Clinical islet of Langerhans xenotransplantation: How close are we?

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Introduction

The encouraging results recently reported by the Edmonton group in patients receiving allogeneic islet grafts, all of whom achieved at least temporary insulin-independence, has rekindled interest in transplantation of islets of Langerhans as a cure for diabetes [1, 2]. As successful clinical islet transplantation currently requires 2–4 human donors per recipient [1], the shortage of organ donors might prevent most eligible diabetic patients from receiving a graft. Currently, less than 100 cadaveric organ donors become available for clinical transplantation each year in Switzerland. In contrast, the population of type 1 diabetic patients is estimated at approximately 0.2% of the total Swiss population, i.e. around 14,000 persons. Unlimited islet transplants could be performed if a suitable tissue source was identified. Xenotransplantation of porcine islets is a potential solution to this shortage.

Although in comparison to pigs, nonhuman primates are genetically closer to humans, but the pig remains the most suitable source of organs for humans due to a number of practical, safety, and ethical reasons [3]. With respect to the treatment of diabetes it is noteworthy that pig islets are known to be metabolically suitable, since pig insulin has for many years been used to treat diabetic patients; its structure differs from human insulin by only one amino acid residue. The implantation of xenogeneic tissue has provoked ethical and epidemiological controversies [4]. Balanced against the benefits of successful xenotransplantation is the possibility of transmission of porcine endogenous retroviruses (PERV) from porcine cells to the xenograft recipient, as infection of human cells has been demonstrated in vitro [5, 6]. However, neither PERV transmission nor clinical infection or disease have been observed in patients who have been exposed to living porcine tissues [7, 8].

The first clinical experience of porcine islet xenotransplantation into human patients was announced at the XIXth International Congress of...
the Transplantation Society in Miami in August 2002, that Gal-knockout pigs were born and were fully healthy and viable [14]. These pigs do not express Gal on their tissues and represent a major advance in the progress towards clinical trials of xenotransplantation. Organs of these pigs will be transplanted shortly into primates.

Xenotransplantation of islets presents some possible advantages over that of a whole organ. With non-vascularised grafts, such as islets, the absence of immediate vascularisation prevents contact between the recipient’s circulating natural pre-existing antibodies and the endothelial cells of the islets. Until recently, cellular immunity was believed to be predominant in the rejection of tissue xenografts [15, 16], but the exact mechanism remains incompletely understood. Long-term survival of pig [17] and human [18] pancreatic islets in athymic nude

Figure 1.
Purified porcine islets stained with dithizone.

Figure 2.
Immunosuppressive regimen in baboons receiving porcine islets included splenectomy, nonmyeloablative whole body irradiation, T cell depletion (with ATG or anti-thymocyte globulin), cyclosporine (CyA), mycophenolate mofetil (MMF), complement depletion with cobra venom factor, a course of an anti-CD154 monoclonal antibody and anti-pig antibody adsorption using a specific plasmapheresis technique prior to porcine islets transplantation (Tx).
mice suggests a T cell-mediated process, in which CD4+ T cells have been shown to play a major role [19]. However, the use of conventional immunosuppressive agents that block the T cell response in immunocompetent recipients allows only a modest prolongation of survival of xenografted islets [20].

Regarding experiments using pig-to-nonhuman primate models, we have transplanted porcine islets (figure 1) by intraportal injection to baboons receiving either conventional triple drug immunosuppressive therapy, or a more intensive regimen (figure 2), including depletion of T cells and complement, removal of anti-Gal antibodies by a specific plasmapheresis technique and the use of a new monoclonal antibody blocking T cell signaling (anti-CD154 monoclonal antibody) [21]. In the group receiving conventional immunosuppression, porcine C-peptide was detected only transiently after porcine islet injection, and histological examination of liver biopsies taken between days 2 and 19 did not reveal viable islets. In the group receiving more intense immunosuppression, porcine C-peptide was detected up to 5 days after transplantation. Biopsies showed viable islets up to day 14, but not thereafter, with a progressive mononuclear cell and macrophage infiltration. These results suggest that powerful immune responses are involved in rejection of discordant xenogeneic islets and that adequate immunosuppressive regimens still need to be developed.

Outlook on the future

The transplantation of animal cells and tissues into humans could play an important role in the treatment of a great variety of disorders that result from tissue loss or dysfunction, diabetes being the most common. The serious shortage of available human organs for transplantation will certainly favor new clinical xenotransplantation trials.

New immunosuppressive therapies are continuously developed and tested. Our preliminary results have shown that innate immune responses are involved in the rejection of pig islets in baboons. The use of macrophage-depleting agents such as gadolinium chloride, has allowed significant prolongation of xenoislet survival in rodent models [22]. Experiments investigating its efficacy will be performed in large animal models.

New monoclonal antibodies inducing T cell signaling-blockade, such as anti-CD154, have been shown to efficiently block allograft rejection in small and large animal models of organ and islet transplantation [23, 24]. Only a few reports have investigated the ability of costimulatory blockade to prevent xenograft rejection. Anti-CD154 monoclonal antibody therapy is able to delay T cell-mediated rejection of porcine skin grafts in mice [25] and also to block T cell-dependent antibody production in the pig-to-baboon model [21, 26].

FTY720 is a new molecule that interferes with the circulation of T cells and thereby prevents interaction of T cells with the graft [27]. FTY720 in combination with cyclosporine has been shown to prolong survival of xenotransplanted islets [28].

Xenotransplantation also offers the first real opportunity for modifying the donor as opposed to the recipient. This opens up great possibilities, particularly in this era of rapidly developing techniques such as genetic engineering, gene transfer and cloning. The pig tissue may be transgenic for one or more human complement-regulatory proteins and, ideally, would express no or little Gal. The breeding of a pig with a vascular endothelial structure against which humans have no preformed antibodies should be a major advance.

To achieve successful xenotransplantation it will probably be necessary to combine several therapeutic techniques and/or agents, as is the case with allotransplantation today. There will almost certainly be several steps of development, but clinical application could start within the near future.

References


11 Valdes-Gonzalez BA, Elliot RB, Dorantes LM et al. Porcine islet xenografts can survive and function in type 1 diabetic patients in the presence of both pre-existing and elicited anti-pig antibodies. Abstract presented at the XIXth International Congress of the Transplantation Society, Miami, USA 2002.


