Role of Donor-Derived Monocyte Chemoattractant Protein-1 in Murine Islet Transplantation

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Monocyte chemoattractant protein-1 (CCL2/MCP-1) is a proinflammatory chemokine produced by several cell types, including pancreatic islets. High levels of donor-derived CCL2 have been associated with poor islet allograft outcome in patients with type 1 diabetes; however, the causal relationship is unknown. The constitutive and inducible expression of chemokines and their receptors by pancreatic islets in vitro were investigated, specifically the role of donor-derived CCL2 in marginal mass murine islet transplantation. The results showed that inflammatory cytokine stimulation of islets induced de novo expression of CCL2, CCL5/RANTES, CXCL9/MIG, and CXCL10/IP-10 and increased expression of CXCL2/macrophage-inflammatory protein-2. CCL2 mRNA and protein were highly expressed within 2 d in cultures. Transplantation of islets with high levels of CCL2 into syngeneic recipients led to a significantly greater influx of CCR2+ cells and higher expression of monocyte/macrophage-associated inflammatory cytokines compared with low CCL2-donor islets. The level of pretransplantation CCL2 inversely correlated (P < 0.0001) with isograft function. In contrast, in CCR2−/− recipients, this correlation was not present. A direct toxic effect of CCL2 on islets was excluded by assessing cell viability and insulin release in vitro. In conclusion, CCL2 secretion by islets plays an important role in the immediate islet graft function. Strategies to decrease islet-derived CCL2 release may increase the success of islet transplantation.


Received September 8, 2004. Accepted November 10, 2004.
Published online ahead of print. Publication date available at www.jasn.org.

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ISSN: 1046-6673/1602-0444
W.A. Kuziel (Department of Microbiology, Institute for Cellular and Molecular Biology, University of Texas, Austin, TX), and deletion was confirmed by genotyping (15).

**Islet Isolation, Culture, and Transplantation**

Islet isolation and culture and transplantation were previously described in detail (5). Briefly, 3 ml of cold Hank’s buffer/collagenase P solution (1.5 mg/ml; Roche Diagnostics, Mannheim, Germany) was infused into the pancreatic duct in situ, and the removed pancreas was digested at 37°C for 20 min. Islets were purified on a discontinuous Ficoll gradient (Sigma). For marginal mass syngeneic transplantation,digested at 37°C for 20 min. Islets were purified on a discontinuous

**Glucose-Stimulated Insulin Secretion**

Groups of 30 isolated islets or 3 × 10⁴ β cells were cultured with complete CMRL 1066 medium (10% FBS, 100 U/ml penicillin, 0.1 mg/ml streptomycin, and 2 mM L-glutamine) that contained 5.5 or 16.7 mM glucose in 24-well tissue culture plates (Corning, Corning, NY).

**CCL2 Protein Assay**

Aliquots of various pancreatic islet preparations (50 islets/ml; n = 13) were cultured in 24-well plates, and supernatants were harvested at different time points and stored at –80°C until assayed. CCL2 was measured with a sandwich ELISA kit from R&D Systems according to the manufacturer’s instructions. Absorbance was measured at 450 nm.

**Quantitative Real-Time PCR**

Kinetic PCR was performed on a LightCycler (Roche Diagnostics) by using FastStart QuantiTect SYBR Green PCR kit (Qiagen, Valencia, CA) as a double-strand DNA-specific binding dye using the following primer pairs or as described previously (5,18). CD64 sense 5'‐GGGAAGACACCGCTCACAT‐3'; antisense 5'‐GGGAGTGACA CGGATGCTCT‐3'; CD68 sense 5'‐CCATTCAGGTGGAAGAAA‐3'; antisense 5'‐ATGGG TAACCTCAACAATCT‐3'; IL‐1β sense 5'‐CAACAAAAGTGAAGATTC‐3'; antisense 5'‐ATGGGCGATGGAACAGA‐3', antisense 5'‐ATGGG AGTGAACAAGTCAAAA‐3', antisense: 5'‐ATGGGAGTGAACAGTCAAAA‐3', 70 arbitrary units/ml.

**cDNA Array**

The relative mRNA expression of 67 chemokines and chemokine receptors and four different housekeeping genes was analyzed with a nonradioactive GEArray Q series (SuperArray, Bethesda, MD), according to the manufacturer’s protocol. Two micrograms of total RNA was reverse-transcribed into cDNA with Moloney murine leukemia virus reverse transcriptase (Life Technologies BRL). Biotin-labeled cDNA probes were hybridized to chemokine and chemokine receptor gene-specific cDNA fragments that were spotted on the GEArray membranes. The image was analyzed by SuperArray software. The relative expression level of each gene is determined by comparing the signal intensity of each gene in the array after normalization to the signal of the housekeeping gene cyclophilin A. Arbitrary units were calculated with the following formula: (chemokine signal – background signal)/ (cyclophilin A signal – background signal). Results of <5% were considered negative. For the cDNA array expression analysis, a twofold increase in gene expression was considered to be significant for genes with basal expression values significantly over background values, which was defined as >5% of the housekeeping gene.

**In Situ Hybridization**

In situ hybridization was performed as described previously (5). Negative controls included hybridization performed on replicate tissue sections using the sense riboprobe.

**Statistical Analyses**

All experiments were repeated at least three times. Groups were compared using two-sided t test for continuous variables. Values are expressed as the mean ± SEM. No corrections were made for multiple comparisons. Linear regression and correlations were calculated using InStat 2.01 software.

**Results**

**Differential Expression of Chemokines and Their Receptors in β Cells and Isolated Islets under Basal and Stimulated Conditions**

We first characterized the constitutive and stimulated expression of chemokines and chemokine receptors of islets in vitro.
As islets are composed of different residential cell populations, an established β cell line (β-TC3) was also studied to delineate the contribution of this cell type. Immediately after the isolation and purification procedure, islets expressed the transcripts of specific chemokine genes, namely CCL6, CCL7, CCL17, CCL19, CCL21, CCL28, CXCL2, CXCL5, CXCL11, and CXCL15. The expression of CCL2 was induced after 24 h in culture. In addition, most of the chemokines identified immediately after isolation were further upregulated after 24 h in culture. The same chemokine mRNA expression pattern was observed in β-TC3 in long-term culture. Transcripts for the chemokine receptors CCR7 and CXCR5 were found in both β-TC3 and isolated islets (Table 1).

One mechanism by which invading mononuclear cells destroy β cells is by local production of cytokines such as TNF-α, IL-1β, and IFN-γ. To study whether proinflammatory conditions result in the induction of chemokines in islets, we exposed cells in culture to a combination of TNF-α, IL-1β, and IFN-γ for 24 h at a concentration used previously (10,11). Cytokine stimulation of islets led to an induction of CCL2, CCL5/RANTES (regulated on activation normal T cell expressed and secreted), CXCL2/MIP-2, CXCL9/MIG, and CXCL10/IP-10. With the exception of CXCL2, all genes were also induced in the β-TC3 cells, suggesting a source other than β cells within the islets for CXCL2 (Table 2). These findings were confirmed by QPCR (data not shown).

To determine whether CCL2 mRNA expression was associated with protein synthesis and release, we determined CCL2 levels in culture medium by ELISA and found them to correlate well with the pattern of mRNA expression. Islets that were cultured up to 2 d had a progressive increase in CCL2 production (Figure 1). These in vitro data suggest that islets and β-TC3 cells constitutively expressed the mRNA for several chemokines and chemokine receptors, and exposure to proinflammatory cytokines upregulated additional potent chemokines, with the potential to attract cells expressing CCR2, CCR5, and CXCR3, such as activated T cells and monocytes/macrophages.

### Table 1. Chemokine and chemokine receptor gene expression in murine β -TC3 cells and islets immediately after isolation (0 h) and after 24 h in culture, without the addition of cytokines, detected by cDNA array

<table>
<thead>
<tr>
<th>Gene</th>
<th>Other Name</th>
<th>β-TC3 0 h</th>
<th>Islets 0 h</th>
<th>β-TC3 24 h</th>
<th>Islets 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCL1</td>
<td>TCA3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CCL2</td>
<td>MCP-1</td>
<td>–</td>
<td>–</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>CCL3</td>
<td>MIP-1α</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CCL4</td>
<td>MIP-1β</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CCL5</td>
<td>RANTES</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CCL6</td>
<td>C10</td>
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<td>35</td>
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<td>MCP-3</td>
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<td>19</td>
<td>151</td>
<td></td>
</tr>
<tr>
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<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CCL17</td>
<td>TARC</td>
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<td>69</td>
<td></td>
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<tr>
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<td>MIP-3β</td>
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<td>28</td>
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<tr>
<td>CCL20</td>
<td>MIP-3α</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
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<td>6</td>
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<tr>
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<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
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<td>Eotaxin-2</td>
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<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>CCL25</td>
<td>TECK</td>
<td>–</td>
<td>–</td>
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<td>–</td>
</tr>
<tr>
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<td>CTAK</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CCL28</td>
<td>MEC</td>
<td>12</td>
<td>9</td>
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</table>

### Table 2. IL-1β, IFN-γ, and TNF-α induced chemokine gene expression in islets and cultured β -TC3 cells detected by cDNA array

<table>
<thead>
<tr>
<th>Chemokine</th>
<th>β-TC3 0 h</th>
<th>Islets 0 h</th>
<th>β-TC3 24 h</th>
<th>Islets 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>CCL2</td>
<td>MCP-1</td>
<td>&gt;+10</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>CCL5</td>
<td>RANTES</td>
<td>&gt;+2</td>
<td>&gt;+2</td>
</tr>
<tr>
<td>CXC</td>
<td>CCL2</td>
<td>MIP-2</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>CCL9</td>
<td>MIG</td>
<td>&gt;+10</td>
<td>&gt;+10</td>
</tr>
<tr>
<td></td>
<td>CCL10</td>
<td>IP-10</td>
<td>&gt;+10</td>
<td>&gt;+5</td>
</tr>
</tbody>
</table>

aData are presented as fold variation in gene expression compared with their respective controls (untreated cells). A twofold change of gene expression comparing stimulated to unstimulated cells was considered significant. When genes were not detectable in unstimulated controls, the fold change was expressed as >+2, +5, or +10 depending on expression level.

aData are presented as percentage of the housekeeping gene cyclophilin A. Genes in bold signify expression level >5% from background.
High Levels of Pretransplantation CCL2 Effectively Recruit CCR2+ Monocytes/Macrophages and T Cells

To assess whether donor-derived CCL2 has the potential to attract CCR2+ cells in vivo, we analyzed intragraft mRNA expression in isografts by QPCR and localized it with in situ hybridization. By using the isografts, we were able to determine recruitment independent of allogeneic stimulus. High levels of pretransplantation CCL2 by islets resulted in greater intragraft CCR2 mRNA expression (Figure 2). In situ hybridization localized a significant CCR2+ mononuclear cellular infiltrate surrounding the islet cells (Figure 3). Molecular markers for leukocytes suggested increased recruitment of monocytes/macrophages (CD64, CD68) and T cells (CD3) into the CCL2-expressing donor grafts (Figure 2), with early recruitment of monocytes/macrophages on day 1 followed by late recruitment of T cells on day 4.

Intragraft Cytokine mRNA Expression Pattern

Expression of seven cytokines was analyzed on days 1 and 4 posttransplantation of cultured and uncultured islets to assess their local production. There was no detectable expression of IL-2 and IFN-γ (data not shown). Both cytokines are mainly produced by T cells and natural killer cells after their activation, suggesting that significant T cell activation does not occur within 4 d posttransplantation. In addition, there was no difference of IL-10 expression in the two groups and time point’s analyzed (data not shown).

In contrast, there was evidence for production of monocyte/macrophage-derived cytokines. Cultured islets showed higher expression of IL-1β, TNF-α, TGF-β1, and MIP-1α when compared with freshly isolated islets after transplantation (Figure 4). MIP-1α is a product of monocytes and macrophages and primary stimulator of other proinflammatory cytokines such as IL-1, IL-6, and TNF-α. This is consistent with the pattern of cytokine production seen in cultured transplanted islets. These

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Figure 1. Effect of islet cell culture on CCL2 secretion. CCL2 secretion of 13 different islet preparations immediately after isolation (0 h), 1 and 2 d of culture. CCL2 concentration is given as pg/ml supernatant and pg/islet.

Figure 2. Isograft CCL2, CCR2, monocyte/macrophage marker CD64 and CD68, and T cell marker CD3 mRNA expression. Grafts were analyzed by QPCR 1 and 4 d after transplantation of cultured or freshly isolated islets (*P < 0.05 freshly isolated versus cultured islets).
Islet-Derived CCL2 on Islet Isograft Function

We next examined whether the islet cell culture or the infiltrating mononuclear cells are detrimental to islet grafts using a marginal mass transplantation model in streptozotocin-induced diabetic syngeneic C57BL/6 mice. In this model, the degree of glucose reduction, expressed as percentage reduction of the pretransplantation glucose concentration, reflects islet graft function in vivo. The mean glucose reduction over 4 d posttransplantation was significantly lower when islets were transplanted after 2 d of culture compared with freshly isolated islets grafts (−40 ± 15.9 versus −55 ± 7.7%; P = 0.038). We then examined whether pretransplantation CCL2 levels ranging from 0.46 pg/islet (22.9 pg/ml) to 4.12 pg/islet (206 pg/ml) correlated with islet graft function. We found that the glucose reduction 1 d posttransplantation inversely correlated with the level of CCL2 secretion of islets (P < 0.0001; Figure 5). This effect was independent of the time interval analyzed (mean posttransplantation glucose reduction day 1 to 2 r = −0.923 (95% confidence interval [CI], −0.98 to −0.74), day 1 to 3 r = −0.921 (95% CI, −0.98 to −0.74), and day 1 to 4 r = −0.915 (95% CI, −0.98 to −0.72). Isografts that were transplanted to CCR2−/− recipients demonstrated reduction of glucose independent of the level of CCL2 production by islets (Figure 5). Although the CCR2−/− animals were significantly protected from this effect, damage to the islets could not be completely accounted for by MCP-1/CCR2 interaction because a minimal decrease in percentage of glucose reduction was seen in the absence of the receptor, suggesting a role for other cytokines or chemokines.

CCL2 Is not β Cell Toxic and Does not Impair Insulin Release In Vitro

We and others have shown that islet cell expression of CCR2 mRNA can be induced under various conditions (5,19). Using the more sensitive QPCR assay (data not shown), we demonstrated that islet cells constitutively expressed small amounts of CCR2 mRNA. Therefore, to determine whether the detrimental effect of high levels of CCL2 secretion was due to direct toxicity, we measured in vitro glucose-stimulated insulin release and β cell viability, in the presence of recombinant CCL2 at concentrations similar to those produced by cultured islets (Figure 1). Islet cell insulin release at basal (5.5 mM) or high glucose (16.7 mM) conditions was unaffected by rCCL2 at a range of concentrations (100 to 1000 pg/ml; Figure 6). β-TC3 cells that were incubated with rCCL2 concentrations ranging from 100 to 10⁵ pg/ml were also evaluated for cell viability using the MTT method. We found that rCCL2 had no direct effect on β-TC3 cell proliferation or viability (Figure 7). These results strongly suggest that CCL2 itself had no deleterious effect on β cell viability or endocrine function.

Discussion

Highly differentiated pancreatic β cells have prominent chemokine-producing capabilities and, therefore, the potential to induce or alter inflammatory as well as noninflammatory processes (5–11). Murine islet cells are not passive bystanders of their own destruction but have the potential to secrete CCL2, and this study is the first to show that this is detrimental for immediate posttransplantation graft function. The important role of the CCR2 pathway in conjunction with low-dose immunosuppression has been demonstrated in a murine allogeneic islet transplantation model (18,20). However, few data are available to support the role of donor-derived chemokines in transplantation (21). Our data suggest that islets have the capacity to behave in a similar manner to cells of the immune system, recruiting leukocytes from the blood stream, resulting in the amplification of inflammatory processes and their deleterious effect on islet graft function.

Figure 3. CCR2 was localized by in situ hybridization using an antisense riboprobe, demonstrating mRNA expression (in situ signal indicated by the deposition of silver grains) by infiltrating mononuclear cells. As negative controls, serial sections were hybridized with the CCR2 sense probe, demonstrating a very small number of nonspecifically deposited silver grains. Original magnification ×400.

Figure 4. Isograft cytokine mRNA expression. Grafts were analyzed by QPCR 1 and 4 d after transplantation of cultured or freshly isolated islets (P < 0.05 freshly isolated versus cultured islets).

data suggest that mainly monocyte/macrophage-derived cytokines and not T cell–derived cytokines are likely mediators for the impaired islet graft function.

Effect of Islet-Derived CCL2 on Islet Isograft Function

We and others have shown that islet cell expression of CCR2 mRNA can be induced under various conditions (5,19). Using the more sensitive QPCR assay (data not shown), we demonstrated that islet cells constitutively expressed small amounts of CCR2 mRNA. Therefore, to determine whether the detrimental effect of high levels of CCL2 secretion was due to direct toxicity, we measured in vitro glucose-stimulated insulin release and β cell viability, in the presence of recombinant CCL2 at concentrations similar to those produced by cultured islets (Figure 1). Islet cell insulin release at basal (5.5 mM) or high glucose (16.7 mM) conditions was unaffected by rCCL2 at a range of concentrations (100 to 1000 pg/ml; Figure 6). β-TC3 cells that were incubated with rCCL2 concentrations ranging from 100 to 10⁵ pg/ml were also evaluated for cell viability using the MTT method. We found that rCCL2 had no direct effect on β-TC3 cell proliferation or viability (Figure 7). These results strongly suggest that CCL2 itself had no deleterious effect on β cell viability or endocrine function.
the mononuclear cell infiltration within the islet itself. This supports the data of a recent study in islet transplant patients with type 1 diabetes that found a correlation with high basal donor islet CCL2 production before transplantation with a poor clinical outcome (6). Data in the literature are conflicting as to whether islets’ expressing CCL2 constitutively may be due to the differences in species and technique sensitivities. The data that islets express and secrete CCL2 as soon as they are cultured are consistent with an inflammatory function for CCL2 in this setting, and migration studies with isolated monocytes have shown that CCL2 secreted by islets is biologically active (6,7). Our data in vitro culture of islets augmented CCL2 secretion are in agreement with previous data on human islets cultured up to 6 (6) or 11 days after isolation (22). Our in vivo experiments showed that the inflammatory mediator CCL2 exerts a biologic effect by providing a gradient to attract CCR2+ cells to the site of inflammation. Moreover, the amount of CCL2 produced negatively correlated with islet graft func-

Figure 5. Effect of islet-derived CCL2 on islet isograft function after marginal mass transplantation of streptozotocin-induced diabetic mice. (A) Linear regression of pretransplant CCL2 concentration with glucose reduction 1 d posttransplantation. Linear coefficient (r) and its 95% confidence interval and P-value are shown. High pretransplant CCL2 significantly correlated with poor islet graft function in wild type recipients. This correlation was absent when the CCR2 pathway was disrupted by transplanting CCR2−/− mice. (B) Recipients divided into low and high donor-derived CCL2 and the effect on glucose reduction. CCL2 cutoff value was the 50th percentile (82 pg/ml).

Figure 6. Effect of CCL2 on islet and β-TC3 insulin secretion. Cells were cultured for 12 h with 0 (vehicle control), 100, and 1000 pg/ml rCCL2 and then exposed to 5.5 mM or 16.7 mM glucose for 1 h. Supernatants were analyzed for insulin content with ELISA. Data are shown as mean insulin secretion ± SEM.

Figure 7. Effect of CCL2 on β-TC3 cell viability was measured by MTT metabolism. Data are % of control mean ± SEM of three experiments performed in quintuplicate. β-TC3 were plated in 96-well plates and cultured for 48 hours in the presence of rCCL2 at various concentrations.
tion, a correlation absent when the CCR2 pathway was disrupted.

Our data suggest that the primary cause of transplanted islet dysfunction is antigen-nonspecific inflammation at the graft site mediated by the monocyte/macrophage-associated inflammatory products IL-1β, TNF-α, and MIP-1α. Recent data also documented significant expression of macrophage-associated inflammatory genes, including IL-1β, IL-6, TNF-α, and CCL2, in islets from a brain-dead donor (23), and these islet grafts were found to have a decreased functionality in vivo and in vitro (24). Together, the data suggest that donor-derived CCL2 leads as well as recruitment of inflammatory cells and angiogenesis is unclear in which revascularization of the islets is required for successful therefore, of possible importance during islet transplantation.

CXCL10 are not only chemoattractant but also angiostatic and, after treatment with cytokines. It is interesting that CXCL9 and vitamin B derivative nicotinamide (28).

in human islets can be decreased by cyclosporine and the target for pretransplantation, mild insulitis might affect islet graft function. Our results exclude, however, that CCL2 is directly β cell toxic, as it did not affect β cell viability or the release of insulin, confirming previous studies with human islets (6).

Our data have several potential clinical implications. First, they provide evidence that islet cell culture affects islet graft function in vivo. Transplantation of islets immediately after isolation was done in the original description of the Edmonton protocol (26) and may explain the high success rate not reached in other sites despite the same immunosuppressive protocol (27). At this point, however, it is unknown whether islet cell culture has a negative impact on graft function in immunosuppressed recipients. Second, measurement of pretransplantation CCL2 level may be a useful tool to preselect islets to increase engraftment success rates. Third, strategies to prevent in vitro CCL2 secretion might offer new approaches in clinical islet transplantation. Of note, NF-κB was found to play an important role for CCL2 expression in β cells and might be a potential target for pretransplantation, ex vivo gene therapy (9). In addition, it was previously shown that the in vivo CCL2 expression in human islets can be decreased by cyclosporine and the vitamin B derivative nicotinamide (28).

Using a cDNA array approach, we also identified the induction of potent chemokines CCL5, CXCL9, CXCL10, and CXCL2 after treatment with cytokines. It is interesting that CXCL9 and CXCL10 are not only chemoattractant but also angiostatic and, therefore, of possible importance during islet transplantation, in which revascularization of the islets is required for successful engraftment (29). However, the role of these chemokines in the recruitment of inflammatory cells and angiogenesis is unclear and needs to be studied further. We have also shown that islets as well as β-TC3 cells expressed the chemokine receptor CCR7, along with both its ligands CCL19/SLC and CCL21/MIP-3β.

Expression of both CCL19 and CCR7 was also found in glomerular mesangial cells, where this pathway was important for cell survival, suggesting a homeostatic or regulatory role for chemokines expressed by nonlymphoid tissue (30).

In conclusion, high pretransplantation CCL2 concentration has a negative impact on immediate islet graft function as a result of increased inflammatory cell recruitment. Therefore, strategies to decrease CCL2 release by islet preparations or blocking the CCL2/CCR2 pathway in the recipient might increase the success of islet engraftment and long-term insulin independence in human islet transplantation.

Acknowledgment
B.M. was supported by National Institutes of Health research grant ROI AI 49289-01.

References


