Analysis of the Th1/Th2 Paradigm in Transplantation: Interferon-γ Deficiency Converts Th1-Type Proislet Allograft Rejection to a Th2-Type Xenograft-Like Response

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The rejection mechanisms for fetal proislet allografts and pig proislet xenografts in mice are characterized by different intragraft cytokine mRNA profiles and cellular responses. Allograft rejection is predominantly CD8 T-cell-dependent and is associated with a Th1-type cytokine pattern (i.e., IFN-γ, IL-2 but no IL-4 or IL-5 mRNA). In contrast, xenograft rejection is CD4 T-cell-dependent and is accompanied by a strong Th2-type response (i.e., enhanced expression of IL-4 and IL-5 mRNA) and by marked eosinophil accumulation at the graft site. We have now examined and compared the regulatory role of IFN-γ in both proislet allograft and xenograft rejection processes. The histopathology and intragraft cytokine mRNA profile of BALB/c (H-2^d) proislet allografts were examined in IFN-γ-deficient and wild-type C57BL/6J recipient mice. The survival of pig proislet xenografts was also assessed in IFN-γ −/− and wild-type hosts. Both proislet allografts and xenografts were acutely rejected in IFN-γ −/− and wild-type mice. Unlike the conventional allograft reaction, which lacks eosinophil infiltration, the rejection of proislet allografts in IFN-γ-deficient hosts correlated with intragraft expression of IL-4 and IL-5 mRNA (i.e., a Th2-type response) and eosinophil recruitment. The rejection of proislet allografts and xenografts can therefore occur by IFN-γ-independent pathways; IFN-γ, however, regulates the pathology of the allograft reaction but not the xenograft response. The immune destruction of proislet allografts is not prevented by Th2 cytokine gene expression; instead, the latter correlated with the recruitment of unconventional inflammatory cells (eosinophils), which may play an accessory role in effecting graft injury. Significantly, the Th1-to-Th2-like switch resulted in the novel conversion of an allograft rejection reaction into a xenograft-like rejection process.

Key words: Allograft; Xenograft; Proislet; Rejection; IFN-γ deficient

INTRODUCTION

The Th1/Th2 paradigm classifies activated CD4 T cells on the basis of the pattern of cytokines secreted: Th1 cells produce IL-2, IFN-γ, and lymphotoxin, Th2 cells produce primarily IL-4, IL-5, IL-6, and IL-10, and both Th populations produce IL-3, GM-CSF, and TNF (20). Similarly CD8 T cells can also be classified as T1- or T2-like depending on their cytokine profiles (28). Inflammatory responses in vivo can be characterized by the repertoire of cytokines produced. For example, protective immunity in C57BL/6J mice to cutaneous infection with *Leishmania major*, a protozoan parasite, is CD4 T-cell-dependent and is characterized by a Th1 response (high IFN-γ, undetectable IL-4) (15); IFN-γ

alone has been shown to regulate the resistant phenotype (2,40). In contrast, susceptibility to infection in BALB/c mice correlates with a Th2 response (high IL-4) (15). Such a correlation between opposing phenotypes and the presence/absence of Th2 cytokine responses has provided in vivo support for the Th1/Th2 paradigm.

In relation to pancreatic islet transplantation, the rejection of adult islet allografts is T-cell mediated and has been shown to be associated with mRNA expression for IL-2 and IFN-γ (24) (i.e., a Th1-type response). We have previously reported that the rejection of murine fetal proislet allografts is predominantly a CD8 T-cell-dependent process (34). In this model, also, rejection correlates with the intragraft expression of Th1-like cytokine mRNA (IL-2, IFN-γ) and absence of expression

of the Th2 cytokines IL-4 and IL-5 (32). In contrast, the acute rejection of pig proislet xenografts is specifically associated with CD4 T-cell-dependent expression of mRNA for the Th2 cytokines IL-4 and IL-5 (19). Using IL-2 gene knockout recipient mice Steiger et al. (38) failed to demonstrate an essential role for IL-2 in the rejection of adult islet allografts. In the present study we examine the role of IFN-γ in the rejection of both proislet allografts and pig proislet xenografts. Using IFN-γ −/− recipient mice we have shown that the acute rejection of neither proislet allografts nor xenografts requires IFN-γ production; furthermore, in the context of proislet allografts, the absence of IFN-γ gene transcription led to induced intragraft expression of Th2-type cytokine mRNA without inhibiting graft destruction.

MATERIALS AND METHODS

Animals

IFN-γ −/− male mice (6–15 weeks old) (8) and corresponding wild-type C57BL/6J (B6; H-2^b) male mice (7–12 weeks old) were provided by the Animal Services Division, The Australian National University (Canberra, Australia) and were used as transplant recipients. BALB/c fetuses at 17 days of gestation and fetal piglets (SLA^{dd} haplotype; 75 days of gestation) were used as donors of pancreas tissue for the isolation of proislets (33,35,37). Pregnant SLA^{dd} gilts/sows were obtained from the inbred pig colony maintained at the Animal Services Division, The Australian National University, Canberra. This colony was derived from the inbred SLA^{dd} herd (16) developed by Professor David H. Sachs (Boston, MA).

Preparation and Transplantation of Fetal Proislets

Proislets (islet precursors) were prepared from BALB/c (H-2^d) fetal pancreases (17 days of gestation) by collagenase digestion followed by culture of the digested tissue in 10% CO_2, 90% air for 4 days (35,37). Fetal pig proislets were prepared from fetal pig pancreas by collagenase digestion followed by organ culture of the digested tissue for 5–6 days in 10% CO_2, 90% air (19,36). Mouse proislets (four to six donor equivalents) and pig proislets (one tenth fetal pig pancreas equivalent) were transplanted beneath the kidney capsule of IFN −/− and wild-type C57BL/6J recipient mice (35,37).

Harvest of Transplants for RNA Extraction and Immunohistochemistry

Grafts were harvested from recipient mice at 3–14 days posttransplant. For RNA extraction, approximately 80% of the transplant was stripped from the kidney and frozen in liquid nitrogen (19). The remainder of such transplants or entire additional transplants were frozen in situ in liquid freon (preequilibrated with liquid nitro-

gen) for histology and immunohistochemistry. BALB/c proislets and kidney tissue harvested from IFN-γ −/− and wild-type C57BL/6J mice were also frozen in liquid nitrogen as control tissues for RNA extraction and subsequent analysis of cytokine mRNA by RT-PCR.

Histology and Immunohistochemistry

Freon-frozen graft tissue was sectioned (6 μ thickness) and stained for the presence of infiltrating CD4 and CD8 T cells using avidin-biotin-peroxidase immunostaining methods (33). Eosinophils were identified in control sections incubated with PBS due to their high level of endogenous peroxidase activity (19,33,36). Immunostained sections were counterstained with Mayer's hematoxylin. Additional frozen sections were stained with hematoxylin and eosin to assess graft integrity/rejection.

RNA Extraction and Reverse Transcription

Total graft/tissue RNA was extracted using the guanidine isothiocyanate method (6) and reverse transcribed as previously described (19,33). Grafts to be directly compared were reverse transcribed concurrently using the same reverse transcriptase mix; cDNA samples were stored at −20°C.

PCR Analysis

Semiquantitative polymerase chain reaction (PCR) was performed as previously described (19,32). In brief, cDNA (20 μl) was amplified in a 50-μl reaction volume containing 0.2 mM (each) dNTPs, 1–5 mM $MgCl_2$, 0.4–1 μM primers, 1.4–2.75 U Taq (Biotech. International, Australia), and reaction buffer (supplied with enzyme). The reaction mix was overlaid with mineral oil (Sigma); 10 μl aliquots of the reaction mix were sampled at 5-cycle intervals from 20 to 45 cycles. Standard reaction parameters were 96°C (1 min), 55–72°C (1 min), 72°C (1 min). Primers for β-actin were used as controls to indicate that there were similar levels of amplifiable cDNA in tissue samples. Annealing temperatures and nucleotide sequences of the primer pairs were as previously described (32,33), with the following exceptions:

IFN-γ   AGAAGTAAGTGGAAGGGCCCAGAAG and
(54°C)   AGGGAAACTGGGAGAGGAGAAATAT;
IL-5   TTGACAAGCAATGAGACGATGAG
(64°C)   CTTCCATTGCCCACTCTGTACT

Tissues used as positive controls for mRNA expression were Con A (2 μg/ml) and PMA (5 ng/ml)-activated mouse spleen cells (IL-2, IFN-γ, IL-4, IL-10, and β-actin), WEHI-3B cells (IL-3), and D10.G4.1 cells (IL-5) (33). PCR products were size-fractionated by electrophoresis through 1.5% agarose gels; the gels were stained in ethidium bromide solution (2 μg/ml) for

10–20 min and photographed under UV illumination. The sizes of the PCR products were verified against a marker of known standards (1-kb DNA ladder, Gibco, BRL, Life Technologies Inc., Gaithersburg, MD).

RESULTS

Histologic and Immunohistochemical Analyses of BALB/c Proislet Allografts and Pig Proislet Xenografts in IFN-γ –/– Recipient Mice and Wild-Type B6 Hosts

Proislet Allografts in IFN-γ –/– and Wild-Type B6 Hosts. BALB/c proislet allografts transplanted to wild-type B6 recipient mice contained intact developing islet tissue and duct epithelium at 3 days posttransplant (Table 1). Damaged islet tissue was visible at 5–7 days posttransplant and correlated with marked CD4 and CD8 T-cell infiltration of the grafts. Peak infiltration by CD4 and CD8 T cells occurred at 8 days and there was no evidence of graft tissue remaining by this time (Fig. 1a). By 2 weeks posttransplant, only scar tissue remained at the graft site and there was little evidence of mononuclear cell infiltration. Eosinophils were not detected at any time point throughout the course of the rejection response in B6 recipient mice (Table 1, Fig. 1b). In IFN-γ –/– transplant recipients, intact developing islet tissue and duct was observed at 3–4 days posttransplant. Evidence of some cellular infiltration into islet tissue and duct was detected at 5 days posttransplant; gross islet and duct destruction at 6 days correlated with peak cellular infiltration of the graft. From 6 to 10 days, the cell infiltrate contained numerous eosinophils (Fig. 1d); CD4 and CD8 T cells also participated (see Table 1). Generally, there was no evidence of graft tissue from 7 days posttransplant. Like wild-type B6 recipients, IFN-γ –/– mice acutely rejected BALB/c proislet allografts (Fig. 1c). In contrast to the wild-type rejection reaction, IFN-γ –/– hosts displayed an intense eosinophil response to allogeneic proislet tissue; in addition, the peak CD8 T-cell infiltrate identified at 6–8 days in wild-type mice was not detected in IFN-γ –/– recipient mice. These findings indicate that IFN-γ gene transcription is not essential for allograft destruction; however, absence of IFN-γ significantly alters, at the cellular level, the phenotype of the immune response.

Comparison of Proislet Allografts and Pig Proislet Xenografts in IFN-γ –/– and Wild-Type B6 Hosts. Xenografts of pig proislets were completely rejected by 7 days posttransplant in wild-type B6 recipient mice (Fig. 2a). At 7–14 days posttransplant, the cellular infiltrate was composed mainly of CD4 T cells and eosinophils (Fig. 2b); CD8 T cells were a minor component of the rejection reaction (see Table 1). Similarly, pig proislet xenografts were also acutely rejected by 7 days in IFN-γ –/– transplant recipients (Fig. 2c); the immunopathol-

ogy of the xenorejection response was essentially identical to that displayed by the wild-type hosts (i.e., the grafts were invaded predominantly by CD4 T cells and eosinophils) (Fig. 2d). Comparison of the allograft and xenograft reactions in the wild-type B6 mice (Table 1) identifies several major differences: whereas allograft rejection is characterized by a major involvement of CD8 T cells, CD4 T cells, and the absence of eosinophil recruitment to the graft site, the xenograft rejection reaction is distinguished by intense eosinophil accumulation, CD4 T cells, and a minor CD8 T-cell response. These disparities are consistent with the differences observed between the rejection of proislet allografts and xenografts in CBA/H recipient mice (32). Unlike the allo- and xenorejection reactions in CBA/H recipient mice (32), the tempo of these two rejection processes in the B6 recipient mice was similar. In addition, the cellular response subsided more quickly following allograft destruction in B6 recipients; an intense cellular infiltrate persisted at 2 weeks postxenotransplantation but had dissipated by the same 2-week time point after allotransplantation. Significantly, the rejection of proislet allografts and pig proislet xenografts in IFN-γ –/– mice showed the striking similarity of an intense eosinophil response; furthermore, like the weak CD8 T-cell response to proislet xenografts, the CD8 T-cell reaction to proislet allografts was dampened in IFN-γ –/– hosts. These findings indicate that in the absence of IFN-γ gene transcription/translation, the proislet allograft response is transformed into a "xenograft-like" reaction.

Cytokine mRNA Profile in Proislet Allografts Harvested From IFN-γ –/– and Wild-Type B6 Transplant Recipients

Figure 3 compares the cytokine mRNA expression in rejecting BALB/c proislet allografts taken from IFN-γ –/– and wild-type B6 recipient mice at 3–10 days posttransplant. Compared to wild-type B6 recipients, IFN-γ –/– hosts showed intragraft expression of IL-4 mRNA (day 6 and day 8). In contrast to B6 hosts, which failed to exhibit IL-5 mRNA, IL-5 transcripts were strongly detected at days 4–10 posttransplant in IFN-γ –/– recipient mice, with peak expression at day 8. There were no differences in the kinetics of IL-10 transcript expression between the two recipient strains; onset of expression of IL-2 and IL-3 mRNA was delayed by 1 day in IFN-γ –/–deficient mice. Whereas IFN-γ transcripts were identified at days 5–8 posttransplant in wild-type mice, there was no expression in IFN-γ –/– transplant recipients. These findings demonstrate that in the absence of IFN-γ, the transcription of IL-5 and IL-4 was induced in response to a proislet allograft. This expression of Th2-type cytokines correlates with the unconventional recruitment of eosinophils in the allograft reaction in IFN-

Table 1. Histological and Immunohistochemical Assessment of Proislet Allografts and Pig Proislets Xenografts in IFN-γ −/− and Wild-Type Recipient Mice

Transplant	Day Posttransplant (No. in Group)	Recipient Strain	Total Cell Infilt.[a]				CD4 T-Cell Infilt.[a]				CD8 T-Cell Infilt.[a]				Eosinophil Infilt.[b]				Proislet/Duct Integrity[c]			
			0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Allograft	3–5 n=3	B6		2	1			2	1		1	1	1		3						2	1
	6–8 (n=6)	B6			2	4		5		1		4		2	6				2	4		
	10–14 (n=6)	B6		4	2			5	1			3	3		6				6			
	3–5 (n=3)	IFN-γ-/-		3			1	2			1	2			3						1	2
	6–8 (n=3)	INF-γ-/-			1	2		1	2			2	1		2	1			2	1		
	10–14 (n=6)	INFγ-/-		1	3	2		3	3			2	4		4	2			5	1		
Xenograft	7–14 (n=4)	B6			2	2		3	1			3	1			2	2		4			
	7–14 (n=4)	IFN-γ-/-			2	2		4				4					2	2	4			

[a]Score for total cell, CD4 and CD8 T-cell infiltrate: 0, none or few infiltrating cells; 1, scattered infiltrate or focal accumulation; 2, moderate infiltrate; 3, intense cell infiltrate. [b]Score for eosinophil infiltrate: 0, none or few peroxidase positive cells; 1, sparsely scattered infiltrate; 2, mild infiltrate; 3, marked or intense infiltrate. [c]Score for proislet/duct integrity: 0, only tissue remnants or no evidence of islet/duct tissue; 1, much damaged islet/duct tissue; 2, intact islet/duct tissue + damaged tissue present; 3, much intact islet/duct tissue.
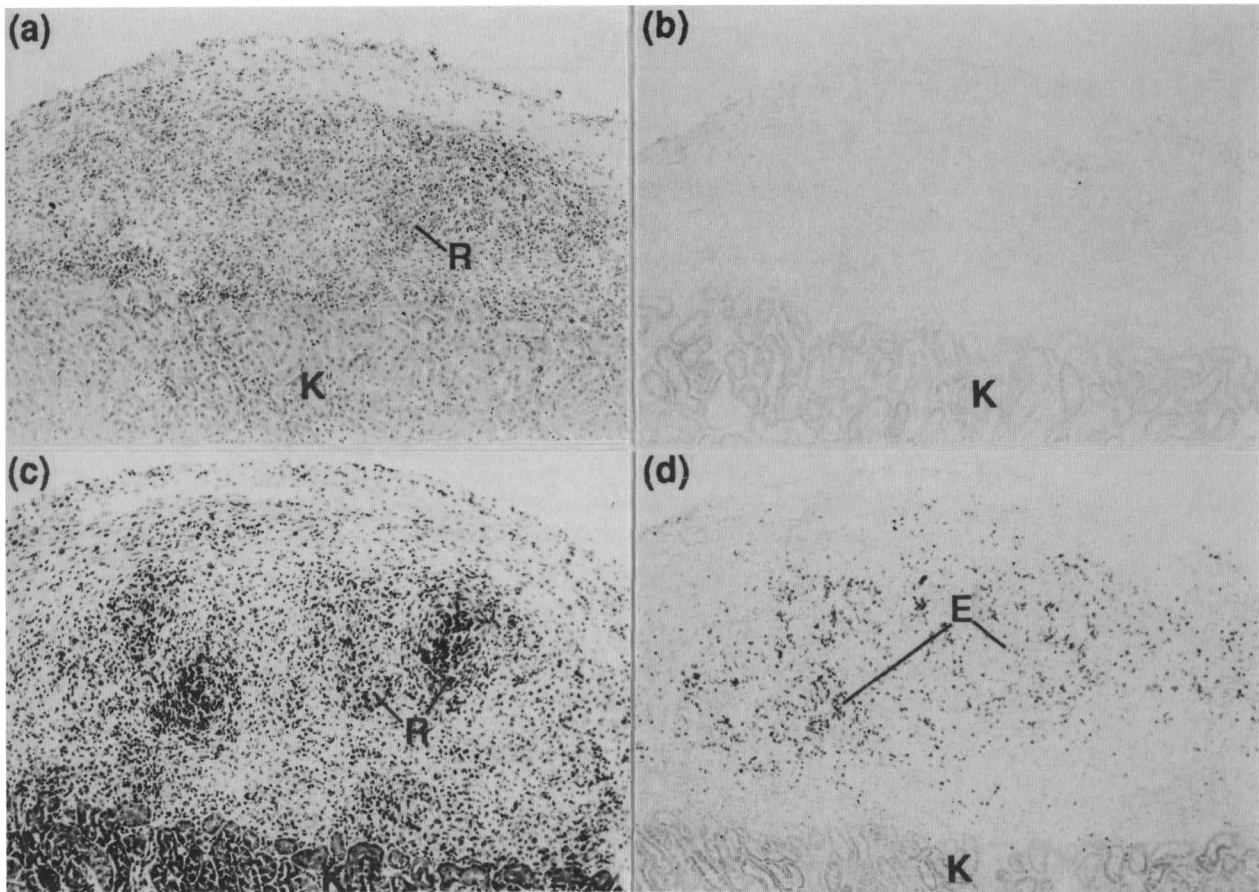
Figure 1. Rejection of BALB/c proislet allografts at 8 days after transplantation to wild-type B6 (a, b) and IFN-γ –/– (c, d) recipient mice; note absence of eosinophils in (b) and numerous infiltrating eosinphils (E) in (d). Only remnants of donor tissue (R) can be identified in (a) and (c). (a, c) Hematoxylin and eosin, ×108; (b, d) PBS, ×108.

γ –/– recipient mice (see Table 1) and resembles the cytokine profile that characterizes rejecting proislet xenografts in both CBA/H and B6 recipient mouse strains (19,32,33).

DISCUSSION

The conventional rejection of proislet allografts, like adult islet allografts (24), is characterized by a Th1-type response with enhanced expression of IFN-γ mRNA (32). Our present study demonstrates acute rejection of proislet allografts in IFN-γ-deficient mice, thereby indicating that allograft destruction is not dependent on IFN-γ transcription or translation. Interferon-γ has been shown by others to increase expression of MHC class I antigen(s) on adult islets, thereby rendering them more effective targets for CD8 T-cell-mediated attack (14). We suggest that in the case of proislet allografts in IFN-γ –/– hosts, either such an increase in class I MHC

antigen expression on proislet cells is not required or is induced by one or more other cytokines. Of further significance in the present study were our findings that the intragraft cytokine mRNA profile and the phenotype of graft infiltrating cells in IFN-γ –/– recipients was dramatically altered, compared to corresponding wild-type B6 hosts. In contrast to wild-type recipients, which demonstrated no eosinophil accumulation, allograft rejection in IFN-γ –/– mice was characterized by prominent eosinophil infiltration and by a less vigorous CD8 T-cell response. The most striking difference between the cytokine profiles was the expression of IL-5 and IL-4 mRNA in IFN-γ –/– mice but not in wild-type recipients. The kinetics of IL-4 and IL-5 mRNA expression in IFN-γ –/– hosts correlated with the influx of eosinophils into the graft site. Enhanced in vitro production of Th2 cytokines (IL-4, IL-5) by spleen cells has previously been reported following infection of IFN-γ –/– mice with influenza virus (12). Abnormal accumulation of eosino-
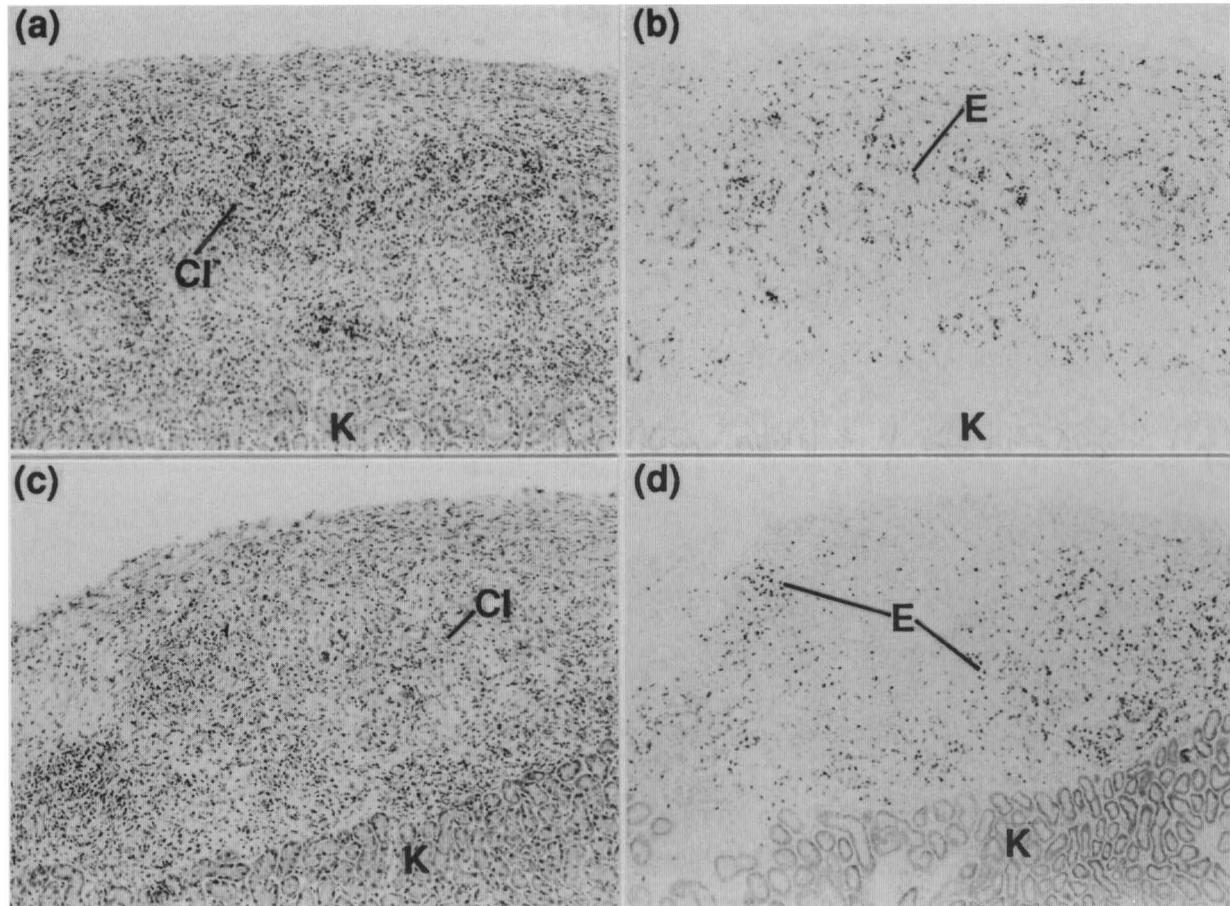
Figure 2. Acute rejection of pig proislet xenografts at 7 days posttransplant to wild-type B6 (a, b) and IFN-γ −/− (c, d) recipient mice; note prominent recruitment of eosinophils (E) to the graft site in both recipient mouse strains (b, d). CI, cell infiltrate; K, kidney. (a, c) Hematoxylin and eosin, ×108; (b, d) PBS, ×106.

phils has also been correlated with induction of Th2 cytokine transcripts in immediately vascularized cardiac allografts undergoing rejection in CD8 T-cell-depleted hosts (4). Likewise, the immune destruction of neovascularized proislet allografts is not prevented by Th2 cytokine gene expression.

Pig proislet xenografts, like xenografts of pig islet-like cell clusters (30), were acutely rejected in IFN-γ-deficient recipient mice. In comparison to proislet allografts, the cellular response to pig proislet xenografts in IFN-γ −/− and wild-type B6 mice was identical; total graft destruction was achieved by 7 days and characteristic eosinophil infiltration was exhibited by both recipient strains. Xenograft rejection and eosinophil recruitment were therefore IFN-γ independent. We have previously reported that the mobilization of eosinophils during xenorejection was directly attributable to the Th2 cytokines IL-5, IL-4, and IL-3 (33). We suggest that eosinophil recruitment into rejecting proislet allografts in

IFN-γ −/− mice also appears to be regulated by intragraft expression of IL-4 and IL-5 mRNA. We further speculate that during the conventional immune response to proislet allografts (i.e., in wild-type hosts), the expression of Th2 cytokine mRNA is depressed by marked IFN-γ production; consequently, eosinophils are not recruited. This notion is consistent with the IL-5-associated recruitment of eosinophils into the airways of antigen-treated mice and, conversely, the inhibition of this eosinophil response following host treatment with aerosolized IFN-γ (21). Previously we have reported that eosinophils are not essential for the rejection of pig proislet xenografts because xenodestruction occurs in their absence (33). Similarly, eosinophils are not essential for the rejection of proislet allografts; nevertheless, their recruitment in IFN-γ −/− mice acts as a sentinel for identifying a Th2-type cytokine response. This study demonstrates that in the presence of a normal T-cell repertoire, the intragraft cytokine profile and the immunopathology
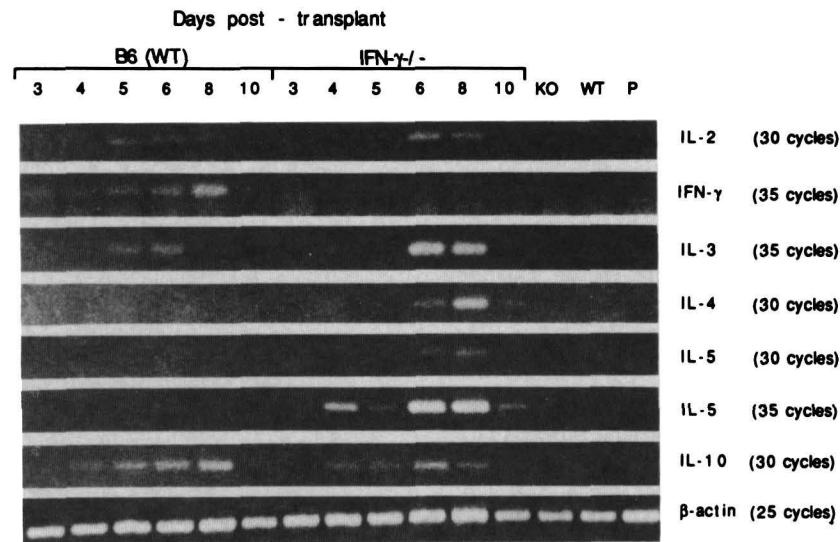
Figure 3. Analysis of cytokine mRNA expression in BALB/c proislet allografts transplanted to wild-type B6 and IFN-γ –/– recipient mice. Allografts were harvested on days 3, 4, 5, 6, 8, and 10 posttransplant. Optimal amplification(s) selected from semiquantitative analyses is shown for each primer pair. Semiquantitative analyses of β-actin expression showed that all samples had similar levels of cDNA at each cycle tested (20–35 cycles); plateau levels of amplification of β-actin cDNA were achieved at 30 cycles. Control tissues were KO, IFN-γ –/– kidney; WT, wild-type B6 kidney; P, BALB/c proislets.

accompanying proislet allograft rejection can be profoundly altered without inhibiting graft destruction. We report the novel finding that in IFN-γ gene knockout recipient mice, allograft rejection is converted into a xenograft-like reaction.

A number of experimental models of inflammation, including antigen-induced airway hyperresponsiveness (10,11) and parasite infection (5,9,29), have provided support for the Th1/Th2 paradigm in the potentiation/inhibition of protective immune responses; such studies have also identified a key regulatory role for IFN-γ (2,9,40). Our present study, on the other hand, shows that although induced expression of an atypical Th2-type cytokine response altered the immunopathology of the allograft reaction, graft destruction persisted. Thus, in the case of pancreatic islet tissue allografts, the presence/absence of Th2 cytokine transcripts does not determine the differentiation of nondestructive and destructive immune responses, respectively. The capacity for the Th1/Th2 paradigm to adequately explain the rejection or acceptance of other types of tissue transplants has been controversial (7,22,26). For many different tissues and organs, graft rejection is associated with a Th1-type cytokine response (3,4,24,31). Consequently, a major endeavor in the transplantation field has been to identify conditions that will divert the cytokine response

to a tissue or organ allograft away from a Th1 bias and towards a Th2-type profile. A number of studies have correlated survival of heart allografts in rodents with a Th2-type cytokine profile (31,39); alternatively, allograft rejection has been inhibited by a combination of treatments including the administration of Th2 cytokine (18). In contrast, some organ allograft models in which Th2 cytokines have been induced have either failed to show allograft survival (27) or at best have demonstrated a delay in rejection (13,17,25). Steiger et al. (38) demonstrated islet allograft rejection in IL-2 knockout recipient mice without upregulation of the Th2 cytokine IL-4; in that model, therefore, the capacity for Th1-to-Th2 profile switching to modify allograft outcome or pathology could not be addressed. Nevertheless, demonstration of long-term islet allograft survival and function following CTLA4Fc therapy in IL-4 knockout mice clearly indicated that IL-4 gene expression and hence a Th2 cytokine response was not required to prevent allograft rejection (23). The present study is novel because it represents the only model of neovascularized pancreatic islet tissue allotransplantation in which direct induction of a Th2 cytokine pattern has been achieved; we clearly demonstrate that a polarized Th2-type response fails to prevent allograft rejection and instead elicits molecular and cellular responses analogous to a xenograft

rejection reaction. It is also significant that in a previous study of pig proislet xenotransplantation in IL-4 gene knockout recipient mice we demonstrated the conversion of a Th2-biased cytokine response to a Th1-type response, without preventing xenorejection (33). Because the kinetics of the rejection of proislet xenografts and allografts are very different (xenorejection occurs much quicker) (19,32), it is likely that the destructive mechanisms are also dissimilar; for this reason separate examination of the role of cytokine profiles in the allograft reaction has been mandatory. Our previous xenograft analyses together with our present study of proislet allograft rejection clearly indicate that polarizing cytokine responses away from the conventional profile (Th2 or Th1) does not dictate the suppression of pancreatic islet transplant rejection. Consequently, our in vivo data suggest that whereas the cytokine pattern influences the composition of the inflammatory reaction it does not constitute the trigger for initiating destruction of proislet allografts and xenografts (i.e., our in vivo data do not support the Th1/Th2 paradigm).

Ablation of IL-2 gene expression (38) or, as shown in the present study, of IFN-γ gene expression has failed to prevent the rejection of pancreatic islet tissue allografts (i.e., neither of these individual Th1 cytokines alone regulates allograft rejection). Nevertheless, we have demonstrated that IFN-γ regulates the pathology of the allograft but not the xenograft rejection reaction. Ahmed et al. (1) have reported that islet allograft rejection proceeds in the absence of both perforin/granzyme and Fas/FasL cytolytic pathways of destruction. Together these findings suggest that the mechanism of rejection for pancreatic islet tissue allografts can be modified qualitatively by the intragraft cytokine profile; the actual process of tissue destruction may result from one or more inflammatory mediators (derived from the graft infiltrating cells) or from some alternative cytolytic mechanism. It is evident that IFN-γ plays no regulatory role in proislet xenograft rejection; however, we have previously reported that the Th2 cytokines, IL-4, IL-5, and IL-3, influence the pathology of the conventional xenograft reaction (33). The rejection of both pancreatic islet tissue allografts and xenografts is T-cell-dependent; while it is clear that different T cell-derived cytokines control the cellular composition of the rejection response to allografts and xenografts, it is apparent that the mechanism of tissue destruction is regulated by other factors.

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