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REVIEW

Beta cell mass in diabetes: a realistic therapeutic target?

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Abstract Beta cell deficiency underlies both type 1 and type 2 diabetes, and restoration or replacement of beta cell function is therefore the logical long-term solution to therapy. This review sets out to describe the defects in beta cell mass and function in both forms of diabetes, summarises current understanding of the underlying causes of beta cell death, and the methodological limitations of determining beta cell mass in vivo. Finally, the potential effects of current and future treatment regimens on beta cell mass and turnover are considered.

Keywords Apoptosis · Beta cell imaging · Beta cell turnover · Beta cell rest · GLP-1 · Proliferation · Sulfonylureas · Type 1 diabetes · Type 2 diabetes

Abbreviations

DPP-4	dipeptidylpeptidase 4
ER	endoplasmatic reticulum
GLP-1	glucagon-like peptide 1
MRI	magnetic resonance imaging
VMAT2	vesicular amine transporter 2

Introduction

While it has long been held that type 1 diabetes results from an irreversible loss of beta cells, and that type 2 diabetes is primarily caused by impaired insulin action, there is now increasing evidence linking both types of diabetes to defects in beta cell mass and insulin secretion. Furthermore, the former dogma that postnatal beta cells are irreversibly postmitotic and thus not capable of replicating during adult life has been challenged over the past years. These advances offer the potential of targeting beta cell regeneration as a future treatment of diabetes. In this review we will describe the defects in beta cell mass and function in both type 1 and type 2 diabetes, summarise the underlying causes of beta cell death, and evaluate the methodological limitations of determining beta cell mass in vivo. Finally, we will discuss the potential effects of current and future glucose-lowering treatment regimens on beta cell mass and turnover in patients with diabetes.

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Beta cell mass in diabetes

Both type 1 and type 2 diabetes are characterised by deficits in beta cell mass (~99% deficit in long-standing type 1 diabetes [1, 2], ~65% deficit in long-standing type 2 diabetes [3]; Fig. 1). While there is little doubt regarding the importance of increased autoimmune-mediated beta cell death in type 1 diabetes [2], recent studies suggest that the frequency of beta cell apoptosis is also significantly increased in type 2 diabetes [3], although other factors, such as the failure of beta cell mass to expand adequately in response to rising secretory demands, cannot be excluded. This loss of beta cells in both types of diabetes implies that restoration of endogenous insulin secretion and normalisation of hyperglycaemia in such patients might be accomplished through the replacement or regeneration of islet cells [4]. Indeed, hyperglycaemia in both types of diabetes is reversed by pancreas transplantation [5], and intraportal transplantation of isolated islets temporarily

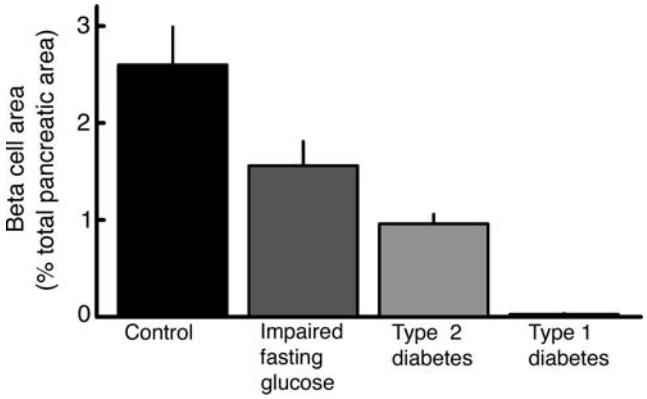

Fig. 1 Fractional beta cell area in the pancreas of obese non-diabetic individuals, individuals with impaired fasting glucose, patients with type 2 diabetes and patients with type 1 diabetes. Modified from [3] and [2]

restores glucose control [6]. Unfortunately, replacement of beta cell mass by islet or pancreas transplantation is associated with both surgical morbidity and the adverse effects of chronic immunosuppression [7]. Moreover, there is an insufficient supply of pancreases available for the increasing number of people with diabetes, thus preventing the widespread implementation of this intervention [7]. There is therefore a need for alternative approaches for restoring functional beta cell mass in patients with diabetes.

Both type 1 and type 2 diabetes are characterised by a significant deficit in beta cell mass, presumably caused by beta cell apoptosis.

Type 2 diabetes

Type 2 diabetes is characterised by a combination of insulin resistance and beta cell dysfunction [8, 9]. The risk of developing type 2 diabetes rises exponentially with increasing obesity and insulin resistance. Temporary restoration of glucose control in patients with type 2 diabetes is often achieved through weight loss and increased physical activity. These observations have led to the misconception that insulin resistance is the primary defect underlying the development of type 2 diabetes [9]; however, a number of points argue against such reasoning. First, even though the risk of developing diabetes is increased in obesity, ~80% of obese individuals remain non-diabetic [10]. Likewise, even severe insulin resistance, such as that induced by glucocorticoid therapy or pregnancy, leads to the development of diabetes only in small percentage of patients. Second, the maximal insulin secretory responses to intravenous glucose, arginine and other secretagogues are greatly diminished in patients with type 2 diabetes [11–13]. In particular, the pulsatile pattern of prehepatic insulin release is abnormal in type 2 diabetes. Defects in insulin secretion have also been described in certain populations at high risk of developing type 2 diabetes (e.g. individuals with impaired glucose tolerance, first-degree relatives of diabetic patients), even though the interpretation of some of these studies is hampered by the potential dampening of insulin responses by the different baseline glucose levels [14]. Based on such cross-sectional studies, defects in insulin secretion appear to even precede the development of insulin resistance [14]. Third, insulin resistance is found not only in type 2 diabetes, but also in type 1 diabetes, presumably as a consequence of impaired insulin secretion [15]. Fourth, as mentioned above, there is a beta cell deficit in patients with long-standing type 2 diabetes (~65% beta cell loss), and this is also seen in individuals with impaired fasting glucose (~50% beta cell loss; Fig. 1) [3]. Fifth, a similar 50% experimental or surgical reduction of beta cell mass leads to the development of diabetes in various animal models as well as in humans [16–18]. Sixth, the typical metabolic defects of type 2 diabetes (impaired insulin secretion, hepatic insulin resistance, hyperglucagonaemia) can be mimicked in animals with a progressive beta cell loss reminiscent of that in patients with type 2 diabetes [19]. Seventh, despite the overt presence of insulin resistance, hyperglycaemia in type 2 diabetes can be offset by restoration of beta cell mass through pancreas transplantation [20, 21]. Taken together, these studies support the postulate that the clinical syndrome of hyperglycaemia develops in both type 1 and 2 diabetes in large part as a consequence of a deficit in beta cell mass.

Potential causes of beta cell loss in type 2 diabetes The beta cell loss in type 2 diabetes is accompanied by a marked increase in beta cell apoptosis, as shown in human pancreas autopsy specimens and in isolated islets [3, 22]. Several mechanisms have been proposed as triggers for the increased beta cell loss in type 2 diabetes (Fig. 2). These include high concentrations of glucose (‘glucose toxicity’) [23] and NEFA (‘lipotoxicity’) [23, 24]. However, to a large extent, the studies in this field have been carried out in vitro and in rodent models and are therefore not generalisable to humans. In fact, in humans, prolonged exposure to high lipid concentrations has even resulted in an increased insulin secretory response [25]. Other potential factors leading to beta cell death in type 2 diabetes are toxic oligomers of human islet amyloid polypeptide [26], reactive oxygen species [27], endoplasmatic reticulum (ER) stress [28], and inflammatory cytokines such as IL-1β [29]. In reality, the clinical syndrome of type 2 diabetes is likely the consequence of more than one cause, and loss of beta cells probably involves more than one mechanism. Based on cross-sectional studies, normoglycaemia can be maintained until ~50% of beta cell mass is lost [30], with greater losses typically resulting in deterioration of glucose control [3, 17, 30]. However, the wide range of beta cell mass in non-diabetic individuals suggests that the timing of diabetes onset at a given degree

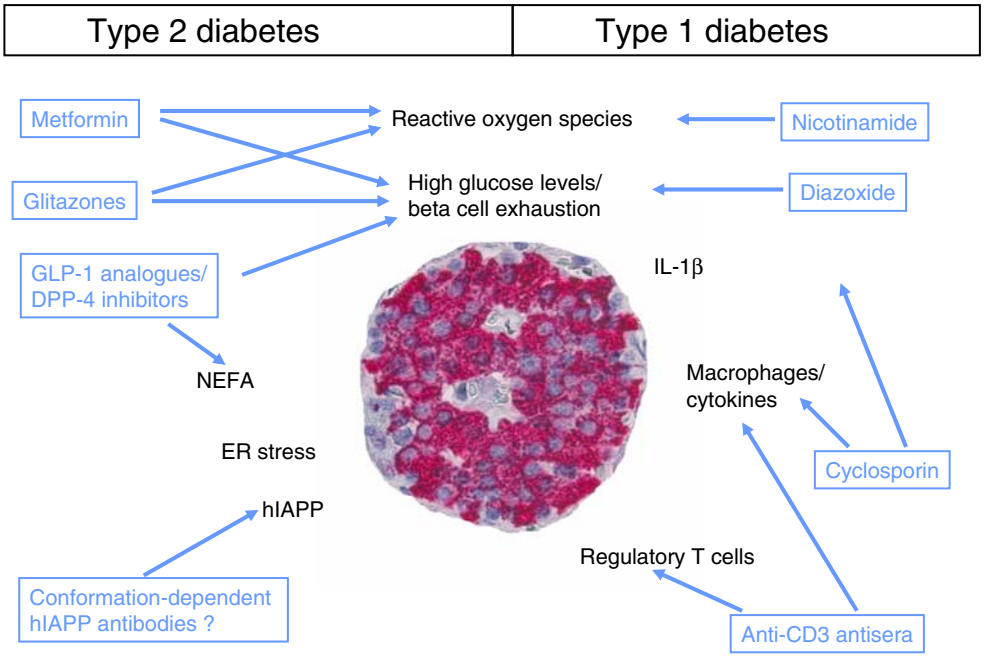

Fig. 2 Different factors inducing beta cell apoptosis (black) in type 2 diabetes (left side), type 1 diabetes (right side) or both types of diabetes (middle). Blue boxes show drugs with a potential to preserve beta cell mass in patients of diabetes through inhibition of these factors. hIAPP, human islet amyloid polypeptide

of beta cell loss varies from person to person and is influenced by other factors such as insulin sensitivity [3].

Type 1 diabetes

In type 1 diabetes, beta cell loss occurs as a consequence of immune-mediated beta cell destruction [1, 2, 31] (Fig. 2), although the trigger(s) for this process remains unknown. This depletion within the islet is beta cell-specific, perhaps mediated through insulin serving as an antigen attracting auto-reactive T lymphocytes and macrophages. Similar to the pathogenesis of type 2 diabetes, the destruction of beta cells in patients with type 1 diabetes seems to precede the clinical manifestation of the disease, and impaired insulin secretion can be detected several years prior to the onset of hyperglycaemia [32]. Based on histological studies of pancreas specimens from patients with new-onset type 1 diabetes, beta cell mass is reduced by ~80–90% at this time [1, 33–35]. Interestingly, the degree of beta cell dysfunction at this time often exceeds the percentage beta cell loss [36–38], suggesting additional functional impairment in insulin secretion in these patients. Both beta cell mass and function further decline with increasing diabetes duration [33, 37, 39], but preserved C-peptide responses have been reported even after several years of type 1 diabetes [40, 41]. While it has long been held that the beta cell loss in type 1 diabetes is a finite and irreversible process, there is now evidence from several lines of research that some beta cell regeneration may occur even in patients with long-term type 1 diabetes [2]. Thus, even though beta cell mass is markedly diminished in the pancreas of patients with long-standing type 1 diabetes, some beta cells can be detected several decades after the onset the disease [1, 2]. These cells are often associated with T lymphocytes and macrophages, and have an increased frequency of apoptosis, implying that concomitant beta cell formation must be occurring even after several years of type 1 diabetes [2]. This hypothesis has been supported by reports of restoration of beta cell mass after the onset of hyperglycaemia in NOD mice [42], and of a marked increase in beta cell replication at the time of diabetes onset in mice and in humans [36, 38].

The potential for restoration of beta cell mass

The beta cell deficit in both type 1 and type 2 diabetes provides a rationale for novel therapeutic strategies aimed at restoring (or at least preventing further loss of) beta cell mass. In fact, enhancement of endogenous insulin secretion may theoretically provide several advantages over the administration of exogenous insulin: (1) the kinetics of endogenous insulin secretion are much faster than those of subcutaneously administered insulin [43, 44]; (2) under physiological circumstances, insulin is secreted in distinct pulses occurring at ~4–5 min intervals [45], and endogenous insulin secretion is regulated in a strictly glucose-dependent manner [46]; (3) alpha cell secretion is controlled by the pulsatile release of insulin from islet beta cells [18, 47]; (4) endogenous pulsatile insulin secretion has a direct effect on hepatic glucose metabolism, whereas exogenous insulin replacement primarily acts on peripheral insulin-sensitive tissues. The hypothetical consequences that might arise from restoration of beta cell mass for glucose control in patients with diabetes have been summarised in Fig. 3.

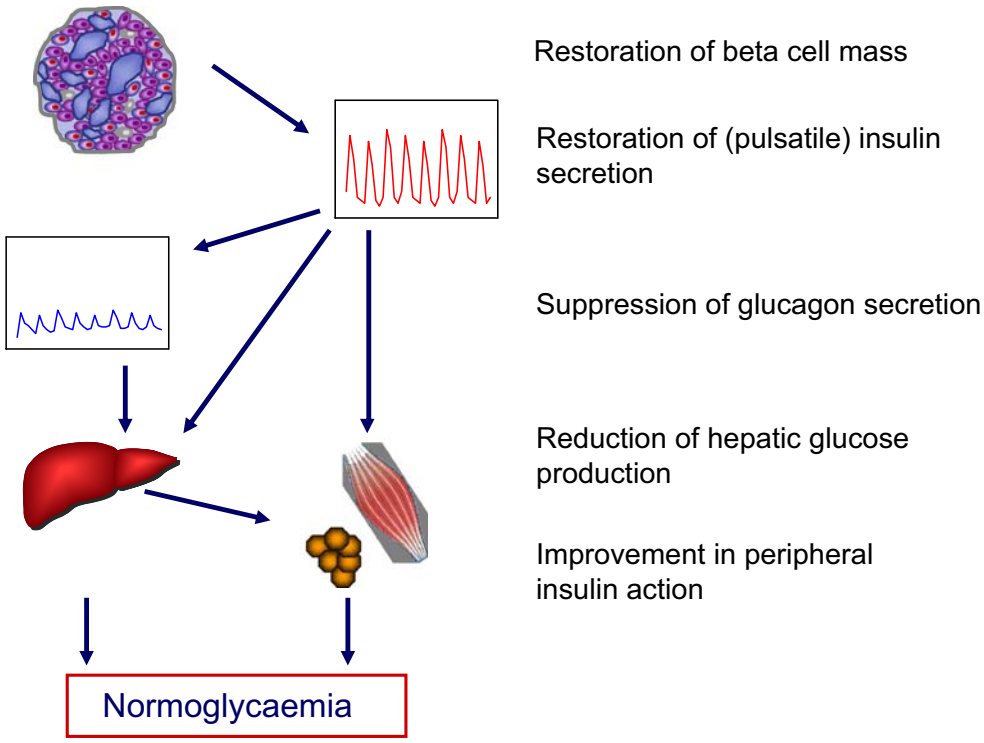

Fig. 3 Hypothetical diagram illustrating the potential consequences of beta cell regeneration for glucose metabolism. Theoretically, beta cell regeneration will lead to restoration of beta cell mass, which in turn will restore a physiological, pulsatile pattern of insulin secretion. Improved insulin secretion will subsequently lead to intra-islet suppression of alpha cell secretion and, in concert with lower glucagon levels, suppress the excessive hepatic glucose production. Finally, insulin action in muscle and adipose tissue will improve secondary to increased insulin secretion and reduced hepatic glucose output. Collectively, these changes may restore normoglycaemia in patients with diabetes

Strategies for beta cell regeneration

Embryonic stem cells One potential way of replenishing beta cell mass is the ex vivo generation of insulin-secreting cells from embryonic stem cells through directed differentiation [4]. Indeed, this field has advanced over recent years, in particular as a result of the development of more specific incubation regimens, allowing for a coordinated differentiation of human embryonic stem cells through different stages resembling definitive endoderm, gut tube endoderm, pancreatic endoderm and endocrine precursor cells [48]. Such human embryonic stem cell-derived preparations have been shown to release insulin upon challenge by different secretagogues, but reported to be particularly unresponsive to glucose stimulation [48]. In addition to this lack of glucose responsiveness, ethical hurdles associated with the generation of insulin-secreting cells from human embryos complicate the further development of this approach. Moreover, under physiological conditions, beta cells are embedded into the complex structure of the islet, which allows for the multi-modal control of insulin secretion through neural (e.g. sympathetic nerve fibres) [49], endocrine (e.g. intraislet glucagon) [18, 47, 50] and paracrine (e.g. somatostatin) [50] mechanisms. Given the technical difficulties associated with the generation of a single cell type, it seems unlikely that the complex organisation of the pancreatic islet can be replicated through targeted differentiation of embryonic stem cells. On the other hand, the importance of non-beta cells for glucose control following islet transplantation has been challenged by recent experiments in rats [51]. Finally, it is as yet impossible to control the proliferative activity of such cells, which poses a risk for tumour formation [4].

New beta cells derived from embryonic stem cells may be an interesting future strategy for the treatment of diabetes, but this approach appears to be far from ready for clinical application.

Extrapancreatic stem cells Not only human embryonic stem cells, but also mature cells of different origin, including liver, spleen, bone marrow and exocrine pancreas, have been reported to generate insulin-producing cells [4]. However, the overall plasticity of such differentiated cells appears to be even lower than that of human embryonic stem cells, and such cells typically lack other important beta cell components required for a coordinated mode of insulin secretion, such as glucokinase and GLUT-2.

Beta cell replication and islet neogenesis An alternative strategy for the restoration of beta cell mass in patients with diabetes is to foster beta cell regeneration from endogenous sources [4]. Some evidence suggests that beta cell mass is dynamic and capable of undergoing adaptive changes in response to different secretory demands [52]. In humans, beta cell mass increases by ~50% in obesity [3], and both insulin secretion and beta cell mass have been shown to increase in pregnant women [53, 54]. Likewise, beta cell mass in rodents increases by ~2.5-fold towards the end of pregnancy, and is rapidly decreased through increased apoptosis and reduced replication postpartum [52, 55, 56].

There is ongoing debate as to the potential origin of new beta cells in adults, and two major pathways have been proposed. On the one hand, replication of pre-existing beta cells in the pancreas has been convincingly demonstrated in adult mice [57, 58], rats [59, 60] and humans [3, 36, 61, 62] (Fig. 4), and recent lineage tracing studies indicated that new beta cell formation in postnatal mice exclusively results from the replication of existing beta cells [57]. On the other hand, the close association between exocrine ducts and beta cells has been interpreted as evidence that beta cells might also arise from stem cells residing in the ductal epithelium [63, 64] (Fig. 4). However, since it is as yet impossible to determine the exact origin of mature beta cells in cross-sectional studies, the importance of this pathway has not been convincingly proven. In the absence of a reliable beta cell precursor marker, the percentage of ductal cells producing insulin has often been used as a surrogate marker for this ductal neogenesis [65], and significant increases have been described in rodents after partial pancreatectomy [63, 66] and after prolonged hyperglycaemia or glucagon-like peptide 1 (GLP-1) treatment [67, 68]. Beta cells have been observed to be colocalised with exocrine ducts in human embryonic tissue [69] and in adult human pancreas specimens from individuals with or without diabetes [2, 3] (Fig. 4). Despite this obvious association between exocrine ducts and beta cells, the possibility remains that this phenomenon merely represents a residuum of fetal pancreas development and that the observed increases in the number of these insulin-positive cells within or adjacent to exocrine ducts relate more to a general expansion of beta cell mass, without a causal relationship to the ductal epithelium.

While the presence and quantitative significance of new beta cell formation from exocrine ducts remains to be proven, there is little doubt that beta cell replication continues over a lifetime (see above). However, the overall frequency of beta cell replication is extremely low in the adult pancreas, thereby complicating its quantitative assessment [59]. The rate of beta cell replication in adult rats was recently estimated to be ~0.07% per day using BrdU labelling [59], but subsequent studies have cautioned against the use of this technique, since prolonged infusion of BrdU may independently suppress cell proliferation [70].

Despite the slow rate of beta cell turnover under normal steady-state conditions, there appears to be a remarkable capacity for increased proliferation in situations of high secretory demand. In rodents, beta cell replication increases by approximately five- to tenfold after partial pancreatectomy, during pregnancy, during chronic glucose infusion and after treatment with GLP-1 analogues [63, 66], thereby illustrating the remarkable plasticity of the endocrine pancreas in rodents. In humans, the overall capacity for beta cell replication is much lower than in rodents, and very few replicating beta cells (one cell in ~50 islets of ~100 beta cells each per cross-section) can be found in adult human pancreas [3]. There is, however, a capacity for increased beta cell replication in humans. Beta cell replication has been reported to be more than ten times higher in human pancreas adjacent to gastrin-producing tumours [62] and in the pancreas of a patient presenting with the recent-onset type 1 diabetes [36].

The different turnover rates of beta cells in rodents and in humans have important implications for interpreting studies designed to replenish beta cell mass.

A number of recent studies have suggested that human beta cells maintain some capacity for regeneration even very late in life.

Detection of beta cell mass

Determination of the success of therapeutic strategies designed to enhance beta cell regeneration requires reliable methods for the assessment of beta cell mass. In animal models, beta cell mass can be easily calculated as the product

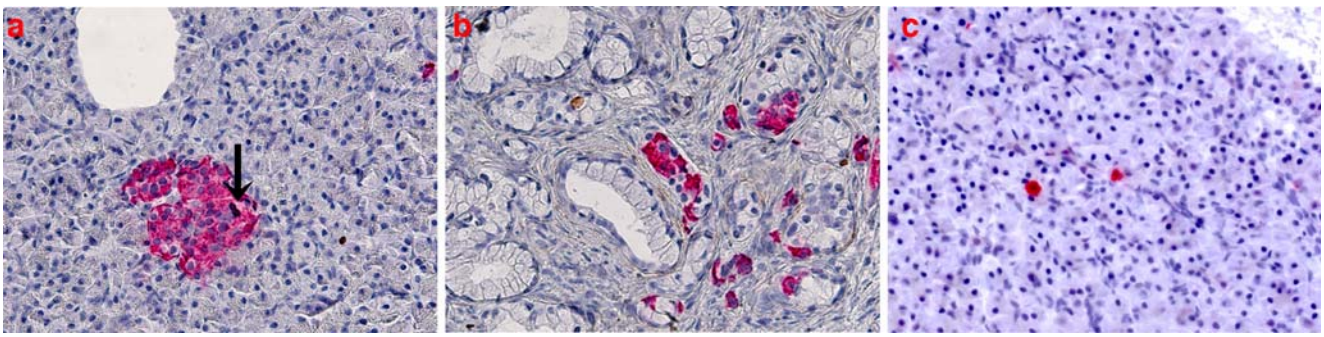

Fig. 4 Potential sources of new beta cell formation in adult human pancreas. Pancreatic sections were stained for insulin (red) and Ki67 (brown) and imaged at ×400 magnification. **a** A pair of replicating beta cells positive for Ki67 (arrow). **b** Multiple beta cells within or adjacent to exocrine ducts. This finding has often been interpreted as evidence of new islet formation from ductal progenitor cells. **c** Two single beta cells in the exocrine parenchyma. Beta cells are often seen scattered throughout this tissue, a finding often interpreted as indicating transdifferentiation of exocrine cells into beta cells

of pancreatic weight and the fractional beta cell area in cross-sections from different regions of the pancreas [19, 58]. However, in light of the obvious inaccessibility of the human pancreas for repeated biopsy sampling, non-invasive procedures are warranted to quantify beta cell mass in vivo. Two different approaches have been used to determine the functional beta cell mass in living humans, described below.

Imaging strategies to determine beta cell mass

While the volume of endocrine organs such as the thyroid gland or adrenal gland can be calculated with a reasonable accuracy using common imaging techniques such as ultrasonography, computed tomography or magnetic resonance imaging (MRI), the scattered distribution and relatively small size (~200 m in diameter) of islets have so far hampered the reliable quantification of beta cell mass. Furthermore, the differences in density and echogeneity between exocrine and endocrine pancreatic tissue are relatively minor. Alternative approaches have relied on the specific labelling of beta cells using enzymes, cell receptors or surface structures that are predominantly or exclusively expressed on beta cells. Tags such as these can be detected by positron emission spectroscopy, MRI, or single photon emission computed tomography. However, since the beta cells occupy only ~1–2% of the total pancreatic mass, any putative beta cell marker would be required to be at least 100:1 times more specific for beta cells than exocrine cells to give a labelling specificity of 50%. To date, a number of different beta cell structures, including GLP-1 receptors, sulfonylurea receptors, vesicular amine transporter 2 (VMAT2) and gangliosides, have been used as targets for these labels. In addition, the IC2 antibody and antibodies directed against D-mannoheptulose and alloxan have been used because of their specific uptake by, or binding to, pancreatic beta cells. These studies have recently been summarised elsewhere [71]. However, to date, none of these markers has provided approximations of beta cell mass with sufficient sensitivity and specificity to justify their routine application in humans. Ongoing clinical trials are using VMAT2 as a surrogate marker of insulin production and the radioligand ^{11}C-labelled dihydrotetrabenazine for the determination of beta cell mass in type 1 diabetic patients and controls. The final results of these trials are awaited.

Functional assessment of beta cell mass In the absence of a reliable imaging test to determine beta cell mass in humans in vivo, functional tests of insulin secretion have been applied. These tests are based on the assumption that the amount of insulin secreted in response to a secretagogue is proportional to the number of beta cells present in the pancreas. However, some theoretical caveats should be kept in mind with respect to the interpretation of such tests. Insulin secretion may well change independently from beta cell mass. In fact, insulin secretion in obese individuals can be increased by a factor of five to ten [72], whereas beta cell mass has been shown to be only ~50% higher in obese compared with lean individuals [3]. In line with this, a linear relationship has been observed between the mean nuclear diameter of beta cells and BMI, suggesting that the transcriptional activity of beta cells increases with higher insulin demands [61]. Furthermore, glucose-induced insulin secretion is subject to considerable day to day variation, and can be modulated to a large extent by pharmacological interventions, such as an overnight infusion of a GLP-1 analogue [73], temporary inhibition of insulin secretion [74] or prolonged glucose normalisation by the administration of exogenous insulin [75]. Most likely, these differences relate to differences in beta cell granule content, which determines subsequent insulin secretory responses. The second potential caveat relates to the different volumes of distribution between lean and obese individuals—the secretion of a certain number of insulin molecules in an obese individual with a large plasma volume will produce a lower plasma concentration than the secretion of the same number of molecules in a lean individual. Finally, differences in hepatic insulin clearance may alter systemic insulin levels [72, 76].

Despite the theoretical concerns, indirect testing of beta cell function currently represents the most reliable method of estimating beta cell mass in humans. The relationship between different indices derived from metabolic tests and the actual beta cell mass has recently been summarised elsewhere [77]. Generally, the closest correlation with beta cell mass has been obtained for arginine-induced insulin secretion and for glucose potentiation of arginine-induced insulin secretion (~70% accuracy) [78, 79]. It is also important to note that the assessment of glucose-induced insulin secretion will only provide reliable results when individuals are tested at similar glucose concentrations [12].

Given the lack of reliable routine methods to determine beta cell mass in humans in vivo, functional tests of insulin secretion may be a suitable alternative.

Therapeutic strategies to maintain or restore beta cell mass in diabetes

As a result of the growing interest in beta cell regeneration as a potential cure for diabetes, a number of different treatment strategies aimed at increasing beta cell mass have been evaluated. Owing to the limitations of directly quantifying beta cell mass in humans in vivo, different surrogates for beta cell regeneration have been used. These include (1)

inhibition of beta cell apoptosis and/or stimulation of beta cell regeneration in beta cell lines and/or isolated (human) islets in vitro; (2) increasing beta cell mass in animal models (primarily rats and mice) in vivo; and (3) functional improvements (or at least preservation) of insulin secretion in long-term studies in patients with diabetes in vivo. The effects of various current and future pharmacotherapies for type 1 and type 2 diabetes on beta cell mass and turnover at these experimental levels have been summarised in the Table 1.

Importance of beta cell rest and exhaustion for diabetes therapy

When evaluating the effects of glucose-lowering treatment regimens on beta cell turnover, one key aspect determining the fate of the beta cells may be the individual's demand for insulin secretion. There is some evidence from in vitro studies that constant stimulation of insulin secretion by either prolonged high glucose exposure or sulfonylurea treatment (particularly glibenclamide, known as glyburide in the USA and Canada) may result in beta cell degranulation and the induction of cell death [80, 81]. These potentially detrimental effects of sulfonylureas may serve to explain the relatively high rates of beta cell failure during sulfonylurea therapy in the a Diabetes Outcome Progression Trial (ADOPT), even though the rate of beta cell failure in sulfonylurea-treated patients was not increased in the UK Prospective Diabetes Study (UKPDS) [82, 83]. Insulinotropic agents with a shorter duration of action (e.g. repaglinide, nateglinide) or glucose-dependent properties (e.g. GLP-1, gastric inhibitory polypeptide) have been

Table 1 Therapeutic strategies with a potential direct effect on beta cell mass and turnover in different experimental models

Treatment	Effects on beta cell turnover in vitro	Effects on beta cell mass in rodents in vivo	Long-term effects on beta cell function in humans	References
Type 1 diabetes				
Anti-CD3 antisera	No direct effect	Prevention and reversal of diabetes in NOD mice	Preservation of beta cell function in new-onset type 1 diabetes	[42, 88]
Cyclosporin	Beta cell apoptosis ↑	Prevention of diabetes in NOD mice	Preservation of beta cell function in new-onset type 1 diabetes	[89]
Nicotinamide	Beta cell apoptosis ↓	Prevention of diabetes in NOD mice	No prevention of type 1 diabetes in high-risk subjects No preservation of beta cell function in new-onset type 1 diabetes	[90]
Potassium channel openers (e.g. diazoxide)	Beta cell apoptosis ↓ Replenishment of insulin granules	Not examined	Preservation of beta cell function in new-onset type 1 diabetes	[85, 91]
Type 2 diabetes				
GLP-1 analogues	Beta cell proliferation ↑ Beta cell apoptosis ↓	Increase in beta cell mass in diabetic rats and mice	Stable glucose control over 52 weeks of treatment No prolongation of islet graft survival after transplantation No long-term studies available	[68, 84, 92, 93]
DPP-4 inhibitors	No direct effect (indirect action via GLP-1 and GIP)	Increase in beta cell mass in diabetic rats and mice	Stable glucose control over 52 weeks of treatment No long-term studies available	[94, 95]
Metformin	Beta cell apoptosis ↓ Markers of oxidative stress ↓	No direct effect on beta cell mass	Slow rate of deterioration of glucose control (ADOPT trial)	[22, 83, 96]
Glitazones	Beta cell apoptosis ↓	No direct effect on beta cell mass	Slow rate of deterioration of glucose control (ADOPT trial)	[83, 96, 97]
Sulfonylureas	Beta cell apoptosis ↑	Modest and transient increase in beta cell mass (shown in one study only)	Progressive deterioration of glucose control over prolonged treatment periods in the ADOPT trial No increased rate of deterioration of beta cell function in the UKPDS	[80, 82]
ACE inhibitors (e.g. ramipril)	Beta cell apoptosis ↓ Markers of oxidative stress ↓	Increase in beta cell mass	No significant effect on diabetes incidence in randomised prospective trials	[98, 99]

ADOPT, a Diabetes Outcome Progression Trial; GIP, gastric inhibitory polypeptide; UKPDS, UK Prospective Diabetes Study

shown to be less detrimental, or even protective, under in vitro conditions [81, 84]. While beta cell exhaustion may potentially accelerate the loss of beta cells in type 2 diabetes, induction of beta cell rest, i.e. the temporary inhibition of insulin secretion, appears to confer a certain degree of beta cell protection. In isolated human islets, temporary inhibition of insulin secretion using potassium channel openers has led to subsequent improvement of glucose-induced insulin secretion, increased islet insulin content, and inhibition of beta cell apoptosis [29, 85].

The mechanisms linking beta cell exhaustion to the induction of cell death have not been elucidated in detail, but many studies have suggested a key role of oxidative stress. There is accumulating evidence that beta cell insulin depletion leading to an increasing demand for proinsulin biosynthesis eventually results in the induction of ER stress, which in turn leads to the initiation of apoptosis. Consistent with this hypothesis, recent studies have found increased levels of ER stress markers in the islets of patients with type 2 diabetes [86].

From a clinical point of view, the simplest way of inducing beta cell rest is to reduce the peripheral insulin demand by either improving insulin sensitivity (e.g. through physical activity or pharmacologically, using metformin or glitazones) or by lowering blood glucose levels through the administration of exogenous insulin. In a prospective trial on patients with type 2 diabetes, induction of beta cell rest induced by bedtime administration of NPH insulin resulted in significant improvements in endogenous insulin secretion in response to glucose [75]. Likewise, in a study that compared insulin with glibenclamide over 2 years, recently diagnosed patients with type 2 diabetes treated with insulin exhibited a significantly greater endogenous insulin secretory response and a lower proinsulin:insulin ratio [87]. Nevertheless, as yet, there is no direct evidence for the induction of beta cell apoptosis by sulfonylurea drugs or for the preservation of beta cell mass by either metformin, glitazones or exogenous insulin in patients with type 2 diabetes in vivo.

A number of glucose-lowering agents (e.g. incretin mimetics, dipeptidylpeptidase 4 [DPP-4] inhibitors) have been suggested to prevent beta cell apoptosis, but their long-term effects on beta cell mass in patients with diabetes remain to be elucidated.

Outlook

In response to the increased recognition of the important role of beta cell mass in the development of diabetes interest has grown in targeting beta cell mass for the treatment for diabetes. A number of recent studies have suggested that beta cell mass might be restored by fostering endogenous beta cell replication, combined with concomitant inhibition of apoptosis. However, our current understanding of postnatal beta cell turnover is primarily based on experiments performed under in vitro conditions or in rodent models, the results of which are not fully generalisable to the situation in humans in vivo. Debate is ongoing as to the potential effects of various glucose-lowering treatments on beta cell death and proliferation, and some drugs have been proposed to accelerate beta cell loss (e.g. glibenclamide), whilst others have been suggested to be somewhat protective (e.g. GLP-1 receptor agonists, DPP-4 inhibitors). However, before any of these treatment regimens can be accepted as safely modulating beta cell turnover, changes in beta cell mass need to be demonstrated in patients with diabetes in vivo. In light of the absence of direct imaging methods to quantify beta cell mass in living humans, functional indices of insulin secretion derived from metabolic tests appear to provide the most meaningful estimates of beta cell mass. It is hoped that future long-term trials involving metabolic testing in patients with diabetes will determine changes in beta cell mass in response to various glucose-lowering treatment regimens. Such information will enable physicians to not only focus on glucose control, but perhaps also to modulate the natural progression of diabetes.

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