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THERAPEUTIC APPROACHES TO PRESERVE ISLET MASS IN TYPE 2 DIABETES

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■ **Abstract** Type 2 diabetes is characterized by hyperglycemia resulting from insulin resistance in the setting of inadequate β-cell compensation. Currently available therapeutic agents lower blood glucose through multiple mechanisms but do not directly reverse the decline in β-cell mass. Glucagon-like peptide-1 (GLP-1) receptor agonists, exemplified by Exenatide (exendin-4), not only acutely lower blood glucose but also engage signaling pathways in the islet β-cell that lead to stimulation of β-cell replication and inhibition of β-cell apoptosis. Similarly, glucose-dependent insulinotropic polypeptide (GIP) receptor activation stimulates insulin secretion, enhances β-cell proliferation, and reduces apoptosis. Moreover, potentiation of the endogenous postprandial levels of GLP-1 and GIP via inhibition of dipeptidyl peptidase-IV (DPP-IV) also expands β-cell mass via related mechanisms. The thiazolidinediones (TZDs) enhance insulin sensitivity, reduce blood glucose levels, and also preserve β-cell mass, although it remains unclear whether TZDs affect β-cell mass via direct mechanisms. Complementary approaches to regeneration of β-cell mass involve combinations of factors, exemplified by epidermal growth factor and gastrin, which promote islet neogenesis and ameliorate diabetes in rodent studies. Considerable preclinical data support the concept that one or more of these therapeutic approaches, alone or in combination, may potentially reverse the decline in β-cell mass that is characteristic of the natural history of type 2 diabetes.

INTRODUCTION

Type 2 diabetes, also known as non-insulin-dependent diabetes mellitus, accounts for >90% of diabetes worldwide. It is characterized by impaired insulin action (insulin resistance) in peripheral tissues, principally muscle, adipose tissue, and liver, in association with a deficient β-cell insulin-secretory response to glucose. The pathogenesis of type 2 diabetes involves a combination of genetic and environmental/lifestyle factors and is frequently associated with obesity (1). Patients with type 2 diabetes have an increased risk of developing both microvascular and macrovascular disease and associated complications, including nephropathy, neuropathy, retinopathy, and cardiovascular disease. The global incidence of type 2

diabetes has been increasing steadily in the past several years, partly because of an increased prevalence of obesity, a more sedentary lifestyle, and a rise in the average age of the general population (2). There has also been a significant rise in the incidence of obesity and type 2 diabetes among children and adolescents (3). Thus, type 2 diabetes is now a major public health problem that places a severe economic burden on health care systems.

Traditional medications for type 2 diabetes, including insulin, sulfonylureas, glitinides, acarbose, metformin, and thiazolidinediones, lower blood glucose through diverse mechanisms of action. Studies such as the United Kingdom Prospective Diabetes Study (UKPDS) clearly illustrate that better glycemic control achieved with some of these drugs can significantly reduce the development of diabetes-associated secondary complications (4). However, many of the oral hypoglycemic agents lose their efficacy over time, resulting in progressive deterioration in β-cell function and loss of glycemic control.

The reasons why current antidiabetic agents become less effective over time are not well understood, but they appear to include progressive loss of β-cell mass. Autopsy studies demonstrate that β-cell mass is decreased in type 2 diabetes despite a normal capacity for β-cell replication and neogenesis (5–8). β-cell mass is governed by a combination of factors: (*a*) replication of existing β-cells, (*b*) differentiation of new β-cells from ductal and extraislet precursor cells (neogenesis), and (*c*) β-cell apoptosis (9–11). Reduced β-cell mass has been observed in both obese and lean type 2 diabetic humans (5) and in diabetic rodent models of genetic and experimental diabetes (12). Commonly observed in both human and rodent studies of type 2 diabetes is an increase in β-cell apoptosis (5, 13, 14); the mechanisms responsible include chronic hyperglycemia, dyslipidemia, endoplasmic reticulum and oxidative stress, islet amyloid deposition, and actions of inflammatory cytokines (reviewed in 15, 16).

Medications currently used to treat type 2 diabetes cannot prevent β-cell death or re-establish β-cell mass. Moreover, short-term studies demonstrate that sulfonylureas can induce apoptosis in rodent β-cells (17) or cultured human islets (18). Thus, sulfonylurea therapy could theoretically exacerbate β-cell loss in subjects with type 2 diabetes. Consequently, there has been intense interest in the development of therapeutic agents that preserve or restore functional β-cell mass. Several agents with the potential to inhibit β-cell apoptosis and/or increase β-cell mass have been identified in preclinical studies (Figure 1, Table 1).

GLP-1 RECEPTOR AGONISTS

Glucagon-like peptide-1 (GLP-1), a potent glucoregulatory hormone, is produced in enteroendocrine L-cells by tissue-specific post-translational processing of proglucagon and is released into the circulation in response to nutrient ingestion (19). GLP-1 regulates glucose homeostasis by stimulating glucose-dependent insulin secretion and biosynthesis, and by suppressing glucagon secretion, gastric emptying, and appetite (20). GLP-1 may also enhance insulin-independent

TABLE 1 Agents that increase or preserve β-cell mass

Stimulators of β-cell proliferation and/or neogenesis	Inhibitors of β-cell death
GLP-1	GLP-1
GIP	GIP
DPP-IV inhibitors	DPP-IV inhibitors
Epidermal growth factor/gastrin	Growth hormone
TZDs	Hepatocyte growth factor
Growth hormone	Insulin-like growth factors
Hepatocyte growth factor	Parathyroid hormone-related peptide
Human placental lactogen	
INGAP	
Insulin-like growth factors	
Parathyroid hormone-related peptide	
Prolactin	
Keratinocyte growth factor	
Betacellulin	

Abbreviations: GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; DPP-IV, dipeptidyl-peptidase-IV; TZDs, thiazolidinediones; INGAP, islet neogenesis-associated protein.

glucose disposal in peripheral tissues (21–23). Activation of GLP-1 receptor (GLP-1R) signaling also increases β-cell mass by stimulating β-cell proliferation and neogenesis and inhibiting β-cell apoptosis (24, 57).

The actions of GLP-1 have generated a great deal of interest in using this peptide for the treatment of type 2 diabetes (23). However, the therapeutic potential of native GLP-1 is limited by its very short plasma half-life (∼90 s), which is due to rapid inactivation by the ubiquitous protease dipeptidyl peptidase-IV (DPP-IV) and renal clearance (25–29). Consequently, long-acting, DPP-IV-resistant GLP-1R agonists have been developed for clinical use, including exendin-4 (Exenatide) and the fatty-acyl-derivatized GLP-1 analogue liraglutide. These agents are GLP-1 mimetics that bind the GLP-1R with similar affinity and elicit biological actions identical to those of native GLP-1, but they resist DPP-IV-mediated inactivation and renal clearance and thus can sustain protracted activation of the GLP-1R (30, 31).

The ability of GLP-1R agonists to expand β-cell mass via stimulation of β-cell growth and prevention of β-cell death has been demonstrated in studies using islet and β-cell primary cultures or cell lines, as well as in experiments using normal and diabetic rodents. GLP-1 activates the expression of immediate early genes in rat insulinoma-derived, insulin-secreting (INS-1) cells (32, 33), and treatment of pancreatic exocrine cells or rat pancreatic ductal cell lines with GLP-1 or exendin-4 promotes their conversion into islet-like cells that produce and secrete insulin in a glucose-dependent manner (34, 35). GLP-1, exendin-4 and liraglutide (36)

inhibit apoptosis in primary rodent islets, purified β-cells, and islet cell lines that have been exposed to cytotoxic agents (37–40). GLP-1R agonists improve glucose tolerance, enhance β-cell proliferation and neogenesis, and inhibit β-cell apoptosis in rodent models of diabetes, leading to increased β-cell mass (38, 41–48). Moreover, administration of exendin-4 during the prediabetic neonatal period prevents adult-onset diabetes in rats following experimentally induced intrauterine growth retardation (49). Similarly, exendin-4 increases β-cell mass and delays the onset of diabetes in db/db mice and Goto-Kakizaki rats (48, 50). Of direct relevance to the potential use of these agents for the treatment of type 2 diabetes in humans, exendin-4 promotes the differentiation of human fetal islet and pancreatic ductal cells into cells that produce and secrete insulin in a glucose-dependent manner (35, 51, 52), and GLP-1 preserves morphology, improves glucose-stimulated insulin secretion, and inhibits apoptosis in freshly isolated human islets (39, 53).

The physiological importance of the known GLP-1R for the proliferative, neogenic, and antiapoptotic actions of GLP-1 is exemplified by studies employing the GLP-1R antagonist exendin (9–39), or experiments in mice with targeted genetic inactivation of the GLP-1R gene (GLP-1R$^{-/-}$). Exendin (9–39) blocks GLP-1R agonist–mediated differentiation of human pancreatic ductal cells (52) and inhibits the antiapoptotic effects of GLP-1 in mouse insulinoma-derived (MIN6) β-cells (37). Although treatment of wild-type mice with exendin (9–39) did not impair the islet regenerative response to partial pancreatectomy, GLP-1R$^{-/-}$ mice exhibited defective regeneration of β-cell mass and deterioration of glucose tolerance in the same experimental paradigm (54). Furthermore, GLP-1R$^{-/-}$ mice display increased susceptibility to islet apoptosis and worsening hyperglycemia following administration of the β-cell toxin streptozotocin (38). Hence it appears that endogenous GLP-1R signaling is essential for β-cell cytoprotection in vivo.

How does GLP-1R activation lead to increased β-cell mass? The molecular mechanisms are diverse and involve multiple signal transduction pathways downstream of the GLP-1R (Figure 2) (24, 55). The GLP-1R-dependent signaling pathways responsible for the proliferative, neogenic, and antiapoptotic actions of GLP-1R agonists have been examined using human or rodent primary islets, rodent β-cell lines, and diabetic mice (reviewed in 55–57). A common element in all of these GLP-1R-dependent pathways is activation of pancreatic and duodenal homeobox factor-1 (PDX-1), a transcription factor essential for pancreas development and β-cell function (34, 35, 43, 44, 51, 52, 58). The proliferative effects of GLP-1R agonists may also be mediated by transactivation of the epidermal growth factor receptor (EGFR), which leads to increases in phosphatidylinositol-3 kinase (PI-3K) and activation of protein kinase C (PKC) ζ (59) and/or Akt-protein kinase B (PKB) (60). The precise mechanisms involved in GLP-1-dependent β-cell differentiation/neogenesis are poorly defined but may involve activation of PKC and mitogen-activated protein kinase (MAPK) (34). More recent studies have demonstrated that exendin-4 mediates β-cell regeneration in streptozotocin-treated mice by mechanisms that involve upregulating insulin receptor substrate-2 (IRS-2) expression and promoting nuclear exclusion of the transcription factor

Foxo 1 [a key negative regulator of β-cell growth (61)], thereby increasing PDX-1 expression (58).

The antiapoptotic effects of GLP-1R agonists are associated with reductions in the levels of proapoptotic proteins such as active caspase 3 and poly-ADP-ribose polymerase (PARP) cleavage, as well as upregulation of prosurvival factors including Bcl-2, Bcl-xL, and inhibitor of apoptosis protein-2 (IAP-2) (37, 39, 47, 48, 62). GLP-1R-dependent inhibition of β-cell apoptosis is coupled to (*a*) activation of cAMP/protein kinase A (PKA) with subsequent phosphorylation and activation of cAMP response element binding protein (CREB), leading to activation of IRS-2 and induction of the Akt-PKB growth and survival pathway (48, 63), and (*b*) activation of Akt-PKB and enhancement of the DNA binding activity of its downstream target, nuclear factor-κB (NFκB), a transcription factor that plays an important role in the regulation of apoptosis (39).

Clinical studies have demonstrated that GLP-1R agonists can enhance glucose-stimulated insulin secretion, reduce fasting and postprandial blood glucose levels, promote satiety and weight loss, and lower hemoglobin A_{1c} (HbA_{1c}) and plasma levels of free fatty acids (23, 64–68). Hence, GLP1-R agonists may preserve β-cell mass via both direct and indirect actions. Direct activation of GLP-1Rs on pancreatic β-cells or islet precursors can stimulate signal transduction pathways that modify β-cell proliferation, neogenesis, and apoptosis. Chronic treatment with GLP-1R agonists improves metabolic control in type 2 diabetic patients (69–71) by reducing hyperglycemia and levels of circulating free fatty acids, thereby indirectly protecting β-cells from the deleterious effects of high glucose and lipid levels.

GIP

Glucose-dependent insulinotropic polypeptide (GIP) is a 42-amino-acid hormone released from intestinal K-cells in response to nutrient ingestion. Like GLP-1, it enhances glucose-stimulated insulin secretion and biosynthesis and promotes β-cell proliferation and survival (72). Most studies examining the proliferative and antiapoptotic actions of GIP have employed either heterologous cells transfected with the GIP receptor (GIPR) or rodent β-cell lines. Important effectors of GIP action include cAMP/PKA, PKA/CREB, MAPK, and PI-3K activation of Akt-PKB (73–76). In comparison, relatively little is known about the signal transduction pathways that modify GIPR-dependent β-cell growth and survival in vivo. Systemic administration of GIP significantly reduced islet cell apoptosis in diabetic rats (77). GIP inhibits β-cell apoptosis by activation of PI-3K/Akt-PKB and subsequent phosphorylation of Foxo1. Phosphorylated Foxo1 is exported from the nucleus and sequesters within the cytoplasm following GIPR activation, resulting in reduced expression of the proapoptotic *bax* gene and upregulation of the antiapoptotic *bcl-2* gene (77).

Although GIP appears to be a promising candidate for the treatment of type 2 diabetes, humans with type 2 diabetes are relatively resistant to the insulinotropic

effects of exogenous GIP administration (78, 79). Preclinical data suggest that continuous exposure to GIP and/or hyperglycemia promotes downregulation of GIPR expression in vivo (80). However, improvement of glycemic control following four weeks of treatment with a sulfonylurea enhanced the acute insulinotropic response to GIP in subjects with type 2 diabetes (81). Thus, the clinical potential of GIP or long-acting GIPR agonists requires further study.

DPP-IV INHIBITORS

Dipeptidyl peptidase-IV (DPP-IV) is a ubiquitously expressed proteolytic enzyme that specifically cleaves dipeptides from the amino terminus of oligopeptides or proteins that contain an alanine or proline residue in position two (26). DPP-IV is a critical determinant of GLP-1 and GIP inactivation in vivo (25). Both GLP-1 and GIP have an alanine residue in the penultimate position and are rapidly inactivated by DPP-IV, so that, in humans, the plasma half-life for GLP-1 is ~2 min and that of GIP is ~5 min (82, 83). Because of the clinical potential of GLP-1 and GIP for the treatment of type 2 diabetes, DPP-IV inhibitors have been developed to prevent proteolytic inactivation of endogenous GLP-1 and GIP. Several orally active DPP-IV inhibitors are currently being evaluated for the treatment of type 2 diabetes (84).

Numerous preclinical studies with both normal and diabetic animals clearly demonstrate that pharmacological inhibition of DPP-IV activity increases endogenous plasma levels of intact, biologically active GLP-1 and GIP, enhances insulin secretion, reduces peripheral insulin resistance, and improves glucose tolerance (85–93). Moreover, mice with a targeted disruption of the DPP-IV gene exhibit improved glucose tolerance in association with increased levels of plasma insulin and bioactive GIP and GLP-1 (94). Human studies are fewer, but they have established that treatment with DPP-IV inhibitors improves β-cell function, reduces fasting and postprandial blood glucose levels, and decreases HbA_{1c} values in subjects with type 2 diabetes (95–97).

In addition to GLP-1 and GIP, regulatory peptides, neuropeptides, and chemokines are potential substrates for the proteolytic actions of DPP-IV (98). Pituitary adenylate cyclase-activating peptide (PACAP) is a neuropeptide that stimulates glucose-dependent insulin secretion and can reduce blood glucose levels in diabetic animals (99). Transgenic overexpression of PACAP in pancreatic β-cells is associated with increased β-cell proliferation in mice following streptozotocin administration (100). This suggests that PACAP may also play a role in enhancing β-cell mass. Furthermore, inhibition of DPP-IV activity in mice potentiates the insulin-secretory response to exogenous PACAP (101). However, DPP-IV inhibitors do not lower blood glucose levels following acute administration in mice that lack receptors for both GLP-1 and GIP, suggesting that DPP-IV inhibitors mediate their glucose-lowering actions primarily through GLP-1- and GIP-dependent actions (102).

There is active interest in determining whether treatment with DPP-IV inhibitors will increase β-cell mass. Twice-daily administration of the DPP-IV inhibitor

P32/98 for seven days increased levels of bioactive GLP-1, improved glucose tolerance, and enhanced pancreatic insulin content while stimulating both islet neogenesis and β-cell survival in diabetic rats (103). Treatment of mice for eight weeks with the DPP-IV inhibitor NVP DPP728 improved β-cell function and reduced islet size relative to high-fat-fed control mice (104). Conversely, mice deficient in DPP-IV are resistant to streptozotocin-induced reductions in β-cell mass (105). Taken together, the data imply a role for long-term DPP-IV inhibition in the regulation of β-cell mass in type 2 diabetes.

GASTRIN AND EGF

Gastrin is a peptide hormone that stimulates gastric acid secretion and neuroendocrine cell proliferation in the gastric mucosa of adult animals (106). During fetal development, gastrin and its receptors are expressed primarily in the developing pancreas at a time when islet precursor cells are undergoing active proliferation and differentiation to form new islets (107, 108), which suggests a potential role for gastrin in islet neogenesis. Studies in the regenerating pancreas of duct-ligated rats revealed that gastrin stimulates β-cell neogenesis and expansion of β-cell mass from transdifferentiated, but not normal, exocrine pancreas tissue (109). Analyses of epidermal growth factor (EGF) actions demonstrate that it may activate the proliferation of ductal islet precursor cells (110, 111). Early evidence that a combination of gastrin and EGF could stimulate islet neogenesis and increase β-cell mass emerged from studies using single- or double-transgenic mice that express transforming growth factor-α (TGF-α), an EGFR ligand, and/or gastrin under the control of the insulin promoter (112). In gastrin transgenic mice, pancreatic ductal tissue and islet mass are normal, whereas in TGF-α transgenic mice, the number of insulin-expressing pancreatic ductal cells is increased but islet mass is normal. However, TGF-α/gastrin double-transgenic mice exhibit significantly increased β-cell mass. These observations formed the basis for the hypothesis that gastrin and EGFR ligands act synergistically to stimulate islet growth, with EGFR ligands initiating a program of islet differentiation that is completed by gastrin (112).

The therapeutic potential of combined gastrin and EGF was illustrated by studies in which gastrin/EGF reduced hyperglycemia, induced islet regeneration, and increased β-cell mass in rodent models of genetic or chemically induced insulin-dependent (type 1) diabetes, whereas gastrin or EGF alone were not effective (113, 114, 114a). More recent studies have shown that gastrin/EGF can also increase β-cell mass in islet preparations derived from adult human pancreatic tissue (115). Gastrin/EGF increased the number of β-cells in cultured human islets, and this effect was sustained for up to four weeks after removal of gastrin/EGF from the culture medium. Pancreatic ductal cells are consistently present in human islet preparations (116), and the increased β-cell number was attributed to the activation of β-cell neogenesis mediated by EGF stimulation of ductal cell proliferation and gastrin-dependent increases in ductal cell PDX-1 expression and differentiation (115). Gastrin/EGF also increased functional β-cell mass following transplantation

of human islets into diabetic mice (115). The ability of gastrin/EGF therapy to induce β-cell neogenesis from pancreatic ductal cells has potential implications for new approaches to the treatment of type 1 and type 2 diabetes and is currently being evaluated in early-stage clinical trials. Whether cholecystokinin (CCK), acting presumably via the CCK-B receptor, will exert similar trophic effects on pancreatic islet growth is also under active investigation (117).

THIAZOLIDINEDIONES

The thiazolidinediones (TZDs) are ligands for peroxisome proliferator-activated receptor-γ (PPARγ), a nuclear hormone receptor that functions as a transcription factor and regulates the expression of genes that modify cellular differentiation and glucose and lipid metabolism (118). TZDs enhance insulin sensitivity in peripheral tissues, lower blood glucose, exert anti-inflammatory effects, and improve metabolic control in type 2 diabetic individuals (119, 120).

TZDs have also been shown to enhance β-cell function in diabetic humans and rodents and to preserve β-cell mass and delay the onset of hyperglycemia in rodent models of type 2 diabetes (121–124). The TZD rosiglitazone prevented the development of diabetes in Zucker diabetic fatty rats when administered during the prediabetic period (122). Rosiglitazone also inhibited the well-characterized progressive loss of β-cell mass in these animals by maintaining β-cell proliferation, thereby preventing increases in overall net β-cell death (122). In human islets, the TZD pioglitazone inhibited hyperglycemia- or cytokine-induced apoptosis by blocking activation of the NFκB pathway, a major proapoptotic signal transduction pathway in human β-cells (125). Thus, in addition to improving peripheral insulin sensitivity, TZDs can also preserve β-cell mass in the setting of type 2 diabetes or β-cell injury. However, whether TZDs mediate these effects directly, via activation of pancreatic β-cell PPARγ receptors, or indirectly, by normalizing blood glucose levels and improving metabolic parameters, is not known. Moreover, whether TZD-mediated enhancement of β-cell function and preservation of β-cell mass are related to reduced β-cell secretory demand as a consequence of improved insulin sensitivity remains to be determined. Longitudinal studies of the effects of TZDs on β-cell function in human subjects are under way.

MISCELLANEOUS PEPTIDE GROWTH FACTORS

Several peptides and growth factors promote expansion of β-cell mass in preclinical studies via effects on β-cell proliferation and/or apoptosis, or via stimulation of ductal proliferation and neogenesis (Table 1). Agents that act primarily on islet cells include insulin-like growth factor-1 (126), hepatocyte growth factor (127, 128), human placental lactogen (129), and parathyroid hormone-related peptide (130).

Treatment of rodents with keratinocyte growth factor induces pancreatic ductular proliferation and increases the number of functional insulin-secreting cells

following transplantation of human fetal islet preparations into rats (131). Administration of synthetic peptide fragments derived from islet-neogenesis-associated peptide (INGAP) promoted islet neogenesis in short-term studies of normal hamsters, and treatment of diabetic rodents with a pentadecapeptide derived from INGAP increased β-cell mass and improved glucose homeostasis in several preclinical studies (132). The molecular mechanisms activated by INGAP that result in expansion of β-cell mass remain incompletely understood.

CONCLUSIONS

Progressive reductions in β-cell mass contribute significantly to the pathogenesis of type 2 diabetes. A major goal of diabetes research is to restore the β-cell mass typically lost during the natural progression of type 2 diabetes. The ability of GLP-1R agonists, and related peptides such as GIP, to enhance β-cell survival and stimulate β-cell growth in preclinical studies of diabetic animal models suggests that these agents could provide a noninvasive means to preserve and/or restore functional β-cell mass in patients with type 2 diabetes. Moreover, if these drugs are used early in the course of the disease, they could potentially delay or even prevent the progression to overt type 2 diabetes. However, whether these agents will produce a sustained improvement in β-cell function following chronic therapy in human patients with type 2 diabetes is currently not known. Long-term clinical studies will be required to answer this question.

DISCLOSURE STATEMENT

LB is a consultant to Merck, Amylin, and Novonordisk. DJD is a consultant to Amylin, Lilly, Conjuchem, Merck, Novartis, Transition Therapeutics, Triad, Bristol Myers Squibb, GSK, and Johnson & Johnson.

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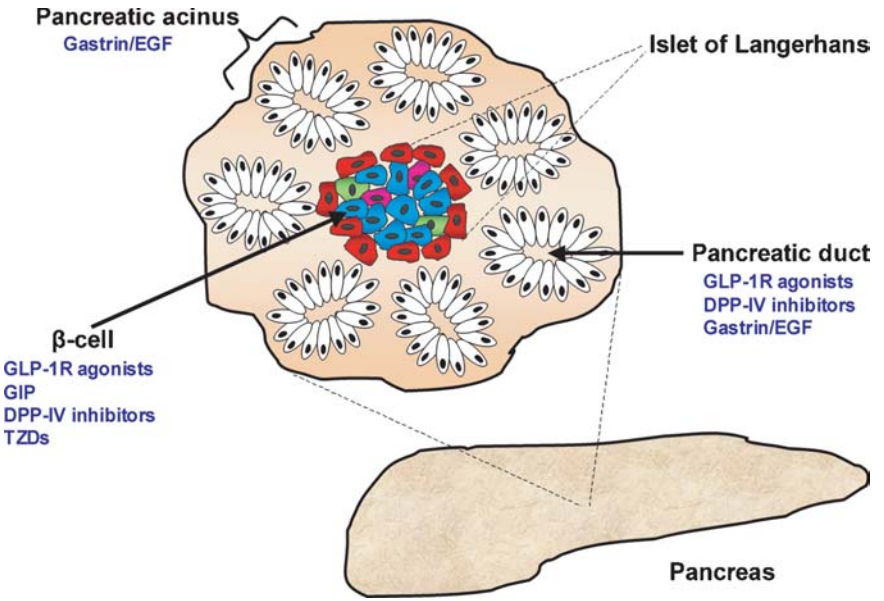

Figure 1 Pancreatic targets for expansion of β-cell mass by agents in clinical trials for the treatment of type 2 diabetes. Some evidence suggests that gastrin/epidermal growth factor (EGF) may increase the number of functional β-cells via the process of transdifferentiation. Glucagon-like peptide-1 receptor (GLP1-R) agonists and dipeptidyl peptidase-IV (DPP-IV) inhibitors exert their effects directly on islet β-cells and possibly on the pancreatic ductal epithelium. GIP, glucose-dependent insulinotropic polypeptide; TZDs, thiazolidinediones.

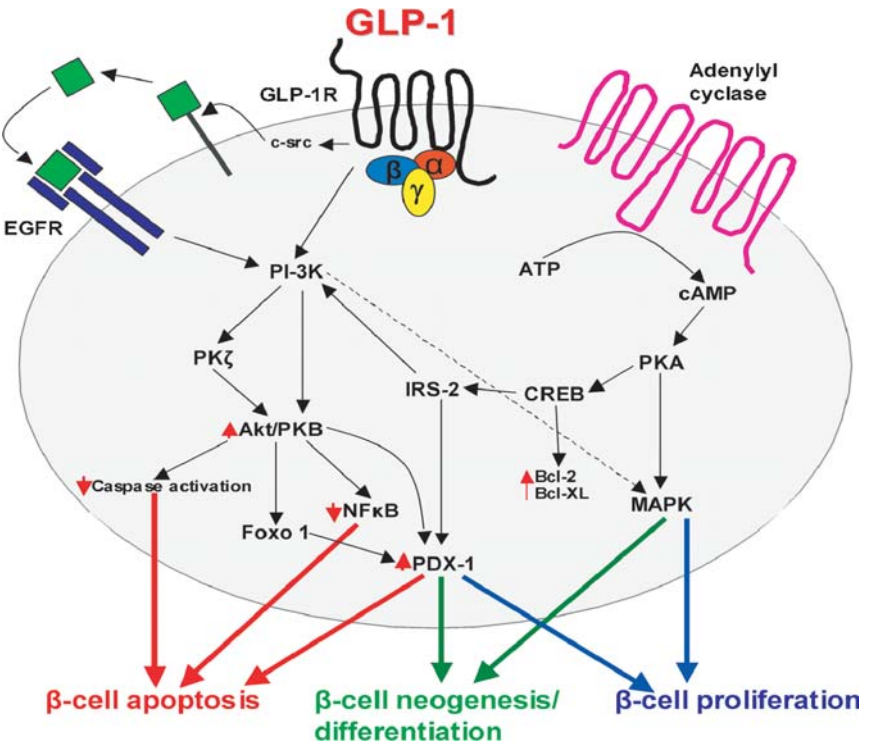

Figure 2 Signal transduction pathways coupling GLP-1 receptor activation to expansion of β-cell mass.