Review

MOLECULAR METABOLISM

Islet cell plasticity and regeneration

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ABSTRACT

Insulin-dependent diabetes is a complex multifactorial disorder characterized by loss or dysfunction of β-cells resulting in failure of metabolic control. Even though type 1 and 2 diabetes differ in their pathogenesis, restoring β-cell function is the overarching goal for improved therapy of both diseases. This could be achieved either by cell-replacement therapy or by triggering intrinsic regenerative mechanisms of the pancreas. For type 1 diabetes, a combination of β-cell replacement and immunosuppressive therapy could be a curative treatment, whereas for type 2 diabetes enhancing endogenous mechanisms of β-cell regeneration might optimize blood glucose control. This review will briefly summarize recent efforts to allow β-cell regeneration where the most promising approaches are currently (1) increasing β-cell self-replication or neogenesis from ductal progenitors and (2) conversion of α-cells into β-cells.

Keywords Diabetes; Islet architecture; β-cell regeneration; β-cell proliferation; β-cell neogenesis; Pancreas plasticity

1. β-CELL DEGENERATION AND REGENERATION

Diabetes mellitus is a metabolic disorder characterized by progressive loss or dysfunction of pancreatic insulin-producing β-cells. This results in hyperglycemia causing multiple complications and organ damage. Although diabetes is manageable, β-cell failure is progressive and no definitive curative treatment has yet been found for both major forms of diabetes. In type 1 diabetes mellitus (T1DM), deficit of insulin is caused by autoimmune destruction of β-cells. The only available curative therapy for T1DM is the replacement of the lost β-cell mass by islet transplantation from cadaveric donors [1]. Due to the shortage of transplantable material, *in vitro* generation of β-cells from an unlimited source of self-renewing stem cells, such as embryonic stem cells, might be an alternative approach [2]. However, until now no functional mature β-cells can be efficiently generated from stem cells *in vitro*. Thus, a major effort is on the way to improve differentiation protocols in order to increase transplantable material to allow successful cell-replacement therapies in the future.

Type 2 diabetes mellitus (T2DM), generally results from high insulin demand due to the insulin resistance of the peripheral tissues triggering β-cell mass expansion and hyperinsulinemia. This in turn leads to gradual β-cell exhaustion and dysfunction (insulin secretion defects), and eventually instigates loss of β-cell mass by apoptosis [3–7]. Recently, de-differentiation of mature insulin-producing β-cells to a "naïve" status has been reported as a novel mechanism of β-cell failure in T2DM [8]. Thus, the only way for a better treatment of insulin-dependent T2DM patients is to replace or regenerate the lost or dysfunctional β-cell mass. This could be achieved by triggering β-cell proliferation or neogenesis, reversing β-cell de-differentiation or blocking β-cell apoptosis [9–12]. However, this requires a thorough understanding of the natural and diseased islet cell niche and the signals and factors that influence β-cell degeneration and regeneration.

2. ISLET ARCHITECTURE AND NICHE

Adult murine pancreatic islets are constituted of 70–90% insulin-producing β-cells, surrounded by α-, δ-, ε-, and PP-cells secreting glucagon, somatostatin, ghrelin and pancreatic polypeptide, respectively [13,14]. These different endocrine cell types are the main regulators of nutrient metabolism and glucose homeostasis. Of note, islet architecture is highly variable from species to species [15]. In rodents for example, β-cells are located in the core of the islet, whereas in humans they are intermixed with other endocrine cell types [16,17]. In mice, β-cells are organized in polarized rosette-like structures around the islet capillaries, which provide oxygen and nutrient and collect hormones secreted by the islet endocrine cells into the blood stream [18–20]. Interaction between blood vessels and pancreatic progenitor cells takes place early during development where neighboring tissue interactions are essential for organ differentiation [21]. During adulthood, islet endothelial cells secrete several growth factors, such as hepatocyte growth factor (HGF) and connective tissue growth factor (CTGF), that together with a specialized extracellular matrix (ECM) control and support β-cell function and proliferation [22]. Interconnection between ECM, cell–cell adhesion and gap junctions maintains β-cells in higher three dimensional (3D)

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order which is crucial to coordinate their function [14]. For example, loss of the gap junction protein Connexin-36 is linked to impaired glucose sensitivity in mice and to increased the susceptibility for T2DM in humans [23,24]. Thus, 3D islet cell architecture with its intricate neighboring cell types and ECM interaction makes it likely to believe that the islet resembles an important niche for β-cell function, growth and homeostasis.

Apical-basal (AB) and planar cell polarity (PCP) of the different islet cell types is required as a base for this higher order 3D organization and function in the islets. One such protein, which regulates AB polarity and energy metabolism in different organs, is Liver Kinase B1 (Lkb1). Lkb1 is a serine threonine kinase that is highly conserved among different species [25,26]. Conditional deletion of Lkb1 in pancreatic tissue, display histological alteration in rosette-like structures of β-cells around the islet capillaries, suggesting that Lkb1 and its targets orchestrate β-cell polarity [27]. Moreover, it has been observed that the loss of Lkb1 leads to increased β-cell volume, improved glucose tolerance in the high-fat diet mouse model and increased proliferation of insulin-producing cells [28]. Thus, for an ordered arrangement of cells in a 3D space both AB and PCP are absolutely required. This is well supported with the presence of PCP proteins already at embryonic day (E) 11.5 in pancreatic epithelial progenitors. Celsr2 and Celsr3 are important PCP core components and their ablation lead to impaired β-cell differentiation from endocrine progenitors during fetal life [29]. Further evidence demonstrating the relevance of PCP in mature islets comes from a study focusing on the role of the Activating Transcription Factor 2 (ATF2). Han and colleagues demonstrated that ATF2, which is involved in Wnt/PCP signaling during morphogenesis [30], plays an important role in the regulation of insulin gene expression in mature islets. ATF2 interacts with key β-cell transcription factors such as MAFA, PDX1 and BETA2 [31]. Altogether, besides classical signaling pathways and growth factors such as Wnt, Hedgehog, Notch etc. known to control β-cell homeostasis, a new light has been shed on islet architecture and its components as factors regulating β-cell function. Thus, it is very likely that 3D architecture of the islet niche actively contributes to preserve β-cell function and if disturbed, might trigger compensatory regenerative mechanisms.

3. CELLULAR PLASTICITY IN THE PANCREAS: CAN WE HARNESS MECHANISMS OF CELLULAR PLASTICITY FOR REGENERATION?

Genetic analysis of endocrine and exocrine cells within the pancreas reveals a certain degree of cellular plasticity under pathological or experimental conditions, which is summarized in Figure 1 and will be discussed in the following sections. Cellular plasticity is defined by the capacity of a specialized cell type to convert into another cell type to compensate for the loss of cellular or systemic function. Thus, the inter-conversion of pancreatic cells into β-cells might be harnessed for novel regenerative therapies.

Lately, several studies have focused their efforts on the generation of β-cells from other pancreatic cells by expressing key transcription factors regulating β-cell development [32–35]. In 2008, Zhou et al. reported the ability of exocrine cells to be reprogrammed directly into insulin-producing β-cells *in vivo*, without cell replication or reversion into a progenitor-like stage [36]. By inducing ectopic expression of a subset of

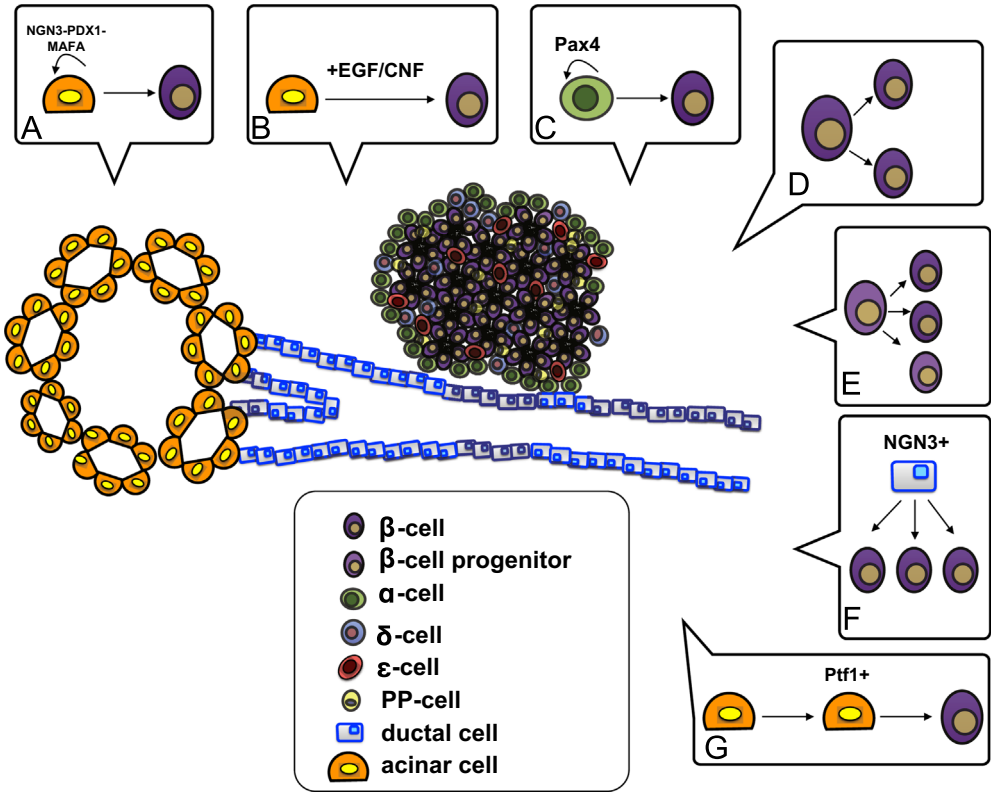

Figure 1: Potential ways of β-cell regeneration. (A) Ectopic expression of NGN3, PDX1 and MAFA in acinar cells triggers the formation of new β-like cells. (B) EGF and CNF treatment triggers the conversion of acinar cells into β-like cells. (C) Ectopic expression of Pax4 in α-cells drives their conversion into β-cells. (D) Proliferation of pre-existing mature β-cells. (E) β-cell regeneration from intra-islet multipotent pancreatic progenitors. (F) Neogenesis of β-cells from NGN3+ ductal progenitors. (G) β-cell regeneration from Ptf1+ acinar endocrine progenitors.

