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Introduction

From substitution of insulin to replacement of insulin producing cells: New therapeutic opportunities from research on pancreas development and stem cell differentiation

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Diabetes mellitus type 1 results from autoimmune destruction of insulin producing β-cells in the pancreatic islets. According to recent statistics of the Centers for Disease Control (CDC) 1.2 million children and adults in the USA have type 1 diabetes and worldwide 5–10% of all patients with diabetes are affected. Prior to the introduction of insulin into diabetes therapy, the loss of β-cells with consecutive lack of insulin was equal to a death sentence for these mostly very young patients. The discovery of insulin by Banting & Best in 1921 and the treatment of the first patient just a few months later in January 1922 represent milestones in medicine [1] and were granted the Nobel award in 1923. Thereafter, patients with access to insulin no longer had to die because of acute diabetes complications, provided they delivered the necessary amount of insulin. However, they were able to experience late complications of diabetes, including diabetic retinopathy with blindness, as well as other micro- and macrovascular complications leading to leg amputations, end stage renal disease, premature myocardial infarction and reduced total life expectancy [2]. Better diabetes control aiming for near normal glucose values with an intensified insulin treatment has the ability to avoid or retard these typical diabetic complications as shown in two landmark studies in 1993 [3,4]. Because of the significant variability of plasma glucose values in patients with type 1 diabetes the strategy of such an intensified insulin therapy is associated with a high frequency of severe hypoglycaemia defined as hypoglycaemic event requiring third party assistance. In the DCCT study it reached 70 events per 100 patient years, i.e. almost one severe hypoglycaemic event per year for each patient [3]. A structured patient education program combined with frequent self-monitored blood glucose is able to reduce hypoglycaemic events considerably while maintaining a reasonable diabetes control [5–8]. Similar improvements in the reduction of severe hypoglycaemic episodes with an acceptable glucose control were described for the use of an insulin pump system combined with a continuous glucose monitoring system [9]. First small clinical trials of the so-called artificial pancreas, where measured subcutaneous glucose autonomously regulates subcutaneous insulin delivery via a pump -with or without

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co-infusion of glucagon-showed some improvements in glucose control, but there still were hypoglycaemic events and significant variation of blood glucose values [10,11].

On the whole the treatment principle for type 1 diabetes i.e., substitution of the missing insulin, did not change since 1922, although the ways to do it improved notably in the past 93 years. Unfortunately, even the best technology available today cannot match the ingenious metabolism secretion coupling system of the pancreatic β-cells which continuously monitor glucose values and adapt insulin release accordingly. The replacement of the pancreatic β-cells either by pancreas transplantation or by transplantation of pancreatic islets has been able to normalize blood glucose and even improve already existing complications of diabetes [12]. Insulin independence after 5 years following islet transplantation can be achieved today in up to 55% of patients with a new modified immune suppression strategy, according to recent studies [13,14]. A wide application of organ transplantation, however, is limited by a shortage of donor organs and the necessity for life-long immune-suppressive treatment to prevent organ rejection.

Apart from organ transplantation the creation of new functional β-cells from existing precursors or stem cells could represent an alternative replacement strategy (for general review see also [15]). The potential sources for the development of such functional β-cells are illustrated in Fig. 1.

Creation of pancreatic β-cells from embryonic or pluripotent stem cells following natures' hints

The isolation of human embryonic stem cells (ESC) in 1998 [16] and later the discovery of the reprogramming abilities of somatic cells into induced pluripotent stem cells (iPS) in mice and men

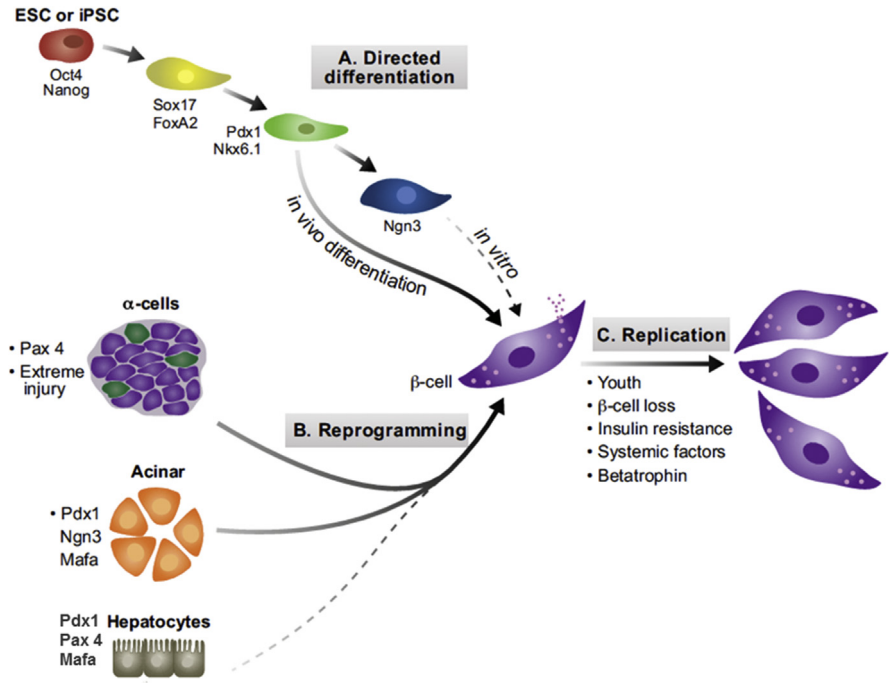

Fig. 1. Strategies to generate new β-cells (adapted from [15], with permission of the author). (A) Directed differentiation using growth factors and small molecules can guide a pluripotent stem cell (red) through the stages of pancreatic differentiation in a manner that mimics normal development. A subset of important genes expressed at each stage is listed. (B) Reprogramming of terminally differentiated cell types, such as acinar or α-cells, can be used to generate β-cells *in vivo*, using the overexpression or injury strategies listed. Reprogramming human hepatocytes into insulin secreting cells was recently described using sequential activation of genes listed [47] (C) Inducing the replication of existing β-cells. Replication may be recapitulated *in vitro* or induced *in vivo* with new small molecules or proteins, factors listed.