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Beta-cell replacement for insulin-dependent diabetes mellitus ☆

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Abstract

Beta-cell replacement is considered the optimal treatment for type 1 diabetes, however, it is hindered by a shortage of human organ donors. Given the difficulty of expanding adult beta cells in vitro, stem/progenitor cells, which can be expanded in tissue culture and induced to differentiate into multiple cell types, represent an attractive source for generation of cells with beta-cell properties. In the absence of well-characterized human pancreas progenitor cells, investigators are exploring the use of embryonic stem cells and stem/progenitor cells from other tissues. Once abundant surrogate beta cells are available, the challenge will be to protect them from recurring autoimmunity.

Keywords: Beta-cell transcription factors; Cell encapsulation; Cell transplantation; Insulin production and secretion; Islet regeneration; Stem cells

Contents

1. Introduction

Diabetes mellitus (DM) is an excellent example for a disease which can benefit from cell therapy. DM consists of two diseases with distinct etiology. Type 1 (insulin-dependent) diabetes, which afflicts about 0.5% of the population, is caused by autoimmune destruction of the pancreatic islet insulin-producing beta cells. In

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contrast, type 2 diabetes results from insulin resistance in muscle, fat, and liver, coupled with inadequate compensation by beta-cell mass and function for the increased insulin demands. The incidence of type 2 diabetes is about 10-fold higher, compared with that of type 1, and is constantly increasing due to modern diet and sedentary life style. In both diseases untreated hyperglycemia leads to microvascular damage in major organs. The current treatments for both types of diabetes delay but do not prevent the microvascular disease, leading in the long run to complications, including heart disease, stroke, blindness, kidney failure, and limb amputations. In type 1 diabetes the difficulty of adjusting the precise amounts of administered insulin to changing physiological conditions results in episodes of hypo- and hyperglycemia. Type 2 diabetes is treated in the first years following diagnosis by diet, exercise, and drugs that stimulate insulin secretion from β cells, reduce hepatic glucose output, and increase insulin sensitivity in target cells. However, about half of type 2 diabetes patients eventually require exogenous insulin. Current research efforts towards therapy of type 1 diabetes are aimed at development of approaches for restoration of regulated insulin supply. This review will focus on type 1 diabetes, however part of the approaches described here may also be of benefit to patients with type 2 diabetic requiring insulin. Due to insulin resistance, the emphasis in type 2 diabetes is on providing an abundant source for a constant insulin supply, rather than on tight regulation of blood insulin levels, which is the main concern in type 1 diabetes.

One way for improving current means of insulin delivery is the so-called "artificial pancreas". This device would include an insulin pump connected in a closed loop to a glucose sensor, which would continuously adjust the amounts of insulin released by the pump. However, besides the mechanical difficulties in wearing such devices, the reliability of glucose sensors is still insufficient to allow "closing of the loop".

At present, replacement of damaged beta cells through regeneration or transplantation represents the most promising approach for a cure of type 1 diabetes. This approach faces a dual challenge: generation of a sufficient mass of cells producing adequate amounts of insulin and releasing it in response to normal physiological signals, and protecting these cells from recurring autoimmunity. To be clinically useful, any cell-based therapy would have to represent a significant advantage in safety and efficacy over the current treatment of insulin administration.

2. Islet regeneration

In a normal adult pancreas a slow rate of beta-cell renewal is responsible for the maintenance of an adequate beta-cell mass. This rate is accelerated in conditions of increased demands for insulin, such as pregnancy [1] and obesity [2]. Beta-cell renewal may also occur in early stages of type 1 diabetes, however newly-formed beta cells would likely be destroyed by the immune system, eventually leading to depletion of the sources for cell renewal. It is not known whether beta-cell renewal in the adult human pancreas relies on replication of differentiated beta cells, or neogenesis from pancreatic progenitor cells. Work in a mouse model provided support for the view that homeostatic beta-cell renewal, as well as islet repair in response to damage, occurs from cells which already express insulin [3]. If this is also the case in human pancreas, the residual beta-cell mass in patients newly-diagnosed with type 1 diabetes may be stimulated to form more beta cells. This prospect depends on understanding the normal renewal process in detail at the molecular level, an ability to deliver locally proteins or genes involved in beta-cell regeneration, and means to prevent recurring autoimmunity. A number of hormones and growth factors are known to stimulate rodent beta-cell renewal [4]. One such factor is exendin-4, a stable analog of glucagon-like peptide 1 (GLP-1), which has been shown to stimulate both beta-cell neogenesis and replication in a rat model of type 2 diabetes involving partial pancreatectomy [5]. In a work using Goto–Kakizaki rats, a non-obese model of type 2 diabetes, injections of GLP-1 or exendin-4 increased the beta-cell mass, resulting in long-term improvements in glycemia [6]. GLP-1 is a particularly attractive candidate because of its additional stimulatory effects on glucose-induced insulin secretion from beta cells [7]. Another example is a combined treatment with epidermal growth factor (EGF) and gastrin, which was shown to increase beta-cell mass and reduce hyperglycemia in rats treated with streptozotocin (STZ) [8] and mice treated with alloxan [9], 2 agents with preferential toxicity to beta cells. Despite these encouraging results, such factors are unlikely to be suitable for systemic treatment due to pleotropic effects in other tissues.

3. Islet transplantation

Beta-cell transplantation may allow ex vivo manipulation of cell immunogenicity and resistance to immune responses in ways which are not possible in islets regenerated in vivo. Pancreas transplantation, although quite successful, represents a rather invasive intervention, which is restricted to patients with advanced complications, requires constant immunosuppression, and is severely limited by donor availability [10]. Progress in human islet isolation and in immunosuppression protocols resulted in restoration of euglycemia in patients that received islets from 2–3 pancreas donors [11]. However, a 5-year follow-up showed that only 10% of the transplanted patients maintained insulin independence [12]. This was due primarily to the difficulty to preserve islet function, and to toxicity of immunosuppression. The requirement of multiple donors to provide a sufficient number of islets for a single recipient emphasizes the need for generation of an abundant source of beta cells for transplantation.

4. Islet expansion in vitro

One obvious approach for obtaining more islet cells is expansion of adult donor islets in tissue culture. However, despite their ability to expand in vivo, islet expansion in vitro has been quite difficult. Adult human islet cells grown on HTB-9 matrix in the presence of hepatocyte growth factor were shown to proliferate for a limited number of population doublings, after which they underwent senescence [13–15]. The replication span could not be extended by expression of the catalytic subunit of human telomerase (TERT), which was introduced into the cells with a retrovirus [16]. However, the major problem in these