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PATHOGENESIS OF TYPE 2 DIABETES AND INSULIN RESISTANCE (M-E PATTI, SECTION EDITOR)

The Beta Cell in Type 2 Diabetes

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Abstract

Purpose of Review This review summarizes the alterations in the β-cell observed in type 2 diabetes (T2D), focusing on changes in β-cell identity and mass and changes associated with metabolism and intracellular signaling.

Recent Findings In the setting of T2D, β-cells undergo changes in gene expression, reverting to a more immature state and in some cases transdifferentiating into other islet cell types. Alleviation of metabolic stress, ER stress, and maladaptive prostaglandin signaling could improve β-cell function and survival.

Summary The β-cell defects leading to T2D likely differ in different individuals and include variations in β-cell mass, development, β-cell expansion, responses to ER and oxidative stress, insulin production and secretion, and intracellular signaling pathways. The recent recognition that some β-cells undergo dedifferentiation without dying in T2D suggests strategies to revive these cells and rejuvenate their functionality.

Keywords β-cell dysfunction · Dedifferentiation · Disallowed genes · ER stress · Oxidative stress · β-cell metabolism

Introduction

In animal models, obesity and insulin resistance have been shown to induce β-cell compensatory responses that include increased insulin synthesis and secretion, and increased β-cell mass via both proliferation and hypertrophy (Fig. 1) [1–3]. Successful β-cell compensation in the face of insulin resistance would stave off progression to type 2 diabetes (T2D). The incidence of T2D increases with age, in part due to a decreased ability of β-cells to respond to proliferative cues as they get older [4–7]. Historically, then, T2D has been thought of as a disease of failed β-cell compensation in the face of insulin resistance (Fig. 1). The onset of overt T2D was thought to be preceded by losses in functional β-cell mass due to two major factors: (1) β-cell exhaustion due to prolonged elevations in glucose metabolism and insulin production, and (2) β-cell death through apoptosis due to gluco/lipotoxicity (Fig. 1) [8–11].

Studies in immortalized cell lines and mouse models of diabetes have revealed increases in β-cell oxidative stress and endoplasmic reticulum (ER) stress in the presence of hyperglycemia and insulin resistance, associated with increased glucose metabolism and insulin production [12, 13]. Postmortem studies comparing human pancreata from T2D donors showed significantly lower β-cell mass (as defined by insulin immunolabeling) compared with non-diabetic (ND) donors [14, 15]. In addition, islets from T2D donors are smaller and on average have fewer than half the islet equivalents (IEQs) of ND donors [16]. Analyses of pancreata from T2D individuals have revealed increased apoptotic β-cells [8, 17]; however, apoptosis may not be the only explanation for a decrease in insulin-positive cells in the setting of diabetes. Given the current inability to longitudinally monitor an individual's β-cell mass using imaging modalities, it is unclear whether β-cell mass declines in those who progress

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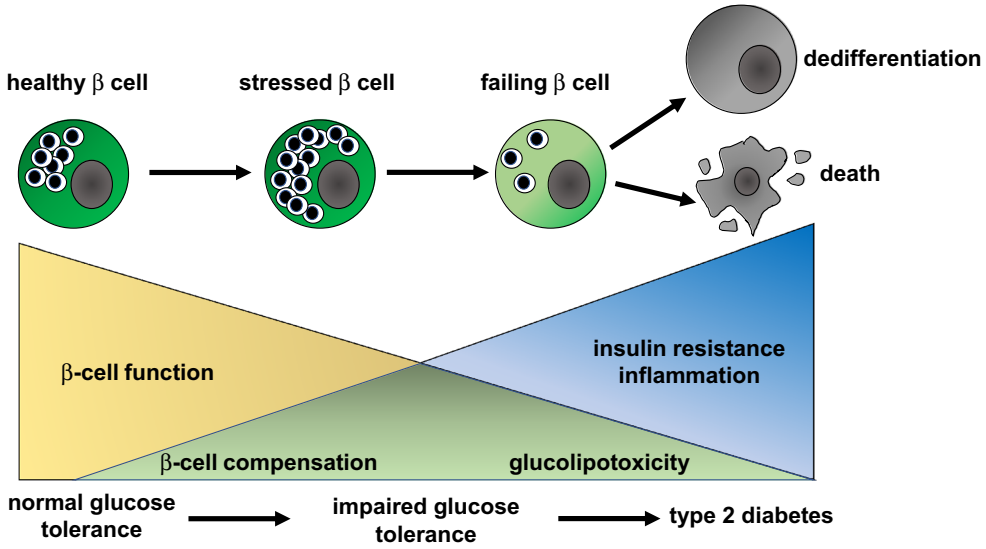

Fig. 1 Schematic of T2D progression. As insulin resistance increases, β-cells initially compensate by increasing insulin production and synthesis and by increased β-cell proliferation (not shown). Prolonged insulin resistance and inflammation can lead to β-cell stress and decompensation, leading to impaired glucose tolerance (or prediabetes). Ongoing hyperglycemia and hyperlipidemia lead to β-cell glucolipotoxicity and β-cell failure. Functional β-cell mass declines due to dedifferentiation and/or β-cell death, leading to type 2 diabetes

to T2D or whether those individuals had a lower β-cell mass at baseline, making them more susceptible to T2D when metabolically challenged [18, 19]. More recently, several groups have suggested that loss of β-cell identity or β-cell dedifferentiation plays an important role in the development of T2D (Fig. 1) [20, 21••, 22]. In this review, we summarize alterations in the β-cell observed in T2D, focusing on changes in β-cell identity and mass and changes associated with metabolism and intracellular signaling.

Loss of Functional β-Cell Mass in T2D

Loss of β-Cell Identity

Currently, there is no consensus definition of a β-cell. The definition can vary depending on the aspect of β-cell biology being examined. Is a β-cell simply any insulin-producing cell, regardless of whether or not it secretes insulin in a regulated fashion in response to changes in glucose? Is a cell only a β-cell if it expresses a specific set of key transcription factors (discussed below) associated with acquisition and maintenance of a β-cell fate? Is a cell no longer called a β-cell if it co-expresses glucagon with insulin? Traditionally, insulin expression as detected by immunolabeling has been used to identify β-cells in tissue sections and quantify β-cell mass. Thus, reduced insulin-positive area was construed as a loss of β-cell number. However, this approach of identifying β-cells may overestimate the actual number of cells lost. Loss of insulin labeling can occur due to β-cell death, dedifferentiation, or degranulation (Fig. 1) [8, 15, 20, 23]. It is therefore important to define what makes a β-cell a β-cell. One operational definition is that a β-cell synthesizes and processes insulin, packages it into secretory granules, and secretes it only in response to an elevation in blood glucose. If one accepts this definition, then a cell that constitutively secretes insulin or inappropriately secretes insulin at low blood glucose would not be considered a β-cell, but would still be considered an insulin-producing cell.

Mature, adult β-cells express a set of lineage-defining transcription factors including Pdx1, Pax6, Nkx6.1, Nkx2.2, FoxO1, and MafA [24–26]. β-cells from mouse models of T2D (such as the db/db mouse) and human T2D donors show loss of some of these transcription factors that are associated with mature β-cell function, such as Pdx1 and MafA [23]. Experimentally induced inactivation or downregulation of β-cell transcription factors in the mouse results in loss of optimal β-cell function and in some cases, the onset of characteristics of other endocrine cell types. For example, inactivation of MafA, the last β-cell identity transcription factor to be expressed in maturing β-cells, impairs β-cell function and glucose-stimulated insulin secretion (GSIS) without affecting β-cell mass [27]. In both db/db mice and in the early stages of human T2D, loss of nuclear MafA is one of the earliest changes observed in insulin-expressing cells [23]. Loss of FoxO1 in adult mouse β-cells induces expression of Neurogenin 3 (Ngn3), Oct4, and Nanog, markers of islet progenitor cells [20]. The loss of β-cell-defining transcription factors has been called "dedifferentiation."

The processes leading to β-cell dedifferentiation are just beginning to be elucidated. β-cell dedifferentiation or loss of identity occurs with prolonged exposure to hyperglycemic conditions [22]. Weir et al. defined dedifferentiation as "an altered phenotype that can lead to loss of key components

responsible for optimal performance including insulin secretion" [22]. This broad definition covers the many changes in β-cells that can result in impaired function such as changes in transcription factor expression and GSIS. However, the term dedifferentiation may best be reserved for situations where β-cells revert to a more immature or progenitor state similar to an earlier stage in their normal developmental program, rather than a novel cell state not normally found in development. It may be more appropriate to use the term "loss of β-cell identity" in the latter case.

β-Cell Transdifferentiation

Transdifferentiation has been defined as the "conversion of one terminally differentiated cell type into another" [28]. This differs from a related process known as reprogramming, which involves conversion of a differentiated cell type into a multi-potent precursor called an induced pluripotent stem cell (iPSC), followed by subsequent differentiation into a particular mature cell type [29]. Both transdifferentiation and reprogramming differ from dedifferentiation, described previously, as dedifferentiation refers to cells that revert to an immature insulin-positive cell or endocrine progenitor phenotype rather than the less restricted pluripotent phenotype seen with reprogramming. Not only have β-cells been shown to transdifferentiate into other islet cell types, several different cell types are capable of transdifferentiating into β-cells. Both of these situations are discussed below, with a focus on transdifferentiation in the setting of hyperglycemia and diabetes.

Several studies have demonstrated that β-cells can transdifferentiate under certain conditions. In one mouse study that used an inducible Nkx2.2 deletion coupled with lineage tracing, some β-cells were observed to induce expression of other islet hormones superimposed on insulin expression, while others completely lost insulin expression upon induction of alternative islet hormones [30••]. These results are indicative of partial and complete transdifferentiation, respectively, and highlight the importance of Nkx2.2 in actively maintaining β-cell identity. In this same study, inactivation of Nkx2.2 in human islets using shRNA led to an upregulation of somatostatin gene expression, although lineage tracing was not done in these studies and the β-cells were not targeted specifically. These studies suggest that in both mouse and humans, Nkx2.2 inactivation leads to β-cell transdifferentiation into delta (δ)-cells. However, since lineage tracing has not routinely been performed in human islet studies, an increase of one islet cell type at the expense of another cannot definitively be attributed to transdifferentiation. Polyhormonal cells have been detected in pancreas tissue sections from donors with diabetes [31], suggestive of transdifferentiation.

β-cell-specific FoxO1 inactivation in β-cells in mice resulted in hyperglycemia under stress conditions such as multi-parity and aging [20]. Lineage tracing revealed that a small number of β-cells in these mice transdifferentiated into glucagon-expressing α-cells. Likewise, loss of Pdx1 in adult β-cells causes them to become more α-cell-like, expressing glucagon and the α-cell transcription factor, Arx [32]. Another study using lentiviral-mediated lineage tracing in cultured human islet cells found that over the course of 4 days, mature β-cells could transdifferentiate into α-cells identical to native α-cells [28]. Knockdown of Arx prevented human β-cells from transdifferentiating to α-cells [28]. In mice, misexpression of Arx in β-cells results in transdifferentiation into α or PP cells [33]. The relevance of these findings to clinical diabetes in vivo is not known since these studies were done with dispersed and reaggregated islets cultured ex vivo. One study examined islets from healthy donors and donors who had T2D and found evidence of β-cell dedifferentiation (loss of lineage-defining transcription factors) and increased expression of β-cell markers in glucagon- or somatostatin-positive cells, which they concluded was evidence of transdifferentiation of β-cells to other islet cell types [34]. However, the directionality of the transdifferentiation here cannot be ascertained. It could just as easily have been transdifferentiation of α- or δ-cells into β-cells, since the starting cell population is unknown. Additional studies with human islets are needed to determine the extent of transdifferentiation that occurs in diabetes and whether this phenomenon is a cause or consequence of the disease [35].

Other islet endocrine cell types are also capable of transdifferentiating to β-cells, particularly under situations of extreme β-cell loss, suggesting that conversion of these cell types into functional β-cells is a potential treatment for T2D. For example, severe β-cell ablation in mice and zebrafish induces α-to-β-cell transdifferentiation, determined by careful lineage tracing [36, 37]. Greater than 95% of β-cells must be destroyed to induce spontaneous α-to-β-cell transdifferentiation [36], suggesting that α-cells "sense" the loss of β-cell mass, initiating, the transdifferentiation process. The signal for α-to-β-cell transdifferentiation has yet to be identified. However, one study suggests that insulin acts as a repressor of transdifferentiation and in situations of severe β-cell loss, this inhibitory signal is reduced, permitting transdifferentiation of other islet endocrine cells to occur [38]. Pancreatic exocrine acinar cells are also capable of transdifferentiating into functional β-cells upon combined activation of the transcription factors Ngn3, Pdx1, and MafA [39, 40], and these newly generated β-cells have been shown to rescue hyperglycemia following streptozotocin-mediated β-cell destruction [39]. There are conflicting results as to whether dedifferentiation precedes transdifferentiation [6, 8, 20, 30••]. Whether dedifferentiation is necessary for transdifferentiation may differ depending on the model system

and experimental methods used. In any case, the excess of acinar cells and the apparent physiological need for only a small number of α-cells makes these pancreas-resident cell types attractive candidates for generating replacement β-cells in vivo.

Most of the studies of transdifferentiation did not determine whether it occurs naturally in vivo during the pathogenesis of T2D. One study that indicates transdifferentiation may occur naturally comes from Huising and colleagues who discovered what they describe as "virgin β-cells" in the periphery of rodent islets. These immature, insulin-positive cells never express urocortin 3 (UCN3) and other markers of mature β-cells, but persist in adult islets [41•]. Based on lineage tracing analysis, the authors proposed that these virgin β-cells represent an intermediary state as α-cells transition state to β-cells. UCN3-negative β-cells have also been detected in adult human islets [41•], but as UCN3 is also lost during β-cell dedifferentiation, it is difficult to determine if these cells represent virgin β-cells or dedifferentiated β-cells. UCN3-negative β-cells have also been found in human islets from young donors [41•], giving support to the idea that virgin β-cells do exist in humans, at least at a young age. Further study is necessary to assess the potential for transdifferentiation in humans and the source of these cells.

Induction of Disallowed Genes

The concept of β-cell identity encompasses not only the genes a β-cell should express, but also the set of genes that must be actively repressed in order to function properly [30••, 42, 43]. These so called "disallowed genes" are upregulated under conditions of metabolic stress, such as high fat diet and T2D, while markers of β-cell identity are concomitantly downregulated. Many of the disallowed genes are in fact expressed in immature β-cells. β-cell disallowed genes were discovered by comparing transcriptome data from mouse islets with other tissues; genes that are highly expressed in other tissues but not in islets fall into the disallowed group [43]. The current number of β-cell disallowed genes that have been identified in at least one study is approximately 60; however, the full complement of β-cell disallowed genes is likely yet to be discovered. As a description of the entire set of disallowed genes is outside the scope of this review, only a small number of β-cell disallowed genes will be discussed herein. These are monocarboxylate carrier 1 (MCT1, encoded by the *Slc16A1* gene), lactate dehydrogenase A (LDHA), low K_m hexokinase I (HKI), and repressor element 1 silencing transcription factor (REST).

Mature adult β-cells express low levels of both MCT1 and LDHA [43]. MCT1 transports pyruvate and lactate (which can be converted to pyruvate by LDHA) across the plasma membrane. Pyruvate is generated during glycolytic glucose metabolism and can stimulate insulin secretion. Thus, MCT1 allows for continued ATP production under anaerobic conditions. In many cell types, MCT1 and LDHA are critical for cellular functions in hypoxic conditions, but it is thought that the high blood flow rates in islets supply enough oxygen to β-cells to make up for low expression of these genes [44]. Inappropriate expression of MCT1 or LDHA in β-cells could trigger insulin release in response to elevated circulating lactate or pyruvate [43, 44], which are released from other cells such as skeletal muscle during exercise [45]. This inappropriate release of insulin could lead to exercise-induced hyperinsulinemic hypoglycemia [46].

Hexokinase enzymes catalyze phosphorylation of glucose to generate glucose-6-phosphate, the first step of glycolysis. There are several isoforms of hexokinase, which are differentially localized in tissues and have different enzyme kinetics. Glucokinase, also known as hexokinase IV, is the hexokinase isoform expressed in β-cells. Unlike the other hexokinase isoforms, glucokinase has a high K_m, which allows glucose to enter β-cells at a rate proportional to blood glucose concentration. Overexpression of the low K_m hexokinase (HKI) leads to increased insulin secretion at low glucose concentrations, but impaired insulin secretion at stimulatory glucose concentrations [47]. Thus, increased expression of this disallowed gene in β-cells in the setting of T2D would result in insulin being released disproportionately to blood glucose concentrations.

REST is expressed in several cell types, including neurons and embryonic stem cells [48]. REST is a transcriptional repressor that serves to maintain chromatin in an inactive state by binding to a specific 21-bp promoter sequence [49]. REST repression is necessary for proper insulin secretion, as overexpression of REST in adult mice decreases expression of SNARE proteins necessary for insulin exocytosis [50]. Expression of REST in developing β-cells in mice also leads to lower functional β-cell mass and diabetes [50]. This may be due in part to the fact that REST activates expression of DYRK1A [50, 51], a kinase known to repress β-cell proliferation [52, 53•, 54•]. Thus, induction of REST expression in β-cells could lead to decreased β-cell compensation in the setting of T2D.

Current studies are focused on understanding how repression of β-cell disallowed genes is actively maintained and how this repression is relieved in the setting of β-cell dysfunction and T2D. Histone modifications, DNA methylation, and microRNAs (miRNAs) have all been shown to be involved in this process: repressive histone methylation is found at the promoters of β-cell disallowed genes, including HKI and REST, and loss of DICER, an enzyme that processes miRNA precursors, leads to β-cell dysfunction and loss of β-cell mass through upregulation of disallowed genes [48].

Alterations in Cell Metabolism and Intracellular Signaling

Effects of Increased Glucose Metabolism and Oxidative Stress

Glucose metabolism is essential for glucose-stimulated insulin secretion (GSIS), and mitochondria play a pivotal role in both the triggering and amplifying phases of insulin secretion [55]. A detailed description of β-cell glucose metabolism is beyond the scope of this review. For an in-depth review of the process, see [55]. In brief, glucose metabolism begins with the entry of glucose into β-cells through glucose transporters and subsequent phosphorylation to glucose-6-phosphate (G6P) by glucokinase. G6P then undergoes glycolysis to generate pyruvate, NADH, and ATP. Pyruvate then enters the mitochondria and is metabolized through the citric acid (TCA) cycle and the electron transport chain to produce ATP with reactive oxygen species (ROS) byproducts [56]. The rise in cytoplasmic ATP results in closure of the K_{ATP} channels, leading to membrane depolarization, calcium influx, and insulin secretion.

Chronic hyperglycemia and persistent glucose metabolism can lead to glucotoxicity [57]. Both glucotoxicity and lipotoxicity contribute to the development and progression of T2D [58]. Glucotoxicity has been demonstrated in both humans and animal models [57]. Although the precise mechanisms by which this occurs are not fully understood, increased levels of NADH and ROS have both been linked to β-cell dysfunction in T2D [59, 60]. The good news is that the changes induced in β-cells due to glucotoxicity have been shown to be reversible, although this might depend on the duration of the metabolic insult. β-cell rest has been proposed as a mechanism to prevent or reverse the effects of β-cell exhaustion [61]. In mice that have undergone partial pancreatectomy–induced hyperglycemia, restoration of euglycemia (using phloridzin) quickly reversed the hyperglycemia-induced changes in islet gene expression [25]. In humans with T2D, bariatric surgery has been shown to restore normal GSIS [62, 63]. The precise cause of diabetes remission is not known; however, normalization of blood glucose occurs within days of surgery, before significant weight loss [64]. These data demonstrate that β-cell dysfunction is potentially reversible, at least in some cases.

In T2D, several defects in mitochondrial function have been identified, although it is not clear if these abnormalities are a contributing cause to the development of T2D or simply a consequence of the disease [65]. Mitochondrial dysfunction leads to changes in β-cell metabolism seen in diabetes [66, 67]. Mitochondria in β-cells from human T2D donors appear swollen and fragmented [68], and are also smaller in size [60]. Mitochondria from T2D donors were also present at a higher density than in ND islets, although there were no differences in total number of mitochondria [69]. Mitochondria are one of the major sources of ROS in β-cells. Small amounts of ROS are likely beneficial and can stimulate insulin secretion. Indeed, when ROS were quenched with an antioxidant, insulin secretion was abolished [70]. Conversely, large amounts of ROS or unresolved sustained elevations in ROS can lead to β-cell dysfunction and death [68]. For example, one study in the INS-1 (832/13) immortalized β-cell line showed that chronic exposure to high glucose and/or palmitate (to mimic glucotoxicity and lipotoxicity, respectively) led to a 2.5-fold increase in ROS and severely decreased insulin secretion [71]. This may be due to deleterious effects on MafA, as exposure of β-cells to hydrogen peroxide, mimicking ROS stress, leads to defects in MafA expression and activity [23]. β-cells are particularly sensitive to ROS due to the high levels of oxygen consumption and lower levels of antioxidant enzymes [72]. Indeed, transgenic overexpression of glutathione peroxidase in the face of oxidative stress preserves nuclear MafA and reverses diabetes in the db/db mouse model [73].

Thioredoxin-interacting protein (TXNIP) is another mediator of oxidative stress–induced β-cell glucotoxicity [74]. Circulating levels of TXNIP are increased in patients with prediabetes and further increase as these patients progress to overt T2D [75]. TXNIP is induced by high glucose and promotes β-cell apoptosis, while TXNIP deletion protects against diabetes and promotes insulin secretion in mouse models [74]. The calcium channel blocker verapamil has been shown to inhibit TXNIP expression and retrospective studies in humans suggest that verapamil use is associated with a lower incidence of T2D [74].

Endoplasmic Reticulum Stress and the Unfolded Protein Response

Endoplasmic reticulum (ER) stress is also observed in β-cells in the setting of hyperglycemia due to the increased demand for insulin synthesis and processing [76]. ER stress can lead to the unfolded protein response (UPR) in β-cells [77]. UPR is a normal compensatory response that involves the proteins PERK, IRE1, ATF6, and XBP1, which work together to retard protein synthesis allowing for the refolding or degradation of improperly folded proteins [78, 79]. However, prolonged and unresolved UPR can lead to upregulation of CHOP, a protein involved in apoptosis. This is best exemplified in the Akita mouse model of diabetes in which a spontaneous mutation in one allele of the *insulin2* gene leads to misfolding of the protein, ER stress, UPR, and ultimately β-cell death and diabetes [13]. In humans, mutations in the WFS1 gene, whose protein product wolframin negatively regulates ER stress, cause diabetes in Wolfram syndrome [80]. Overproduction of islet amyloid polypeptide (IAPP) in human β-cells in the setting of insulin resistance is also thought to contribute to β-cell ER stress and T2D [17]. One proposed mechanism of action of the commonly prescribed T2D drug metformin on β-cells is alleviation of oxidative and ER stress [81].

Alterations in Prostaglandin Signaling

Obesity and T2D are diseases of low-grade, chronic inflammation. Prostaglandin E2 (PGE2) production is upregulated in islets from obese diabetic mice as well as humans with T2D [82]. There are four PGE2 G protein–coupled receptors (EP1–4), three of which are expressed in β-cells (EP2, EP3, EP4) [83]. EP2 and EP4 couple to G_s and thus activate adenylyl cyclase, raising intracellular cAMP. In contrast, EP3 couples to G_i, thus inhibiting cAMP production (among other things). Our lab has shown that pharmacological inhibition of EP3 in mouse and human islets ex vivo enhances β-cell proliferation and survival [83]. Likewise, the Kimple group has shown that genetic inactivation of Gαz (an inhibitory G protein coupled to EP3) leads to enhanced insulin secretion, increased β-cell proliferation, and improved β-cell survival [84]. Similar to PGE2, EP3 expression increases in islets in the setting of T2D [83]. The increased EP3 expression in islets in the setting of T2D suggests that increases in its activity contribute to defects in β-cell compensation (proliferation and/or survival). In support of this, our group found that inactivation of EP3 in male mice ($EP3^{-/-}$) results in an increase in β-cell proliferation and β-cell mass after 16 weeks on HFD [85]. In vivo, systemic pharmacological antagonism of EP3 improves glucose homeostasis in *db/db* mice, although the mechanism for this improvement was not reported [86]. Taken together, the existing data suggesting that the increase in EP3 observed in diabetes is maladaptive for β-cell compensation and may contribute to progression to T2D.

Conclusions

The vast majority of T2D susceptibility genes that have been identified to date are β-cell genes, placing the β-cell in a central role in the etiology of the disease. It is likely that specific constellations of β-cell defects leading to T2D differ in different individuals and include variations in β-cell mass development, β-cell expansion, responses to ER and oxidative stress, insulin production and secretion, and intracellular signaling pathways. The recent realization that some β-cells survive the toxic environment of T2D but remain in an altered state of differentiation suggests strategies to revive these cells and rejuvenate their functionality. Likewise, mechanisms that stimulate β-cell expansion or promote β-cell survival are being explored as new therapeutics for the treatment of T2D.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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