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Review

Re-engineering islet cell transplantation

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ABSTRACT

We are living exciting times in the field of beta cell replacement therapies for the treatment of diabetes. While steady progress has been recorded thus far in clinical islet transplantation, novel approaches are needed to make cell-based therapies more reproducible and leading to long-lasting success. The multiple facets of diabetes impose the need for a transdisciplinary approach to attain this goal, by targeting immunity, promoting engraftment and sustained functional potency. We discuss herein the emerging technologies applied to this rapidly evolving field.

Contents

Abbreviations: DC, dendritic cells; ECM, extracellular matrix; ESC, embryonic stem cells; HSC, hematopoietic stem cells; MSC, mesenchymal stromal cells; PDMS, poly(dimethylsiloxane); PEG, poly-ethylene glycol; PERV, porcine endogenous retrovirus; PGA, poly(glycolic acid); PLA, poly(lactic acid); PLGA, poly(lactic*co*-glycolic acid); PLL, polycationic poly-L-lysine; PS, protamine sulfate; PSU, polysulphone; PTFE, polytetrafluoroethylene; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; Tregs, T regulatory cells.

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1. Introduction

1.1. Diabetes mellitus

Diabetes is a metabolic disorder characterized by elevated glucose levels in the blood (hyperglycemia). *Type 1 diabetes mellitus* (T1DM) is caused by an autoimmune-mediated destruction of the insulin-producing β-cells in the pancreatic islets [1]. *Type 2 diabetes mellitus* (T2DM) is associated with dyslipidemia, obesity, initial hyperinsulinemia and insulin resistance in target tissues (fat, liver and muscle), resulting in progressive islet cell dysfunction and ultimately in insulinopenia and need for exogenous insulin therapy [2]. Glycemic metabolism can be controlled, at least to a certain extent, by daily administration of exogenous insulin, frequent monitoring of blood sugar levels combined with diet and exercise. Achieving tight glycemic control is desirable in patients with diabetes [3]. Unfortunately, even with a careful insulin treatment based on the use of improved insulin formulations, infusion systems and continuous glucose monitoring systems, daily glycemic excursions are difficult to keep tightly in the normal range. Thus, chronic and degenerative complications, such as retinopathy, nephropathy, neuropathy, and atherosclerosis, still occur in a considerable fraction of patients with diabetes, contributing to the poor quality of life, reduced life expectancy and to the elevated medical costs associated with diabetes.

1.2. Restoration of physiologic metabolic control

Restoration of physiologic glucose metabolic control is highly desirable in patients with diabetes. Replacement of islet β-cells can be performed either by whole pancreas or isolated pancreatic islet transplantation. The experience of the last three decades supports the positive impact on metabolic control of the biologic replacement of β-cells *via* allogeneic islet and whole pancreas transplantation. Notably, islet transplantation requires less risky implantation approaches than invasive surgery. Moreover, the possibility of engineering the islet transplant to promote its engraftment and long-term function makes of islet transplantation an appealing therapeutic approach to restore β-cell function.

1.2.1. Islet transplantation

The *islet transplantation* procedure is currently performed with a minimally invasive approach consisting of a percutaneous cannulation of the portal vein, through which islets are infused into the recipient's liver [4–7]. This technique has been utilized since the 1970s mainly to prevent or ameliorate metabolic control in patients with chronic pancreatitis requiring pancreatectomy (autologous islet transplantation) [8,9], and to restore metabolic control in patients with unstable T1DM associated with frequent severe hypoglycemic episodes [7,10]. Recently, autologous islet transplantation has also been proposed for patients with resectable neoplastic lesions of the pancreas [11–14]. Clinical islet allogeneic transplantation trials performed in patients with brittle T1DM demonstrated restoration of metabolic control with complete independence from (when adequate islets are implanted) or dramatic reduction of exogenous insulin requirements (*i.e.*, transplantation of suboptimal islet numbers or development of graft dysfunction), as well as prevention of severe hypoglycemic episodes paralleled by improved quality of life [10,15,16]. Interestingly, preliminary data suggest improvement of diabetes complications following islet transplantation [10,17–19].

1.2.2. Current challenges of islet transplantation

Even though islet transplantation has become a promising clinical therapeutic option in recent years, several challenges currently limit its application to the most severe cases of unstable diabetes characterized by hypoglycemia unawareness and frequent debilitating, severe hypoglycemia, at times life-threatening. Amongst the key hurdles recognized to the widespread application of islet transplantation is the variable long-term success of intra-hepatic implantation, which may result from a combination of variables likely secondary to *lack of vasculature* in the early peri-transplant period and to *nonspecific inflammation* triggered by islet isolation and transplantation procedures, collectively resulting in reduced islet engraftment (β-cell death and functional impairment), as well as in triggering of adaptive immunity affecting graft survival.

Cadaveric human donor pancreata represent an unsustainable *source of transplantable islets* since variables related to donor (*i.e.*, age, sex, cause of death and duration of intensive care) and organ characteristics (*i.e.*, warm and cold ischemia, preservation technique utilized, presence of intra-parenchymal fat infiltration, *etc.*), islet isolation (*i.e.*, enzyme and purification methods) and culture conditions may yield quite disparate results in terms of islet integrity, numbers, potency and immunogenicity, all ultimately determining graft outcome after transplantation [20].

Development of reliable tests and algorithms able to predict the success of islet isolation and transplantation based on donor variables [20–22] or final cell product assessment [23–31] may be of assistance in achieving higher success rates after islet transplantation more reproducibly. However, even by refining and expanding donor selection criteria (*i.e.*, use of organ donation after cardiac arrest and marginal donors) and improving the efficiency of organ recovery, the number of pancreata suitable for transplant may fall short of the needs of the large patient population potentially benefiting of a biologic replacement of β-cell function.

Another challenge is the *immunosuppression* utilized in islet transplant recipients, which relies on agents that may impair tissue remodeling and neovascularization (*e.g.*, mTOR inhibitors) as well as affect β-cell function over time (*e.g.*, calcineurin inhibitors, amongst other). Moreover, the immunosuppression required to prevent rejection may not adequately target autoreactive immune responses, in turn allowing progressive loss of graft function to autoimmunity recurrence in patients with T1DM. Development of novel approaches to promote and enhance islet engraftment and long-term function, as well as to modulate immunity are needed to make islet transplantation a more reproducible therapeutic option in the near future.

1.3. Alternative sources for transplantable islet cells

Undeniably, there is an urgent need for *unlimited source of transplantable* '*islets*', which may come from xenogeneic donors (*e.g.*, porcine islet cells), conversion of adult or embryonic stem cells into endocrine pancreatic cells. Islet transplantation of islets obtained from *xenogeneic* donors is appealing. Porcine islets may represent a readily available source, and pilot human clinical trials have been attempted, with demonstration of transient function of implanted islets without adventitious effects related to