Review

MOLECULAR METABOLISM

Human beta cell mass and function in diabetes: Recent advances in knowledge and technologies to understand disease pathogenesis

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ABSTRACT

Background: Plasma insulin levels are predominantly the product of the morphological mass of insulin producing beta cells in the pancreatic islets of Langerhans and the functional status of each of these beta cells. Thus, deficiency in either beta cell mass or function, or both, can lead to insufficient levels of insulin, resulting in hyperglycemia and diabetes. Nonetheless, the precise contribution of beta cell mass and function to the pathogenesis of diabetes as well as the underlying mechanisms are still unclear. In the past, this was largely due to the restricted number of technologies suitable for studying the scarcely accessible human beta cells. However, in recent years, a number of new platforms have been established to expand the available techniques and to facilitate deeper insight into the role of human beta cell mass and function as cause for diabetes and as potential treatment targets.

Scope of Review: This review discusses the current knowledge about contribution of human beta cell mass and function to different stages of type 1 and type 2 diabetes pathogenesis. Furthermore, it highlights standard and newly developed technological platforms for the study of human beta cell biology, which can be used to increase our understanding of beta cell mass and function in human glucose homeostasis.

Major Conclusions: In contrast to early disease models, recent studies suggest that in type 1 and type 2 diabetes impairment of beta cell function is an early feature of disease pathogenesis while a substantial decrease in beta cell mass occurs more closely to clinical manifestation. This suggests that, in addition to beta cell mass replacement for late stage therapies, the development of novel strategies for protection and recovery of beta cell function could be most promising for successful diabetes treatment and prevention. The use of today's developing and wide range of technologies and platforms for the study of human beta cells will allow for a more detailed investigation of the underlying mechanisms and will facilitate development of treatment approaches to specifically target human beta cell mass and function.

Keywords Diabetes; Human; Islet of Langerhans; Beta cell mass; Beta cell function; Pathogenesis; In vitro; In situ; In vivo

1. INTRODUCTION

In diabetes, uncontrolled and elevated blood glucose is the consequence of inadequate levels of plasma insulin, which are insufficient to effectively lower plasma glucose concentrations. Within a systemic environment, plasma insulin levels are usually the result of insulin clearance and, more importantly, insulin production and secretion by beta cells. Hereby, the total amount of released insulin depends on the absolute number of beta cells in the pancreatic islets of Langerhans (beta cell mass) and the output of each of these cells (beta cell function). For decades, the relative contribution of beta cell mass and function to the development of insufficient insulin levels and diabetes has been under debate. However, detailed knowledge on this aspect of diabetes pathogenesis will be crucial for the development of successful treatment approaches. Most of the currently available information on beta cell mass and function in diabetes stems from experiments on mouse models. Yet, many studies have demonstrated that human and mouse beta cells show vastly different characteristics, in particular when it comes to beta cell mass regulation. Thus, studies on human beta cells and islets are indispensable to develop therapies targeting beta cell mass, function, or both to treat diabetes.

The lack of studies on human beta cells is primarily related to limited availability of human samples and a shortage of technologies to comprehensively investigate human beta cell biology. However, in recent years the field has made great progress in the organized procurement of human tissue and the development of novel technologies. Utilizing these experimental platforms to study human beta cells will be necessary to enhance our current knowledge on human beta cell mass and function in diabetes development and bring us closer to effective diabetes therapies.

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2. HUMAN BETA CELL MASS AND FUNCTION IN DIABETES PATHOGENESIS

2.1. Type 1 diabetes

Type 1 diabetes (T1D) is a chronic autoimmune disorder in which the immune system attacks endogenous pancreatic beta cells resulting in insulin deficiency, chronic hyperglycemia, and long-term complications. Creating a successful cure for T1D will need to include stopping the self-damaging autoimmune process and restoring appropriate insulin release from beta cells. Addressing the latter requires detailed knowledge about alterations in beta cell mass and function in the asymptomatic prediabetic period of disease pathogenesis and the contribution of beta cell mass and function to clinical manifestation and the onset of hyperglycemia.

2.1.1. Beta cell mass and function during the prediabetic phase of T1D

Initially, progression of beta cell mass decline prior to the onset of hyperglycemia was thought to be linear [1]. However, in recent years, the model for prediabetic pathogenesis of T1D has been adjusted to reflect the relapsing and remitting progression of disease pathogenesis [2–4] and to acknowledge the heterogeneous progression time from seroconversion to diabetes which can range from weeks to over two decades [5]. Unfortunately, limited information on human beta cell mass is available for the asymptomatic time period [6]. However, it is thought that chronic insulitis reduces beta cell mass in the prediabetic phase by induced cell death via direct cell–cell contacts [7] or secreted proinflammatory cytokines [8]. This hypothesis was corroborated by a recent report measuring unmethylated INS DNA in human blood samples as an indicator for beta cell death [9]. The authors demonstrated that beta cell death is elevated in high risk T1D subjects and increases further towards clinical diagnosis, suggesting that the major reduction of beta cell mass occurs late during the prediabetic phase. This is in line with studies on human donor tissue which found no loss of beta cell mass in autoantibody positive subjects prior to diabetes in comparison to controls [10–12], while demonstrating a massive reduction in recent onset T1D patients [12,13]. Besides changes in the intensity of the autoimmune attack, one explanation for a delayed decrease in beta cell mass despite ongoing cell death might be an increased beta cell proliferation in response to inflammation as seen in mice [14,15]. This would also explain the twofold increased beta cell mass observed in nondiabetic autoantibody positive subjects with insulitis compared to autoantibody positive subjects without insulitis or controls [16].

Despite prolonged preservation of beta cell mass, plasma insulin levels indicate an altered insulin output already in the prediabetic phase, indicating changes in beta cell function. In several perspective, longitudinal studies in patients at risk beta cell performance was assessed by measuring C-peptide, glucose tolerance, and first phase insulin response in metabolic tests. While metabolic tests cannot reliably distinguish between the roles of cell mass and function (see also Section 3.3), these studies strongly contribute to our current understanding of the prediabetic phase in human T1D pathogenesis. An early study on 9 subjects observed no signs of elevated fasting or stimulated glucose levels in the prediabetic phase until immediately before disease onset, while demonstrating a progressive loss of the first phase insulin response [17]. Additional studies followed up on this topic in larger cohorts of patients at risk and showed that loss of first phase insulin release during the prediabetic phase is correlated with age and the number of autoantibody subtypes [18–20]. This is also confirmed by measurements of C-peptide demonstrating maintained fasting but decreasing stimulated C-peptide levels throughout the prediabetic phase [21]. Concentrating on the most recent studies, several groups have shown that a decline in first phase insulin release is already detectable 4–6 years before clinical onset [19,20,22,23]. Taking into account that beta cell mass was found to be unchanged or even increased in the prediabetic phase [10,11,16], early changes in first phase insulin release are presumably the result of functional impairment. Closer to the emergence of hyperglycemia, the decline in first phase insulin release and stimulated C-peptide was observed to be further aggravated [21,23], which might be due to combined beta cell dysfunction and increased beta cell apoptosis close to diabetes onset. Taken together these observations support the hypothesis that, especially in cases of a long prediabetic phase an early, slowly progressing functional impairment of beta cells precedes a late, rapidly advancing morphological destruction and functional decline of beta cells.

2.1.2. Beta cell mass and function at and after onset of hyperglycemia

Inferring from the observations of the prediabetic phase, onset of hyperglycemia is caused collectively by reduced beta cell mass and beta cell dysfunction. However, the extent of morphological and functional insufficiency varies between patients and contributes differently to the development of hyperglycemia. Conceivably, as a result from studying mostly severe and early onset cases, near total loss of beta cell mass (>80% reduction) at disease onset was a long held general paradigm for T1D pathogenesis [24–28]. However, this concept does not coincide with the residual beta cell function seen in subjects with onset in adolescence [29–31], suggesting a more preserved beta cell mass with up to 40% residual insulin-containing islets in older onset subjects [29,32]. Hereby, the remaining beta cell mass and function at onset are determined by age [33,34], degree, and cellular profile of insulitis [29]. In addition, evidence from us and others in mouse and human suggests that beta cell mass might be underestimated as a consequence of degranulation, an almost complete loss of insulin granules resulting in negative hormone staining of exhausted beta cells [14,16,35,36]. After onset, beta cell destruction by the ongoing autoimmune infiltration continues and is additionally exacerbated by the increasing metabolic and glycemic overload causing ER stress and apoptosis [37]. In particular within the initial time period after diabetes onset, beta cell apoptosis is elevated [28], but seems to slow down in long-standing T1D [9], potentially as a result of the decreasing number of beta cells. Nevertheless, even after diabetes onset, compensatory mechanisms might operate against beta cell mass reduction. In a case report from 2006, Meier and colleagues showed enhanced beta cell proliferation in a recently diagnosed 89-year-old patient [38]. Likewise, Willcox et al. showed increased beta cell proliferation in a set of 10 patients with recent onset diabetes (<18 month) [39], which might have been induced by the inflammation itself [14] and/or the elevated glucose levels [40]. Alternatively, the occurrence of small beta cell clusters scattered throughout the exocrine tissue in long-standing T1D patients was interpreted as a cell population that evaded autoimmune destruction or a compensatory beta cell population of yet unknown origin [41,42]. Hence, apoptosis and regeneration might occur simultaneously during disease progression and sustained apoptosis may be explained by continuous beta cell mass compensation through proliferation, transdifferentiation, or neogenesis [41,43].

In addition to reduced cellular mass, beta cell function continues to exhibit an important role at diabetes onset and thereafter. Residual beta cells after onset and in long-standing diabetes show signs of functional exhaustion and degranulation [35,36], while still expressing

