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Review

Novel immunological strategies for islet transplantation

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ABSTRACT

Islet transplantation has been demonstrated to improve glycometabolic control, to reduce hypoglycemic episodes and to halt the progression of diabetic complications. However, the exhaustion of islet function and the side effects related to chronic immunosuppression limit the spread of this technique. Consequently, new immunoregulatory protocols have been developed, with the aim to avoid the use of a life-time immunosuppression. Several approaches have been tested in preclinical models, and some are now under clinical evaluation. The development of new small molecules and new monoclonal or polyclonal antibodies is continuous and raises the possibility of targeting new costimulatory pathways or depleting particular cell types. The use of stem cells and regulatory T cells is underway to take advantage of their immunological properties and to induce tolerance. Xenograft islet transplantation, although having severe problems in terms of immunological compatibility, could theoretically provide an unlimited source of donors; using pigs carrying human immune antigens has showed indeed promising results. A completely different approach, the use of encapsulated islets, has been developed; synthetic structures are used to hide islet alloantigen from the immune system, thus preserving islet endocrine function. Once one of these strategies is demonstrated safe and effective, it will be possible to establish clinical islet transplantation as a treatment for patients with type 1 diabetes long before the onset of diabetic-related complications.

Contents

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Introduction

The major treatment for patients with type 1 diabetes mellitus (T1D) is insulin therapy. Unfortunately, insulin treatment cannot fully prevent chronic complications related to T1D, even with intensive insulin treatment [1,2], and exposes patients, when tight control is searched, to the risk of dangerous hypoglycemia. Different clinical trials [3–5], showed that islet transplantation lead to long-term insulin independence and provide metabolic stability for patients with T1D, improve or stabilize diabetes-related complications, normalize glucose homeostasis and reduce hypoglycemic episodes [3–5]. Islet transplantation is currently performed through percutaneous intraportal injection of purified pancreatic islets in local anesthesia with a relatively safe and low invasive procedure compared with pancreas transplantation [6], suggesting the absence of major procedural obstacles to the spread of the technique.

Outcomes

More than 700 islet transplantation procedures have been performed worldwide (Fig. 1). Historical data from the islet transplant registry headed by the Giessen group showed rates of insulin independence of less than 20% at one year [7]. Clinical outcomes have changed in recent years with the introduction of safer and less toxic immunosuppressive protocols. As of 2000, this rate was increased by the introduction of a steroid-free protocol by the Edmonton group whose success was confirmed by a report in the New England Journal of Medicine [4]. Following the publication of the Edmonton protocol the interest in islet transplantation increased substantially and has received research support from the NIH and JDRF. A more recent publication of the Collaborative Islet Transplantation Registry (CITR) reported an improvement of insulin independence at three years after transplantation from a 27% (1999–2002) to 44% (2007–2010) [8]. In selected protocols insulin independence was observed in 50% of patients [8,9]. Shapiro and colleagues for instance reported 100% of insulin independence in 7 patients with type 1 diabetes and life-threatening hypoglycemia [3]. When compared to whole pancreas transplantation, islet cells transplantation shows reduced number of adverse effects [6], proving the potential for further expansion in these therapeutic area [9]. Islet transplantation is associated with better glycometabolic control if compared to intensive medical therapy [10], and slows the progression of advanced diabetic complications and improves the quality-of-life in the transplanted patients [10]. However, multiple islet infusions are required to sustain insulin independence and islet graft survival rates remain far below those of other grafts [6]. In the long term, while a partial islet function is often maintained for a long period of time, the insulin-free survival rate falls to 25–50% at 5 years, narrowing the window of clinical benefit (Fig. 2) [6,11–13]. Considering the potential advantages of islet transplantation on diabetic complications and the relatively low invasiveness of the procedure, much research has focused to make islet cell transplantation as successful as other solid organ transplantation [14]. In parallel with the development of new immunosuppressive regimen combinations, research has also concentrated on the development of tolerogenic protocols to obtain indefinite graft acceptance without immunosuppression. Indeed tolerance induction in islet transplantation is particularly challenging because the transplanted islet are subjected to both allo- and autoimmune response [15,16]. Moreover, chronic immune suppression in individuals with T1D is unacceptable because of the associated burden of malignancies, infections and nephrotoxicity.

Islet xenografts

Widespread application of β-cell replacement therapy for T1D requires a readily accessible source of insulin-producing cells. Xenotransplantation from porcine donors represents an attractive solution to the overwhelming problem of limited availability of human donors, but also allows for less variability in graft quality and manufacturing outcome. The achievement of graft acceptance across xenogenic barriers is challenging, but recent papers have contributed to dramatically improve this field [17,18]. One of the major obstacles to tolerance in xenobiology is the galactose α-1,3-galactose (Gal) epitope. Humans and nonhuman primates (NHP) have natural preformed antibodies directed against the Gal epitope as well as against non-Gal antigens that can cause hyperacute or acute humoral rejection [19,20]. Elimination of the Gal epitope prevented hyperacute rejection of pigs to NHP in a model of heart xenografts [21]. Unfortunately, the success has been less obvious with nonvascularized grafts (e.g., islets). Islet endocrine cells expressed Gal epitope to a lesser extent compared with other tissues (approximately ~5% of adult pig islet endocrine cells expressed Gal) [22]. Consequently, cultured xenoislets from genetically wild-type pigs transplanted intraportally into NHP seemed to undergo primarily cellular rejection [23]. Hering et al. reported in 2006 [17] the reversal of diabetes for more than 100 days in cynomolgus macaques after intraportal transplantation of islets from genetically unmodified pigs without Gal-specific antibody manipulation. Immunotherapy was based on anti-monoclonal antibodies to CD25 and CD154 plus a combination of FTY720 (or tacrolimus), everolimus, and leflunomide [17]. Graham et al. interestingly evaluated the data on long-term porcine islet xenograft survival in diabetic macaque, revealing some limitations such as chronic-mild hyperglycemia or absence of body weight gain and progressive body weight loss [24]. Another approach was proposed by Cardona et al. [18], who used a combination of anti-interleukin 2 receptor and anti-CD154 antibodies and maintenance with sirolimus and belatacept, a second-generation high-affinity derivative of CTLA4-Ig. Interestingly, this immunosuppressive protocol and the infusion of neonatal porcine islets into NHP resulted in sustained normoglycemia [18].

Encapsulated islets

The idea behind encapsulated islets is primarily to avoid antigen recognition and to protect islets from the immune response. Different groups have recently reported interesting data regarding the use of agarose- and alginate-encapsulated islets [25–27]. The passage of small molecules (such as insulin and glucose), but not of antibodies or large cells, is one of the promises held by the use of semipermeable membranes in islet encapsulation. This would effectively inhibit humoral- and T cell-mediated immunity to exert