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Pancreatic β-Cell Dysfunction in Diabetes

Ansarullah[1] and A. V. Ramachandran[2*]

[1]The Jackson Laboratory, Bar Harbor, 04609, Maine, USA
[2]School of Science, Navrachana University, Vadodara - 391410, Gujarat, India;
avramachandran@nuv.ac.in

Abstract

The decline in functional β-cell mass and β-cell dysfunction causes diabetes. Pancreatic β-cells play a fundamental role in controlling the glucose milieu, and β-cells of diabetic patients poorly respond to glucose. The mechanism underlying the pathology of impaired β-cell function is a unique challenge. This concise review summarizes the identity of β-cells during the progression and established diabetes. Understanding β-cell heterogeneity and the dynamic functional state during health and disease progression would be important for designing diabetes therapeutics to restore the β-cell mass by cell-replacement or regeneration approaches.

Keywords: β-Cell Dedifferentiation, β-Cell Dysfunction, β-Cell Identity

1. Introduction

Diabetes Mellitus was termed based on the Greek word *diabainein,* which means 'siphon' (passing through), and the Latin word *mellitus* meaning sweet[1]. Insulin was discovered almost 100 years ago and is probably one of the most impactful and breakthrough discoveries in medicine. It serves as a therapeutic intervention to treat people who have diabetes. In 1923, Frederick Banting and John Macleod received the Nobel Prize for their remarkable discovery of insulin, with the discovery to which Charles Best and James Collip contributed[2].

Diabetes is a chronic disease with a global prevalence of 9% (463 million) according to the International Diabetes Federation and is projected to rise to 642 million by 2040[3]. Type 2 diabetes (T2D) results from a genetic predisposition. It is associated with progressive β-cell failure, resulting from decreased insulin secretion and decreased functional β-cell mass[4,5]. The molecular mechanisms of β-cell failure and compensation during increased metabolic demand have been documented; however, it remains unclear. Literature report suggests that one of the major pathophysiological mechanisms for developing T2D is β-cell dysfunction and there is growing evidence that demonstrates β-cell dedifferentiation as the aetiology of decline in β-cell mass and function[6]

The biology of insulin-producing β-cell is quite complex since it combines inhibitory and stimulatory signals to elicit a secretory response. Maintaining adequate β-cell mass is critical to metabolic demand, which is firmly regulated by an equilibrium between β-cell proliferation, dedifferentiation, and death. Whether β-cell mass (product of β-cell size and number) is related to β-cell secretory capacity (or secretory dysfunction) – remains debatable.

2. β-Cell Maturation

Paul Langerhans first described the islets of Langerhans in 1969. The pancreatic islets comprise a heterogeneous mixture of endocrine cells (alpha cells-secreting glucagon, beta cells-secreting insulin, delta cells– secreting somatostatin, gamma cells– secreting ghrelin and PP cells– secreting pancreatic polypeptide) that coordinate blood glucose homeostasis.

**Author for correspondence*

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The mice β-cells comprise 50-75% of the total islet mass compared to 60-80% in humans and exist as heterogeneous subpopulations varying in their functionality and maturation state[34]. The Glucose-Stimulated Insulin Secretion (GSIS) is the gold standard, a functional feature of mature adult β-cells, which demonstrates the capability of β-cells to secrete precise amounts of insulin in response to glucose and serves as a marker of β-cell function.

Pancreatic β-cells are formed from embryonic stem cells through a process of differentiation that involves a highly coordinated program regulating (either activation or inhibition of) transcription factors in a temporal fashion that drives the transition from endoderm-multipotent precursor to fully mature β-cells[7,8]. While the β-cell differentiation process is not unidirectional, studies show that under chronic stress conditions, β-cells can lose their functional maturity to a differentiated phenotype and go back to a progenitor precursor-like state[9–11] (Figure 1(a)).

The β-cell maturation has not been studied extensively, and most data come from neonatal mice pancreas development. Maturation in mice occurs during the birth to postnatal weaning stage, and β-cells that follow a biphasic maturation pattern have been ascribed to neonatal diet adaptation. During these maturation stages, β-cells acquire transcriptional machinery required for β-cell identity[12–14].

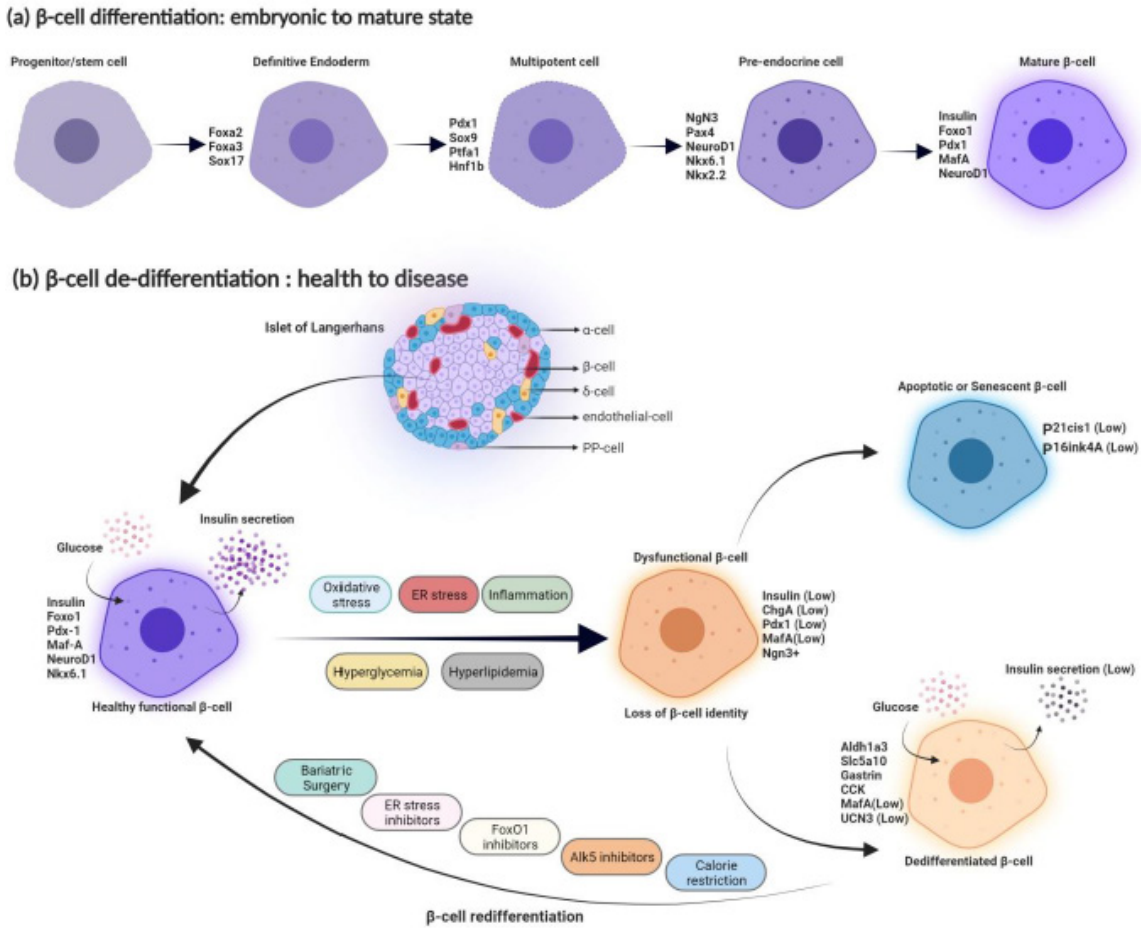

Figure 1. **(a)** Schematic representation depicting various stages during the process of β-cell differentiation involving activation and inhibition of transcription factors which turns on the switch from an embryonic precursor to a fully functional mature β-cell state. **(b)**. Schematic representation displaying healthy adult islets with different endocrine cell types. Healthy functional β-cells exhibiting mature functional transcription factors robustly respond to glucose stimuli (purple), dysfunctional β-cells display loss of β-cell identity markers (orange), dedifferentiated β-cells display low insulin secretion (pale orange), and senescent β-cell (blue).

3. β-Cell Glucotoxicity

An impressive clinical study carried out by Brunzell *et al.* reported that a meager increase in glucose levels was associated with blunt glucose-stimulated insulin secretion[15]. Under normal conditions, β cells are within the glucose range of 70–130 mg/dL and maintain biphasic functionality; however, they can undergo phenotypic and functional changes even with a mild hyperglycemic milieu.

To maintain glucose homeostasis in the background of insulin resistance, β-cell over-work to release higher insulin levels. This is seen during the progression of either type of diabetes. While there have been considerations regarding the loss of glucose-induced first-phase insulin secretion in diabetes progression, the underlying mechanisms are yet to be clarified[16,17]. The conventional concept of glucose toxicity in the field of diabetes is quite comprehensive, wherein the β-cells demonstrate profound changes in gene expression, derangements in insulin secretion and functionality under high-glucose conditions, and are reversed under a normoglycemic state. An important question arises - how does impaired insulin action (on insulin-target tissues) cause increased insulin secretion during the early onset of diabetes? Additionally, it is challenging to understand how β-cells cope with and compensate for insulin resistance when glucose levels are slightly altered. While the mechanism for understanding these events is limited, we think there must be some feedback mechanism between insulin secretion from β-cells and insulin target tissues.

Glucotoxicity leads to β-cell dedifferentiation during hyperglycemia and reduces

the expression of β-cell enrichment genes such as key transcription factors and genes that encode insulin, glucose metabolism, protein processing, and secretory pathways, as

well as upregulation of genes that are suppressed or expressed at low levels in normal β-cells, including forbidden and progenitor cell genes. Under various stress conditions,

mature β-cells may lose their differentiated phenotypes and return to a less differentiated or even a progenitor cell state. β-Cell dedifferentiation is a potential adaptive mechanism to escape cell death during physiologic stress[8].

4. β-Cell Dedifferentiation: Loss of Identity

β-Cell dysfunction is sufficient to cause hyperglycemia, and multiple mechanisms are involved in the progression of diabetes. However, there has been a paradigm shift over the last decade wherein the consensus is that the β-cell identity is no longer thought to be permanent, and alterations in β-cell identity may contribute to the pathophysiology of impaired insulin secretion in T2D. The mechanisms underlying the loss of β-cell identity are not completely understood. Therefore, they are a promising avenue for developing pharmacological targets for restoring β-cells to a mature and functional state. In a neat study by White *et al.*, it was found that many insulin-positive cells were co-positive for glucagon or vimentin (mesenchymal marker) in the pancreatic sections of human T2D, thereby showing disrupted β-cell identity[18].

β-Cell dedifferentiation is called 'loss of mature/differentiated β-cell markers' and is sometimes termed 'degranulated cells'. β-Cell dedifferentiation is displayed by a reduction in the expression of β-cell-identity maturity (MafA, UCN3) and functionality genes (Pcsk1, Glut-2, Gck), which include transcription factors (FoxO1, Pdx1, NeuroD1, NKx6.1, and Nkx6.2), glucose metabolism genes, exocytosis, and secretory pathway genes, and upregulation of β-cell disallowed genes (HK1, Mct1, Ldha) and immature genes (CD81)[19–22]. During this process, when β-cells lose their identity, they acquire a distinct signature termed the dedifferentiation markers, of which Aldehyde-dehydrogenase 1 A3 (Aldh1a3) is a quite prominent one[10,23,24]. (Figure 1(b)).

β-Cell dedifferentiation has been well documented in diabetic mouse models and human pancreas samples to identify the pathways that render β-cells to lose their mature functional phenotype under high-glucose and lipid insults. β-Cell dedifferentiation has been referred to as the dysfunctional β-cells, which have reverted to an embryonic or progenitor-like state[10, 25–28]. For example, when the transcription factor FoxO1 is deleted, this results in β-cell dedifferentiation, displaying loss of markers and insulin expression, thereby switching to a progenitor-like cell state[10]. In corroboration of these data, transcription factors like NKx6.1 and FoxO1 have been reported to be weakly expressed in diabetic human islets[29] (Figure 1(b)).

Cellular senescence is a phase of irreversible cell-cycle arrest. This is closely related to β-cell failure, wherein the cells stop dividing yet remain metabolically active with an altered phenotype. While this field is still new, there are very few markers (p16Ink4a, p21Cis1) of β-cell senescence, and they activate a pro-inflammatory secretome called a senescence-associated secretory phenotype (SASP)[30,31]. Importantly, what pathways regulate β-cell senescence and why only a subset of cells acquire SASP remains to be researched (Figure 1(b))

5. Targeting β-Cell Dedifferentiation

With the advent of single-cell RNA sequencing technologies, it is well established that pancreatic β-cells are heterogeneous and there are transcriptomic differences between β-cell subpopulations (based on their maturity, immaturity, dedifferentiated and exocytosis properties). So, the most important question is whether targeting dedifferentiated β-cells can restore β-cell functionality. Which sub-population of β-cells should be targeted? Whether redifferentiated cells could acquire full potential or they could revert to a dedifferentiated state?

Recently, Kubicek and colleagues demonstrated, using a high-content screening model, wherein they target FoxO1 inhibition to model β-cell dedifferentiation and identified loperamide as a small molecule that could stimulate insulin protein processing and secretion in diabetic islets[32]. In another study using a mouse model of severe diabetes (displaying features of β-cell dedifferentiation), the authors treated the diabetic mice with a combination of insulin and GLP-1-estrogen conjugate. They demonstrated that dedifferentiated β-cells could be protected from ER stress-mediated cell death and restore β-cell functionality[11].

Furthermore, using the scRNA approach, we modeled β-cell dedifferentiation in morbidly obese and overt diabetic db/db mice. We then carried out Vertical Sleeve Gastrectomy (VSG) in these mice and found that VSG improved glycemia and functional β-cell mass and induced β-cell redifferentiation and proliferation to expand β-cell mass to adapt to the insulin demand[33].

6. Conclusions

Over the years, our understanding of β-cell biology has significantly improved, especially with the studies employing single-cell RNA technologies. Spatial transcriptomics combined with functional studies helps uncover the pathomechanisms underlying β-cell failure during diabetes progression, which have enabled researchers to mine for specific markers, signaling pathways, and networks. This information would enable newer therapeutic strategies when we fully understand the fate of β-cell from healthy to disease state (reviewed by Ansarullah *et al*., 2022), especially to pave the way for targeted delivery of drugs/small molecules for restoration of regenerative and redifferentiation pathways (like bariatric surgery, calorie restriction, ALK5 inhibitors, FOXO1 inhibitors, ER stress inhibitors, etc.) for improving overall β-cell functionality[34].

7. References

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