

First-Trimester Human Fetal Pancreas Transplantation for Type 1 Diabetes Treatment

An Alternative Approach for Achieving Long-Term Graft Survival?

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Type 1 diabetes results from immune-mediated destruction of insulin-producing β -cells of the pancreas. The disease manifests itself symptomatically when the resident β -cells become unable to maintain normoglycemia. In human insulinitis, mainly CD8 lymphocytes and B-cells, but also CD4 cells and activated antigen-presenting cells (APCs), are found (1–3). Strikingly, strong upregulation of MHC class I molecules and type 1 interferons have also been observed in noninfiltrated islets from human type 1 diabetic patients, making the involvement of a viral β -cell infection a feasible scenario in terms of disease pathogenesis (4). Among treatments that are currently being evaluated for stable reversal of type 1 diabetes, pancreas or islet transplantation holds promise, since it provides already diabetic patients with new functional β -cells. The routine clinical use of pancreas or isolated intrahepatic islet transplantation is, however, hampered predominantly by the lack of sufficient donor tissue. In addition, islets injected into the portal vein are often lost after 4–5 years, even under optimized immunosuppressive regimens (5), which renders whole pancreas or combined pancreas-kidney transplants important therapeutic alternatives (6).

With this setting, human fetal pancreas derived from therapeutic termination of pregnancies as an alternative source of β -cells has increasingly become an attractive alternative. Potential advantages include its greater proliferative capacity and maturation potential *in vivo*, as well as its immune-privileged status or direct tolerogenic properties. Although pancreas allotransplantation has proven itself successful since the early 1990s following generalized immunosuppression of the host, reductions of chronic immunosuppression and less invasive therapeutic regimens are certainly desirable (7). Statistics also suggest that whole-pancreas tissue, when grafted simultaneously with kidney allograft, is more tolerated by the recipient (8). Nevertheless, novel ways to achieve higher rates of

transplant acceptance, coupled with milder immunosuppressive conditioning, are of great interest.

In the study by Brands et al. (9), the immunogenicity of first-trimester human fetal pancreatic grafts (i.e., those between 6 and 9 weeks of gestation) was compared with that of older, second-trimester human fetal pancreatic grafts. For this purpose, a humanized mouse model was established: first- and second-trimester human fetal pancreata were transplanted under the renal capsule of NOD/Scid mice that, 1 week later, received 5×10^7 human peripheral blood mononuclear cells (PBMCs). Histological examination of the second-trimester grafts revealed an extensive cellular infiltration, and the engrafted pancreata were subsequently completely rejected. In contrast, first-trimester grafts showed reduced infiltration, primarily restricted to the graft-kidney interface, and did not show signs of rejection during the reported observation period (3 weeks after injection of human PBMCs). Micro-array analysis followed by RT-PCR verification comparing the first- and second-trimester grafts showed differential expression levels of several immune-related genes, among them MHC class II molecules, chemokine ligands (CCL19), and costimulatory molecules, such as tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL). These molecules were significantly elevated in the second-trimester grafts, providing a possible explanation for their increased immunogenicity and rejection.

The humanized NOD/Scid mouse model has been chosen many times in the past for allo-/xenograft transplantation studies and is under constant development (10). However, it still represents a somewhat artificial approach because, even in the most promising recent versions (11), engrafted human cells form limited amounts of lymphoid tissue, which is important for providing physiological “congregation areas” for T-cells, B-cells, and APCs to interact. Nevertheless, it is one of the best models currently available for directly studying and manipulating human immune functions. Since NOD/Scid mice lacking the common cytokine receptor γ -chain have more potential to form lymphoid tissue equivalents following engraftment with adult human T-cells, one could suggest that the investigators should have used this model (11). Moreover, the choice of normal, not pre-diabetic or islet auto-antibody-positive, human PBMC donors excludes a possible role of autoreactive T-cells in the rejection/autoimmune process in the present study, which is considered an important mechanism in long-term graft loss.

Nevertheless, the presence of a considerable amount of cells at the graft-kidney interface of the second-trimester transplants suggests that the tissue is being rejected

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MHC, major histocompatibility complex; PBMC, peripheral blood mononuclear cell; Treg, regulatory T-cell.

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through a human allogeneic response. That some cells are also present in the first-trimester grafts makes a longer observation time significant because it is important to know whether these grafts would eventually be rejected as well. Preliminary data mentioned by the authors suggest this is not the case, but of course further follow-up and verification are required.

Although the gene profiling of first- versus second-trimester human fetal grafts supports the reduced immunogenicity hypothesis of the former, it does not provide all available evidence. One would like to see more phenotypic and functional analyses of the transferred human PBMCs in future studies. In addition, it is not known whether first-trimester grafts differentially express embryonic associated antigens and how these might affect the overall immunogenicity of the tissue. Finally, fetal organs contain several stem cells, but at this time it is not clear whether fetal pancreas can provide replicating islet precursors and how much islet neogenesis occurs after transplantation. Another interesting aspect might include the presence of stem cells that could give rise to regulatory T-cells (Tregs). Indeed, current diabetes prevention trials are under way using autologous cord blood stem cells, and one potential mechanism by which cord blood might prevent type 1 diabetes is via the development of Tregs (M.A. Atkinson, M. Haller, D. Schatz, unpublished observations). Understanding these additional aspects will possibly help us to better delineate future interventions and improve the acceptance of islet cell grafts.

In conclusion, fetal tissues are generally believed to show excellent proliferative capacity and to be less immunogenic, which makes them potentially preferred candidates for transplantation. However, their reduced immunogenicity is not enough to completely circumvent the need for immunosuppressive conditioning of the recipient. Moreover, it is unclear from this and previous studies how much human fetal pancreas is needed to achieve normoglycemia in one individual. Thus, direct clinical translation will be hampered by organ availability. However, precise analysis of the underlying mechanisms using enhanced humanized NOD/SCID mice—for exam-

ple, defining the precise surface determinants that make fetal tissue less immunogenic and characterizing β -cell or Treg precursors contained within fetal tissues—should be very useful in discovering interventions that could be directly utilized to prevent or treat type 1 diabetes.

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