INTRODUCTION

Diabetes mellitus afflicts approximately 8% of Canadians, with an increasing incidence and prevalence (1, 2). Most will go on to develop complications, including cardiovascular disease, nephropathy, neuropathy and retinopathy, contributing to over $10 billion per year in health-related costs (2).

While the etiologies differ between type 1 (T1DM) and type 2 diabetes (T2DM), both forms are characterized by a relative deficit in functional β-cell mass such that the insulin requirements of the body are not met and glycemia is uncontrolled. Thus, current therapies treat the symptoms of diabetes by normalizing glycemia, either by improving the insulin secretory output of the remaining β-cells (insulin secretagogues), improving the response to insulin at target tissues (insulin sensitizers), or replacing the missing insulin (exogenous insulin). As it stands, only isolated islet and solid organ pancreas transplantation address the deficit in β-cell mass that underlies diabetes, but these therapies are of limited clinical utility due to the shortage of donor organs and the side effects inherent to the immunosuppression that allo-grafts require. However, recent research suggests that the human pancreas may possess a significant regenerative capacity. Hence, new therapeutic strategies seek to harness this regeneration to re-establish a functional β-cell mass that is sufficient to normalize glycemia and reverse diabetes.

Type 1 Diabetes Mellitus

While the exact nature of the insult remains to be elucidated, T1DM is characterized by the destruction of pancreatic β-cells due to T-cell-mediated auto-immune attack (3). Clinical onset is associated with a residual β-cell mass comprising approximately 20% that of age-matched non-diabetic individuals (4). It is at this point that the remaining β-cell mass is incapable of maintaining normoglycemia, and persistent hyperglycemia occurs.

Thus, the current treatment for T1DM consists of insulin replacement, either by the administration of
exogenous insulin in a manner that seeks to mimic the secretory response of β-cells, or by the replacement of the missing β-cells by the transplantation of solid-organ pancreas or isolated islets allo-grafts. Unfortunately, while exogenous insulin administration may delay or slow the development of diabetic complications, this treatment cannot prevent their occurrence (5, 6). Conversely, solid organ pancreas transplant represents the only available means of providing long-term glycemic control that prevents, and even, reverses diabetic complications (7), by way of re-establishing an appropriately functional β-cell mass. However, life-long immunosuppression, with all the associated side effects, along with the limited availability of cadaveric donor organs, limits any transplantation-based approach. With respect to islet transplantation, it was hypothesized that the islets isolated from one donor organ could be used to treat several recipients, given that overt diabetes is only observed when there is a ≥50% reduction in β-cell mass (4). However, the attrition associated with the isolation process results in several donor organs being required per individual recipient, while the average duration of graft function reaching only 15 months in islet recipients (8), as compared to ten years in pancreas recipients (7). Thus, none of the currently available treatments is ideal.

While it stands to reason that the auto-immune attack responsible for T1DM would eventually result in a complete loss of β-cell mass, recent case reports of elderly individuals with long-standing T1DM indicate ongoing β-cell apoptosis (9, 10), suggesting that attempts at β-cell regeneration within the native pancreas may persist throughout the duration of the disease. The rate of such regenerative mechanisms is obviously eclipsed by the rate of β-cell death in individuals with T1DM, but this observation does suggest nonetheless that the manipulation of rates of β-cell formation and death could be a possible therapeutic target in diabetes.

**Type 2 Diabetes Mellitus**

T2DM accounts for the vast majority of cases of diabetes, and is a heterogeneous disease marked by β-cell dysfunction (11, 12) combined with insulin resistance in target tissues (11, 13, 14). The pathogenesis of the disease involves both genetic (15) and environmental factors, and is frequently associated with obesity (13, 16-18).

With respect to β-cell dysfunction, clinical studies have highlighted the impaired first-phase insulin secretion that is common in T2DM (19-21). Moreover, in vitro studies of isolated human islets indicate that insulin content and the insulin secretory response to a glucose challenge are decreased in T2DM (22-25). Thus, a normal β-cell mass may not necessarily correlate with normal glucose tolerance (26), suggesting that the β-cell deficit in T2DM may be functional, as opposed to absolute (4, 27-34).

It is for these reasons that the current pharmaceutical options for the management of T2DM fall into two broad categories; those of insulin secretagogues – compounds that increase the insulin secretory response of the β-cell – and insulin sensitizers – compounds that potentiate the effect of insulin at its target tissues. While these medications are certainly useful in the management of the disease, the fact remains that a significant proportion of patients with T2DM eventually require exogenous insulin due to the progressive loss of β-cell function and increase in insulin resistance.

However, recent data now suggests that T2DM is also characterized by an absolute deficit in β-cell mass (35, 36). In fact, a step-wise decline in β-cell mass is observed over the progression from normoglycemia to impaired fasting glucose to overt diabetes (35). With respect to the mechanism of this loss of β-cell mass, it would appear that the rate of β-cell apoptosis is increased in T2DM, while the rate of β-cell formation is unchanged (35). Moreover, it seems that the hyperglycemic hyperlipidemic environment that is found in T2DM is directly toxic to pancreatic β-cells (37, 38), further propagating this cycle (39-41). Thus, interventions designed to either slow the rate of β-cell apoptosis, or stimulate the formation of new β-cells may be of clinical utility in the management of T2DM.

**β-Cell Mass**

Pancreatic β-cell mass is not a static entity, but rather is in constant flux, and as such can adapt to the prevailing physiologic needs (42, 43). For example, insulin resistance associated with pregnancy (44) or obesity (4, 35, 45) leads to as much as a doubling of β-cell mass. Conversely, a deficit in β-cell mass is associated with diabetes (9, 35).

Changes in β-cell mass over time reflect the net effect of diametrically opposed pathways; those that serve to increase β-cell mass, and those that serve to decrease it. Possible β-cell mass expansion pathways include β-cell hypertrophy and replication, as well as the formation of new β-cells from non-β-cell sources – neogenesis. Each of these factors has an equivalent opposing force; β-cell atrophy and death, via apoptosis or necrosis, as well as β-cell dedifferentiation, all serve to decrease β-cell mass. However, studies suggest that the three main mechanisms at play in controlling β-cell mass dynamics are β-cell replication, neogenesis and death (35, 46, 47).

Based on these observations, Finegood et al. (42)
proposed a simple mass-balance equation to follow the prevailing trends in β-cell mass:

\[ \frac{d(\beta\text{-cell mass})}{dt} = \text{rate } \beta\text{-cell replication} + \text{rate } \beta\text{-cell neogenesis} - \text{rate } \beta\text{-cell death.} \]

While β-cell mass is highly dynamic, and represents the sum of several processes, the methods for estimating overall β-cell mass and the rates of change are static. Moreover, no current technology exists to accurately assess these parameters \textit{in situ}. Thus, studies of β-cell mass in humans are limited to autopsy cases and cadaveric donor organs, with rates of changes presented as relative, rather than absolute values (35, 36). Nevertheless, these studies provide indications of these mechanisms in non-diabetic humans, and suggest the effects of diabetes on the mechanisms that control β-cell mass.

As indicated earlier, human diabetes is marked by a deficit in functional β-cell mass. While patients suffering from T1DM have a virtual lack of β-cell mass (4), chronic β-cell apoptosis in individuals with T1DM suggests β-cell neogenesis is also ongoing (9, 10). Recent evidence also indicates that increased β-cell apoptosis also leads to a deficit in β-cell mass in T2DM (35). This increased β-cell apoptosis is observed in both lean and obese cases of T2DM, while obese T2DM individuals do show evidence of increased neogenesis and lean T2DM individuals have increased β-cell proliferation indices, suggesting compensatory mechanisms are intact, but outpaced by β-cell apoptosis (35). Thus, these findings suggest that regenerative mechanisms do exist within the human pancreas, and it may be possible to manipulate the rates of the various components to affect overall β-cell mass.

\textbf{Limiting β-Cell Loss}

The mechanisms responsible for depleting β-cell mass are well defined, and are predominated by β-cell death (35, 42), either in the form of apoptosis or necrosis. Increased β-cell death is common to both T1DM (3) and T2DM (35), however efforts at controlling this aspect of β-cell mass have been limited. While the auto-immune nature of T1DM suggests that attenuation of the immune response may help to preserve β-cell mass, results of clinical trials have not supported this therapeutic avenue (48). Likewise, while inhibition of β-cell apoptosis would likely be a useful therapy in T2DM, few agents have any specificity for pancreatic β-cells (49-52), and systemic administration of a generic anti-apoptotic agent is simply unfeasible.

\textbf{Inducing β-Cell Expansion}

The mechanisms of increasing β-cell mass are still highly controversial (53, 54). The two principal mechanisms of increasing β-cell mass are replication – the formation of β-cells by the division of pre-existing β-cells – and neogenesis – the formation of β-cells from non-β-cell precursors (55-59).

\textbf{β-Cell Replication}

While the adult β-cell turnover rate is low (60), \textit{in vivo} and \textit{in vitro} studies have determined that β-cells proliferate in response to physiologic concentrations of relevant growth factors (61-68). Recent evidence suggests that β-cell proliferation may function as a compensatory mechanism in T2DM (35, 46), although proliferating β-cells are also more susceptible to apoptosis (69, 70). Thus, β-cell replication is a real, semi-quantifiable component of β-cell mass dynamics, both in the normal and diseased pancreas. However, unbridled cell proliferation is a hallmark of cancer, and as such care must be taken to ensure a physiologic, self-limiting level of proliferation.

\textbf{β-Cell Neogenesis}

Although β-cell replication and neogenesis are dynamic processes, the availability of detectable markers of cellular proliferation (71, 72) renders the quantification of cell replication much more straightforward than the measurement of neogenesis. Recent advances in lineage tracing techniques have facilitated the process, but questions regarding the cell(s) of origin and inter-species differences mean that neogenesis is still a polarizing subject.

Neogenesis implies that β-cells form from non-β-cell precursors (56-58), though the source and location of such precursors is not specified. Thus, the term neogenesis could be applied to the formation of β-cells from intra- or extra-pancreatic stem cells, as well as the direct or indirect transdifferentiation of other adult cell types. Regardless of the exact nature of the cell(s) of origin, neogenesis represents a means of expanding pancreatic β-cell mass.

\textbf{Regenerative Factors}

A variety of animal models have been developed to study the mechanisms of islet regeneration, and identify the factors involved. These models include partial pancreatic duct obstruction (57, 73) or ligation (74, 75), partial pancreatectomy (58, 76), chronic and acute glucose infusion (77-79), administration of a β-cell-specific toxin (80) and transgenic models (81-83), all of which are associated with an endogenous pancreatic regenerative response. As such, researchers have screened the regenerating pancreas to identify factors that may regulate the response, as well as general changes in gene expression (84, 85).
Several novel therapeutics have been developed based on these studies, all of which are currently in clinical trials as novel therapies for diabetes.

**Gastrin and Epidermal Growth Factor**

Studies of the pancreatic regenerative response to pancreatic duct ligation (74) noted the upregulation of gastrin and transforming growth factor-β, a member of the epidermal growth factor (EGF) family of ligands (75). Subsequent studies indicated that alone, these factors acted mainly as duct cell mitogens (86-88), whereas co-administration or generation of double transgenic animals led to a significant increase in β-cell mass (82, 89, 90). It now appears that the role of EGF ligands may be to generate metaplastic duct-like structures derived from acinar tissue (91, 92), which then go on to form islets in response to gastrin (93).

*In vitro* studies suggest that human tissue can be expanded and differentiated in the same way (94-96). There is also pathologic evidence for such an islet regenerative effect of gastrin, as Zollinger-Ellison syndrome – hypergastrinemia secondary to a gastrinoma – is associated with increased islet neogenesis and replication (97, 98).

Based on the above studies, combination therapy with gastrin and EGF analogues is currently in clinical trials (99), although due to the established carcinogenicity of EGF, more recent trials focus on gastrin and glucagon-like peptide-1 (GLP-1) co-administration (100). Nonetheless, preliminary data from phase IIa clinical trials indicate that EGF and GLP-1 analogue co-administration improve glycemic control, as reflected by HbA1c, fasting glucose and glucose tolerance (101).

While clinically important and suggestive of clinical benefit, the exact mechanism of action of these combinations is not yet clear. In vitro studies suggest that human tissue can be expanded and differentiated in the same way (94-96). There is also pathologic evidence for such an islet regenerative effect of gastrin, as Zollinger-Ellison syndrome – hypergastrinemia secondary to a gastrinoma – is associated with increased islet neogenesis and replication (97, 98).

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**Glucagon-like Peptide-1**

GLP-1 is a product of alternative post-translational modification of preproglucagon (102). While β-cells produce and secrete glucagon, enteroendocrine L-cells of the intestine produce GLP-1 (103). Due to their incretin and other effects (104), long-acting GLP-1 analogues (105) and dipeptidyl peptidase-IV inhibitors (106) are already available for the treatment of T2DM. Additionally, however, GLP-1 has been implicated in islet regeneration (64, 107-113), leading to its study as a regenerative factor.

Data regarding the regenerative role of GLP-1 and related agonists are controversial. There is strong evidence to suggest that GLP-1 receptor activation can protect β-cells from apoptosis (49-52). There is equally convincing evidence of a β-cell mitogenic effect of GLP-1 (49, 64, 108, 114). However, while there are reports of GLP-1-mediated islet neogenesis (64, 109, 112, 113, 115), recent statements by researchers examining the *in vivo* effects of GLP-1 call into question a neogenic response (116-120). Nevertheless, GLP-1 certainly has a role to play in the evolving treatment of diabetes, if not as a neogenic factor then at least with its capacity to act as a β-cell mitogen and anti-apoptotic supplementing its activity as an incretin.

**Reg Proteins**

Given that subtotal pancreatectomy combined with poly(ADP-ribose) polymerase inhibitor treatment promotes islet regeneration (121), researchers screening a cDNA library generated from the regenerating islets identified a novel protein, termed regenerating protein (Reg, now known as RegI) (122). It was later determined that while some Reg proteins are expressed in regenerating islets (123), expression is primarily at acinar tissue (124).

Reg proteins have been postulated to play a role in inhibition of pancreatic stone formation (125), bacterial aggregation (126), regulation of inflammation (127, 128) and cellular adhesion to extracellular matrix components (129), among others. Most interestingly, however, *in vivo* studies suggest that administration of RegI may be sufficient to induce pancreatic regeneration in both surgically-induced (62) and genetic (130-133) models of diabetes. Moreover, RegI-overexpressing mice have increased islet proliferation, and crossing onto a genetic background of diabetes (NOD) delays the onset of diabetes and increases β-cell mass (134). RegI-/- animals are not overtly diseased, although islet proliferation is reduced (134). Reg proteins are mitogenic to islet and ductal cell lines, as well as isolated islets and primary duct cultures (135-137), and may also have anti-apoptotic effects (128, 138).

While the exact Reg mechanism of action and signalling pathways are still contentious (139), it is noteworthy that Reg expression or activity has been associated with other putative regenerative factors. For example, administration of a GLP-1 analogue upregulates pancreatic Reg expression prior to observation of islet regeneration (85), while the effects of gastrin may be mediated by Reg expression (140, 141).

Thus, while results are promising, Reg proteins, with the exception of one, have not elicited much clinical interest.

**Islet Neogenesis-Associated Protein**

The Reg proteins can be divided into three general families; RegI, RegIII and Reg IV (142). The RegIII subfamily is characterized by the presence of a five
amino acid insert, which would likely be found on an outside turn in the three-dimensional structure of the protein, based on available models (143). Islet neogenesis-associated protein (INGAP) is the only RegIII protein identified in hamsters, although two family members exist in humans, and four exist in mice, including one - RegIIIβ - that is highly homologous to INGAP (144).

INGAP was discovered in a surgical model of partial pancreatic duct obstruction associated with increased β-cell mass and what appeared to be foci of islet neogenesis (57). Initial work identified a crude pancreatic extract containing biological activity (145), while subsequent genetic work identified INGAP as the main biologically active compound (135). Based on three-dimensional modelling and sequence comparisons, a synthetic 15 amino acid fragment was designed, which includes the aforementioned five amino acid insert. This fragment (INGAP104-118), termed INGAP peptide, was shown to induce the proliferation of primary ductal cultures and ductal cell lines (135).

While identified initially in partially pancreatic duct-obstructed hamsters, INGAP was subsequently found to be upregulated in other models of islet regeneration, including sucrose administration in hamster drinking water (146), sucrose administration to pregnant hamsters (147), chronically glucose-infused rats and diabetes-prone BioBreeding rats (96).

Administration of INGAP peptide increases β-cell mass sufficiently to reverse chemically-induced diabetes in mice (148). While INGAP peptide did not reverse diabetes in chronically diabetic NOD mice, co-administration with immunosuppression improved survival and indices of diabetes severity (96). Studies on isolated rat islets indicate that acute INGAP peptide treatment can increase both basal and stimulated insulin secretion from isolated rat islets (149).

Interestingly, while administration of INGAP peptide to normoglycemic hamsters (148), mice (47) or monkeys (96) does induce islet neogenesis and β-cell mass expansion, this increase appears to be transient, at least in healthy animals. Based on this observation, it has been proposed that the mechanisms of β-cell mass dynamics are actively regulating β-cell mass, even in the context of induced islet neogenesis (47).

While no direct human homologue appears to exist for INGAP, studies using in vitro cultures of human islet- or acinar-derived tissue indicate that the islet regenerative potential of INGAP peptide also extends to human tissue (95, 150). Clinical trials have also yielded promising results, showing an increase in arginine-stimulated C-peptide levels in T1DM patients (151), and a decrease in HbA1c in T2DM patients (152).

CONCLUSION

While the therapies currently available for the management of diabetes are relatively successful at controlling the symptoms of this disease, the fact remains that the underlying cause of these symptoms goes unaddressed. Thus, the majority of patients with diabetes will develop secondary complications of the disease resulting in shortened lifespan and reduced quality of life. Recent insights into the etiology of diabetes have offered a suggestion as to new therapeutic opportunities for the treatment of diabetes, namely the re-establishment of a functional β-cell mass that is sufficient for glycemic control. Thus, new therapies are being designed and tested that seek to re-establish a significant population of functional β-cells in the endogenous pancreas, either by inhibiting the destruction of pre-existing β-cells, or inducing the formation of new β-cells. However, any therapy that seeks to manipulate the balance between cell death and survival, and differentiation and proliferation, also carries with it the risk of carcinogenicity. This risk is of particular concern given that the clinical interest in these novel therapies is not necessarily reflective of our level of understanding of the mechanisms of control of β-cell mass dynamics. However, given the inherent ability of the body to manipulate β-cell mass in response to specific metabolic conditions (4, 35, 42-45), and a recent report that suggests that the body’s ability to regulate β-cell mass remains intact even in the context of external manipulation (47), it would appear that therapies designed at re-establishing a functional endogenous β-cell mass possess a significant potential as novel therapies for diabetes.

ACKNOWLEDGEMENTS

This work was supported by fellowships from the Canadian Diabetes Association / Canadian Institutes of Health Research and Fonds de Recherche en Santé du Québec.

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Stephen Hanley (M.D., C.M. 2011) completed a BSc in Biochemistry and Pharmacology & Therapeutics (2002) and a PhD in Experimental Surgery (2009), both from McGill University. He is currently a medical student at McGill University, with active research interests in gastrointestinal endocrinology and pancreatic regeneration.