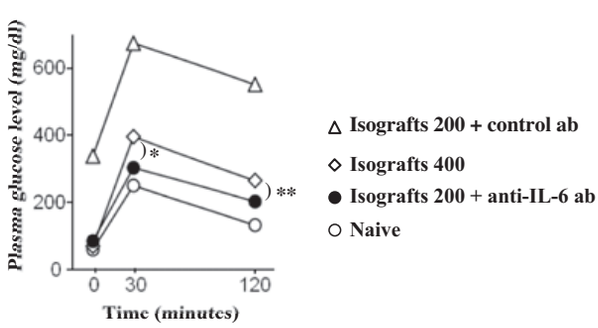

Figure 5. Intraperitoneal glucose tolerance test in mice.
Intraperitoneal glucose tolerance test (IPGTT) was performed in STZ-induced diabetic mice before and at 60 days after islet transplantation. Mice were fasted for 8 hours prior to IPGTT and blood samples were taken from orbital sinuses at 0, 30 and 120 minutes after the IP injection of glucose (1g/kg). Experimental groups include naïve mice (open circle, n=4), diabetic mice receiving 200 syngenic islets and treated with control antibody (open upward triangle, n=7) or anti-IL-6 antibody (closed black circle, n=3), and those receiving 400 syngenic islets (open diamond, n=6).
*; $P<0.01$, **; $P<0.05$.

on prevention of early loss of islet isografts favoring to ameliorate hyperglycemia of STZ-induced diabetic mice receiving islets from a single donor.

Previously, we have shown that pro-inflammatory cytokines including IFN-γ, TNF-α and IL-1β have deleterious effects on islet grafts in the liver of mice soon after transplantation and that the treatment with monoclonal antibody against each pro-inflammatory cytokine has beneficial effects on prevention of early graft loss in association with engraftment leading to ameliorate hyperglycemia of STZ-diabetic mice receiving 200 islets from a single donor (5). Furthermore, the combined use of these three monoclonal antibodies was found to ameliorate hyperglycemia of STZ-diabetic mice receiving 100 islets, indicating that islet transplantation from one donor even to two recipients is feasible by targeting pro-inflammatory cytokines (5). In the present study, we focus on another pro-inflammatory cytokine of IL-6 and determined whether the treatment targeting IL-6/IL-6R signaling has any beneficial effect on engraftment of islet grafts.

The initial experiment revealed that the serum concentration of IL-6 in diabetic mice receiving islets into the liver was elevated with the peak of 4183.2 ± 672.3 pg/ml at 6 hours after transplantation and returned to the pre-transplant level of 74.0 ± 39.9 pg/ml at 7 days after transplantation. Thus, the findings suggest that IL-6 may play a role in early islet graft loss after transplantation. In order to prove directly the involvement of IL-6 in islet graft loss in association with engraftment, we next determined whether the treatments with anti-IL-6 antibody can prevent early islet graft loss in the liver to ameliorate hyperglycemia of diabetic mice receiving 200 islets. All diabetic mice receiving 200 syngenic islets and treated with anti-IL-6 antibody became normoglycemic, while in contrast, those receiving the similar number of islets and treated with control antibody did not. Thus, the finding clearly shows that IL-6 is involved in islet graft loss in association with engraftments. Furthermore, it was found that gp130-Fc has the similar beneficial effects on amelioration of hyperglycemia in diabetic mice receiving 200 islets to those achieved by anti-IL-6 antibody, indicating that either treatment targeting IL-6/IL6R signalings has beneficial effect on prevention of early loss of islet grafts.

Next, we examined the cellular mechanisms responsible for early islet graft loss in association with engraftments in relation to IL-6/IL-6R signaling. Our previous experiment disclosed two major cellular populations, namely NKT cells and Gr-1$^+$CD11b$^+$ cells, responsible for islet graft loss in association with engraftment (4). In the liver of wild-type mice receiving islets, IFN-γ producing Gr-1$^+$CD11b$^+$ cells became accumulated into the liver with the peak at 6 hours after islet transplantation, while, in contrast, in the liver of Vα14 NKT cell-deficient mice receiving islets, the IFN-γ production of Gr-1$^+$CD11b$^+$ cells was down-regulated although Gr-1$^+$CD11b$^+$ cells accumulate similarly to wild-type mice. Importantly, early islet graft loss is prevented in the liver of Vα14 NKT cell-deficient mice and of wild-type mice pretreated with α-galactosylceramide, a synthetic ligand of NKT cells prior to islet transplantation to induce unresponsiveness of NKT cells, where IFN-γ production of Gr-1$^+$CD11b$^+$ cells in the liver receiving islets was down-regulated although their number is similar compared with wild-type treated with control vehicle. Then, how is NKT cell- and Gr-1$^+$CD11b$^+$ cell-mediated islet graft loss after transplantation affected by the treatment with anti-IL-6 antibody or gp130-Fc? FACS analysis revealed that IFN-γ production of Gr-1$^+$CD11b$^+$ cells was down-regulated and that less accumulation of Gr-1$^+$CD11b$^+$ cells was seen in the liver of diabetic mice receiving islets and treated with anti-IL-6 antibody, but not in the liver treated with gp130-Fc. The findings suggests that IL-6 itself induces accumulation of Gr-1$^+$CD11b$^+$ cells and that the blocking of dimerization of gp130 produce down-regulation of IFN-γ production of Gr-1$^+$CD11b$^+$ cells. FACS analysis also disclosed that almost all cellular populations in the liver of mouse including NKT cells and Gr-1$^+$CD11b$^+$ cells express IL-6R on their cell surface (Figure 4). Therefore, the site of action by IL-6 may include the upstream as well as the downstream in the process of NKT cell- and Gr-1$^+$CD11b$^+$ cells-mediated islet graft loss after transplantation.

Regarding the site of IL-6 production, the potential cells to produce IL-6 following islet transplantation may include hepatocytes, vessel endothelial cells and immune cells such as neutrophils. After the transplantation of islets into the liver via the portal vein of recipients, islet grafts become lodged at the periphery of the portal circulation and serve as emboli resulting in ischemic degeneration of the corresponding area of the liver. Thus, these insults to the liver following islet transplantation may trigger the production of IL-6 leading to NKT cell- and Gr-1$^+$CD11b$^+$ cell-mediated islet graft loss.

Concerned with the cellular populations playing a role in early islet graft loss, we currently speculate that another

cellular population of antigen presenting cells other than NKT cells and Gr-1$^+$CD11b$^+$ cells in the liver such as dendritic cells, Ito cells, Kupffer cells and macrophage may participate in islet graft destruction. There may be some unknown factor(s) produced initially in the liver immediately after islet transplantation, directing APC in the liver leading to produce molecules such as IL-12 to activate NKT cells facilitating to stimulate Gr-1$^+$CD11b$^+$ cells producing effecter molecules of pro-inflammatory cytokines including IFN-γ, TNF-α and IL-1β. IL-6/IL-6R signaling may be involved in all the process mediated by APC, NKT cells and Gr-1$^+$CD11b$^+$ cells since IL-6R is expressed in every population in the liver.

From the clinical point view, it is of importance to evaluate to what grade the efficiency of islet transplantation is improved by the treatment. Glucose tolerance of diabetic mice receiving 200 islets and treated with anti-IL-6 antibody was found to be superior to that of those receiving 400 islets, the number of islets isolated from two mice panceases without treatment. Thus, the findings indicate that the efficiency was improved more than two-fold by the treatment with anti-IL-6 antibody.

In summary, the present study shows that the treatment with anti-IL-6 antibody or gp130-Fc at the time of islet transplantation has beneficial effects on early loss of transplanted islets in the liver of mice enabling to ameliorate hyperglycemia of diabetic mice receiving islets from a single donor. Thus, the treatment targeting IL-6/IL-6R signaling may have potential to improve the efficiency of islet transplantation in a clinical setting when the mechanisms involved in early loss of transplanted islets in mice also hold true in humans.

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