Fetal Pancreas as a Source for Islet Transplantation

Sweet Promise and Current Challenges

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The early hope that islet transplantation might offer an attractive treatment modality for late-stage type 1 diabetes has been tempered over the last decade, largely due to the observation that the transplants exhibit reduced insulin production after a few years (1). This limitation could be associated with some form of immune rejection or the inability of the implanted islets to replenish dying islets via stem cell differentiation and self-renewal.

Studies over the past three decades indicate that both immunogenicity and poor self-renewal might potentially be addressed by the use of human fetal pancreatic precursor tissues (2,3). However, considering the ethical issues associated with the use of human fetal tissues and the proven efficacy of pig insulin in humans, the focus of such studies has shifted to xenotransplantation of pig embryonic pancreatic tissue.

While several studies demonstrated the remarkable regenerative capacity of embryonic day (E)28–E42 pig pancreatic tissues in various rodent models (4–7) and the ability of E42 tissue to correct diabetes in nonhuman primates (NHP) (8), the issue of immunogenicity remained highly controversial.

In particular, at the heart of this debate was the suggestion by Rogers et al. that pig embryonic pancreatic (6) or renal (9) tissues harvested at E28 can completely evade graft rejection in fully immune competent mice or rats and, more recently, even in NHP (10). In contrast, Tchorsh-Yutsis et al. (11) reported fierce T-cell–mediated rejection of E28 pig pancreatic tissue in mice or rats, and prompt rejection was likewise demonstrated by Clancy et al. (12), who tested acceptance of allogeneic fetal renal tissue in rats. Further, it has been demonstrated that even embryonic (13) or mesenchymal (14) stem cells cannot evade rejection.

The new report in *Diabetes* by Fourcade et al. (15) provides additional important data regarding the growth potential and immunogenicity of allogeneic fetal pancreatic tissue as a source for transplantation. The authors elegantly demonstrate that a minimal amount of tissue harvested from just two mouse embryos can correct hyperglycemia in diabetic animals. However, their results also dispute the notion that these transplants might evade rejection in immune competent recipients, thereby further emphasizing the importance of defining minimal immune suppression protocols for the implantation of allogeneic/xenogeneic embryonic tissues. This might be accomplished using relatively moderate modalities, like those employed by Tchorsh-Yutsis et al. (11), who demonstrated long-term E42 pig pancreatic tissue survival when transplanted in immunocompetent mice under transient treatment with costimulatory blockade, and maintenance with FTY720, alone. Likewise, rejection of allogeneic fetal renal tissue transplants could be overcome by the use of tacrolimus and FTY720, as shown by Clancy et al. (12).

The relatively mild immunosuppression required to prevent rejection of the fetal tissue could be partially explained by our finding that antigen-presenting cells, including dendritic cells, are not present in the growing implant. Thus, the observed rejection is likely mediated by cross presentation of donor antigens on recipient antigen presenting cells (Fig. 1). However, it should be noted that while such indirect rejection can be controlled in mice or rats by costimulatory blockade as described above, similar protocols might not prove effective in NHP because they are not kept in a sterile environment, and they exhibit high levels of effector memory T cells, which are less responsive to costimulatory blockade (16).

An additional challenge associated with fetal organ transplantation is the relatively prolonged latency period between transplantation and commencement of functional activity of the graft. Presumably, this reflects the time required for differentiation and growth of the grafted tissue after implantation (5). Another obstacle to achieve successful engraftment of fetal tissue is fluctuation in glucose levels in the recipient. This variation interferes with insulin production within the fetal graft. Thus, strict glucose control is required throughout transplantation and later on during the latency period. In the current study, this problem was avoided by destroying the recipient's endogenous islets via infusion of hemagglutinin-specific effector T cells to ins-hemagglutinin transgenic recipients only upon completion of growth of the implant (15). Other groups have used the same strategy in the context of xenotransplantation by the use of alloxan, which selectively ablates rodent islets (17). However, this convenient approach for bypassing the latency period has no clinical application.

In an attempt to enhance fetal pancreas growth and increase the insulin content in the cells after transplantation, studies have been performed using growth factors cocultured in vitro with the fetal islets before transplantation. These include IGF-1, nicotinamide, sodium butyrate, glucagon-like peptide-1, platelet-derived growth factor, or vascular endothelial growth factor, all with variable results (18). In vivo administration of the keratinocyte growth factor resulted in expansion of human fetal β-cells 8 weeks after transplantation into athymic rats, suggesting a positive

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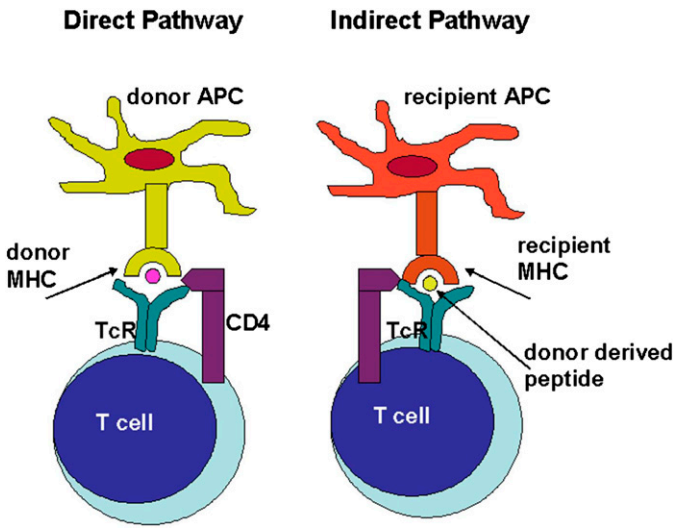

FIG. 1. The direct and indirect pathways of rejection. Recipient CD4$^+$ T cells recognize peptides and class II major histocompatability complexes (MHC) displayed on the surface of antigen-presenting cells (APC). In transplantation between genetically distinct individuals, donor APC transferred together with the transplanted tissue express MHC molecules, which are identified as foreign by recipient T cells. The T-cell receptor (TcR) directly recognizes donor MHC molecules as antigens. Indirect allo- or xenorecognition involves presentation of donor-derived peptides by recipient APC to recipient T cells. Donor proteins are processed by recipient APC, which display the peptides at the cell surface in complex with self-MHC molecules.

regulatory effect of keratinocyte growth factor on growth and development of human fetal islets (19). However, in the current study, it was shown that, similar to transplantation of pig fetal tissue (5,8,11), fresh allogeneic fetal pancreas with no additional treatment enabled adequate implant growth and the consequent complete restoration of normoglycemia. Interestingly, the authors addressed the important effect of the hormonal environment in vivo on graft function by showing delayed insulin production in male relative to female mice, possibly related to low exposure to prolactin in males.

In conclusion, the study of Fourcade et al. (15) demonstrates the feasibility of allogeneic transplantation of embryonic pancreatic tissue for the correction of hyperglycemia in type 1 diabetes. However, it also further emphasizes the need for appropriate immune suppression protocols and for additional strategies to enhance tissue growth, especially in male recipients. Further studies exploring this promising, albeit ethically controversial, source for transplantation are warranted in NHP.

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