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Review

Insulin-secreting cells derived from stem cells: Clinical perspectives, hypes and hopes

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Abstract

Diabetes is a degenerative disease that results from the selective destruction of pancreatic β-cells. These cells are responsible for insulin production and secretion in response to increases in circulating concentrations of nutrients, such as glucose, fatty acids and amino acids. This degenerative disease can be treated by the transplantation of differentiated islets obtained from cadaveric donors, according to a new surgical intervention developed as Edmonton protocol. Compared to the classical double transplant kidney–pancreas, this new protocol presents several advantages, concerning to the nature of the implant, immunosuppressive drug regime and the surgical procedure itself. However, the main problem to face in any islet transplantation program is the scarcity of donor pancreases and the low yield of islets isolated (very often around 50%) from each pancreas. Nevertheless, transplanted patients presented no adverse effects and no progression of diabetic complications. In the search of new cell sources for replacement trials, stem cells from embryonic and adult origins represent a key alternative. In order to become a realistic clinical issue transplantation of insulin-producing cells derived from stem cells, it needs to overcome multiple experimental obstacles. The first one is to develop a protocol that may allow obtaining a pure population of functional insulin-secreting cells as close as possible to the pancreatic β-cell. The second problem should concern to the transplantation itself, considering issues related to immune rejection, tumour formation, site for implant, implant survival, and biosafety mechanisms. Although transplantation of bioengineered cells is still far in time, experience accumulated in islet transplantation protocols and in experiments with appropriate animal models will give more likely the clues to address this question in the future.

Keywords: Diabetes; Stem cells; Insulin secretion; Islets of Langerhans; Transplantation

Contents

Abbreviations: ASCs, adult stem cells; BB rat, biobreeding rat; CTLA4, co-stimulatory receptors for T-cell activation; EBs, embryoid bodies; ECCs, embryonal carcinoma cells; ENSA, α-endosulphine, an endogenous regulator of the K_{ATP} channel; ESCs, embryonic stem cells; FADD, Fas-associated death protein; GAD, glutamic acid decarboxylase; GFP, green fluorescent protein; GVHD, graft versus host disease; IGRP, islet-specific glucose-6-phosphatase-related protein; IL, interleukin; INF-γ, interferon-γ; iNOS, inducible nitric oxide synthase; LIF, leukaemia inhibitory factor; MHC, major histocompatibility complex; NFAT, nuclear factor of activated T-cells; NO, nitric oxide; NOD mouse, nonobese diabetic mouse; SSEA, stage-specific embryonic antigens; SOD, mitochondrial superoxide dismutase; TGF-β, transforming growth factor-β; TNF-α, tumour necrosis factor-α; ZDF rat, Zucker diabetic fatty rat.

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1. Introduction

Diabetes is a degenerative disease in which the destruction of pancreatic β-cells leads to persistent hyperglycaemia [1]. Adult β-cells are located in the islets of Langerhans in the pancreas, and are specialized in insulin production and nutrient sensing coupled to hormone secretion. Therefore, insulin is secreted by the β-cell in response to glucose (the main secretagogue), fatty acids and amino acids, and this response is modulated by certain neuronal signals, hormones and pharmacological agents [2–5]. Insulin participates in nutrient uptake (mainly glucose) from blood into muscle, liver and fat tissues, allowing the recovery of normoglycaemia. Diabetic people fail to produce insulin or they produce insufficient amounts to control body glycaemia. Depending on the underlying causes, there are two types of diabetes: type 1 and type 2 [1].

Type 1 diabetes is due to an autoimmunological attack towards pancreatic β-cells. Type 2 is a more complex pathology presenting a progression from insulin resistance of muscle and fat tissue to a failing compensatory secretion by the β-cells. At the end of this process, the β-cell activates several apoptotic programs that culminate in cell death and insulin absence, evolving to a pathological entity closest to type 1 diabetes [1]. Other less frequent forms of diabetes include gestational diabetes, monogenic forms of diabetes (MODY: maturity onset diabetes of the young), type 2 autoimmune diabetes (LADA), etc. [1].

Daily insulin injections are necessary for patient survival, mainly in the case of type 1 diabetes. However, very often, diabetic people develop long-term complications, such as neuropathy, nephropathy, retinopathy and cardiovascular disorders, due to the poor glycaemic control that this palliative method exerts [1].

1.1. Type 1 diabetes

Although the consequence of the autoimmune attack in type 1 diabetes is obvious, the starting causes that activate the immune response are still not clear. This information could be relevant in all autoimmune diseases susceptible to receive an implant because it should determine the immunosuppressive post-surgery regime in the patient. There are two distinct phases in the progression of type 1 diabetes. The first phase, called insulitis, is characterized by the invasion of islet tissue by a population of leukocytes (T-lymphocytes) in the islet tissue. Insulitis occurs only when β-cell is present, indicating that this is a specific β-cell-targeted process. The second phase corresponds to β-cell destruction and the subsequent lack of insulin [6,7].

Diabetogenic T-cells are classified into two classes: $CD4^+$ helper and $CD8^+$ cytotoxic. Both respond in different ways to autoantigens generated mainly, but not exclusively, in the pancreatic β-cell. For $CD4^+$ cells, these antigens are presented by the class II major histocompatibility complex (MHC), found on specialized antigen-presenting cells such as dendritic cells. For $CD8^+$ cells, the antigens are presented by class I MHC, which are found in the majority of somatic cells [6].

The causes that initiate the autoimmune process are still poorly characterized, but it is believed that T-cells encounter the autoantigens in the islet tissue or in lymph nodes draining islets. To this end, a wave of β-cell death is required at the juvenile stage, allowing the engulfment of cell debris by dendritic cells present in islets. These cells migrate and present the antigens to circulating T-cells that become activated and migrate across tissues to reach the islets [8].

In this context, MHC molecules (HLA in humans) play an important role. The HLA region is a cluster of 200 genes located in chromosome 6, which encodes for cell surface glycoproteins that allow the immune system to discriminate between own cells from “alien” cells (including viruses, bacteria and implants). The function of these glycoproteins is to display peptides that are the result of the proteolysis from intracellular proteins to antigen receptors located on the surface of $CD4^+$ and $CD8^+$ T-cells. The regions that encode the HLA class I and class II molecules are highly polymorphic, leading to many different variants. Class I molecules are encoded by genes within the A, B and C loci, expressed in all cells. Class II