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Editorial

Type 2 Diabetes: Is It Time to Target β-cell Heterogeneity?

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Type 2 diabetes (T2D) is primarily characterized by the hallmarks of increased insulin resistance, with eventual functional loss of pancreatic islets and progressive β-cell dysfunction. The better understanding of the complex network of cross talk between islet cells and their effects on β-cell function is facilitated by pancreatic islet gene expression studies. The heterogeneity of pancreatic islets is well known as the pancreatic islets of *Langerhans* contain a variety of hormone-secreting endocrine cell types, which are mostly comprised of β-cells, followed by α-cells, δ-cells, and a lower proportion of pancreatic polypeptide cells (formally known as γ-cells) and ε-cells.[1] Although the concerted and coordinated action of all these cell types is important, β-cell dysregulation and dysfunction are predominant factors that culminate in insulin secretion defects and glucose homeostasis alterations in T2D.

β-cell heterogeneity

β-cells were originally considered homogeneous because histological studies of mouse or human islets have revealed little morphological distinction between β-cells, except for the cellular granularity variations.[2] However, it has been emphasized recently that relatively huge heterogeneity does exist within the β-cell population. In this context, the evolving purification techniques (*e.g.*, the generation of transgenic reporter lines that express fluorescent indicators such as green fluorescent protein; purification by a panel of specific antibodies or by cell surface markers), as well as molecular technologies (*e.g.*, RNA sequencing) have paved the way for the identification of massive transcriptomes of fluorescence-activated cell sorting-purified pools of β-cell types in both mouse models and humans.[3,4] Interestingly, such studies have offered direction for further exploration in human islet transcriptomics and the subsequent identification of genes that encode proteins specifically expressed in β-cells.[5] Moreover, the functional heterogeneity among β-cells appears to occur in relation to the glucose threshold capacity and insulin secretory response of individual β-cells.[6,7] As reviewed by Mawla and Huising,[4] a landscape of distinct β-cell heterogeneity that is characterized by the changes in the expression of a variety of markers has been reported with regard to the functional state of the β-cells in healthy and diseased individuals. Therefore, it is currently well conceived that pancreatic β-cells are indeed heterogeneous in terms of their function (*e.g.*, the regulation of insulin secretion) and their transcriptional profile. More importantly, the functionally distinct subpopulations of β-cells can be identified and characterized by genetic and cell surface markers or by functional studies using optogenetics and Ca^{2+} dynamics.[8,9]

Loss of β-cell subtype and T2D

Despite the fact that our understanding of β-cell heterogeneity has progressively increased over time, it remains unclear whether perturbations in β-cell heterogeneity can specifically contribute to β-cell dysfunction and T2D. Miranda *et al.*[10] have emphasized that β-cell heterogeneity should be examined from different biological perspectives (*e.g.*, morphological, functional, and transcriptional), taking into account their relevance to topography, maturation, development, and stress response in order to understand their ultimate function in states of health and diabetes.

Although some subpopulations of β-cells are phenotypically different than others, there is a lack of mechanistic clarity on how this heterogeneity affects the functions of glucose homeostasis and insulin secretion in the context of diabetes. Dorrell *et al.*[11] have separated four populations of β-cells with distinct gene expression profiles using two surface markers, namely, CD9 and ST8SIA1. While $ST8SIA1^+$ cells (present in ~15% of healthy donors) were characterized by decreased insulin secretion and lower levels of GLUT2 expression, interestingly, the proportion of these $ST8SIA1^+$ cells were found to be increased in donors with T2D.

A very recent discovery biology study appears to offer milestone evidence for the existence of a subset of β-cells with β-cell dysfunction. Using single-cell transcriptomics and functional assays, Rubio-Navarro *et al.*[12] have identified subsets of pancreatic β-cells. Their work is unique as they validated their results both in preclinical and clinical studies. Their preclinical work analyzed pancreatic islets by single-cell RNA-sequencing from the high-fat-diet-induced mouse model of T2D compared to control animals. Their findings were confirmed in clinical work by the meta-analysis of five single-cell RNA-sequencing studies on human pancreatic islets from donors without T2D and with T2D. Among the four identified subsets of β-cells, one β-cell subset, which was characterized by the high expression of CD63, was found to be enriched in transcripts of genes encoding signatures involved in glucose and mitochondrial metabolism that are essential for glucose-stimulated insulin secretion. Similar metabolic benefits were

Abbreviations: T2D, type 2 diabetes.

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not seen in β-cells that had low levels of CD63 expression. While the engraftment of pseudo-islets originated from mouse β-cells (with high CD63 expression) into insulinopenic diabetic animals effectively restored glucose homeostasis, similar effects were not seen in pseudo-islets from mouse β-cells with low CD63 expression. More importantly and interestingly, the study found that T2D mouse models as well as humans with T2D exhibited decreased proportions of β-cells that express high CD63 levels. In summary, the study emphasizes that distinct changes in β-cell heterogeneity, particularly the loss of a specific β-cell subset with a high expression level of CD63, may lead to T2D.

The finding and its futuristic implications

The above findings emphasize that it is time to focus on β-cell heterogeneity in order to expand our understanding on the molecular pathogenesis of T2D that could be targeted for appropriate prevention as well as precision treatment. Alterations in β-cell heterogeneity might be linked to ethnicity; hence, these findings might have future implications in Asian Indians. Apart from strong predisposition to insulin resistance, it is inferred from recent studies that Asian Indians also exhibit an early decline in β-cell function.[13,14] More importantly, there is a reduction in β-cell function among Asian Indians, even in those with mild dysglycemia, irrespective of age, insulin sensitivity, or family history.[15] In this context, it is worth exploring whether early impairment of β-cell function in Asian Indians is somehow linked to β-cell heterogeneity.

Recently, the heterogeneity of T2D has received much attention, and novel and distinct subgroups of T2D have been discovered worldwide[16] as well as in India.[17] It is my proactive thought that it is important to unravel the role of β-cell heterogeneity in the subtypes of T2D patients, particularly in phenotypic clusters, namely, severe insulin-deficient diabetes as well as combined insulin-resistant and -deficient diabetes.

As a perfect discovery biology finding, the study by Rubio-Navarro *et al.*[12] opens up novel research avenues and poses the following questions: a) Is it possible to reconstitute or maintain subtypes of β-cells with high CD63 expression that may represent a potential antidiabetic therapy? b) Could the number or proportion of high-CD63-expressing β-cells within the pancreatic islets serve as a useful sentinel biomarker to predict the risk of T2D? c) Will maintaining or increasing high-CD63-expressing β-cells improve the glycemic control in patients with T2D and maximize their treatment outcomes? d) Could treatment with glucagon-like peptide-1 receptor agonists sensitize β-cells with low CD63 expression to achieve improvised insulin secretion? e) Will this technology advance the outcomes of cell-based therapies and islet organoid-based treatments?

At present, the underlying pathological mechanisms that culminate in the loss of β-cells with high CD63 expression are not clear, and this is a challenging area of translational research. Future research with ever-evolving technologies should explore and unravel the factors that mediate and contribute to the pancreatic β-cell heterogeneity in order to find ways to preserve and augment the healthy and functional pool of β-cells in patients with T2D.

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Conflict of interest

The author is an editorial board member of *Exploratory Research and Hypothesis in Medicine*.

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