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Cellular signaling pathways regulating β-cell proliferation as a promising therapeutic target in the treatment of diabetes (Review)

WEN-JUAN JIANG, YUN-CHUAN PENG and KAI-MING YANG

Institute of Anatomy, Basic Medical College of Dali University, Dali, Yunnan 671000, P.R. China

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Abstract. It is established that a decrease in β-cell number and deficiency in the function of existing β-cells contribute to type 1 and type 2 diabetes mellitus. Therefore, a major focus of current research is to identify novel methods of improving the number and function of β-cells, so as to prevent and/or postpone the development of diabetes mellitus and potentially reverse diabetes mellitus. Based on prior knowledge of the above-mentioned causes, promising therapeutic approaches may include direct transplantation of islets, implantation and subsequent induced differentiation of progenitors/stem cells to β-cells, replication of pre-existing β-cells, or activation of endogenous β-cell progenitors. More recently, with regards to cell replacement and regenerative treatment for diabetes patients, the identification of cellular signaling pathways with related genes or corresponding proteins involved in diabetes has become a topic of interest. However, the majority of pathways and molecules associated with β-cells remain unresolved, and the specialized functions of known pathways remain unclear, particularly in humans. The current article has evaluated the progress of research on pivotal cellular signaling pathways involved with β-cell proliferation and survival, and their validity for therapeutic adult β-cell regeneration in diabetes. More efforts are required to elucidate the cellular events involved in human β-cell proliferation in terms of the underlying mechanisms and functions.

Contents

Correspondence to: Dr Kai-Ming Yang, Institute of Anatomy, Basic Medical College of Dali University, 1 Xueren Road, Dali, Yunnan 671000, P.R. China
E-mail: 176501584@qq.com

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1. Introduction

Due to an increasing incidence of diabetes and its complications, there is an urgent need to identify therapeutic approaches for diabetes. Both type 1 and type 2 diabetes patients eventually require lifelong insulin replacement therapy. However, long-term exogenous insulin replacement therapy is not only associated with numerous side effects, but can also not delay and/or prevent the development of diabetes and the emergence of its complications. In addition, islet transplantation has been studied but progress in this field is slow due to a lack of islet donors, organ transplant rejection and low survival rates following transplantation in humans (1). Therefore, the realization of endogenous islet cells regeneration has become the focus of all researchers. At present, a fundamental method of treating diabetes is regenerative therapy, which generally involves the development of feasible therapeutic methods that induce an expansion of adult human β-cells (2). In previous studies, a number of mechanisms had been proposed to explain the proliferation of β-cells, including the proliferation of pancreatic duct stem cells (3), the replication of β-cell progenitor cells (4) and the endogenesis of residual β-cells (5). Insight into the network of β-cell signaling pathways that promote β-cell proliferation may help to overcome key difficulties in diabetes therapy. As research methods for the evaluation of cellular signaling pathways have improved, an increasing number of pathways have been identified that are associated with β-cell proliferation, including insulin, growth factors and hormones. However, difficulties remain in various aspects of diabetes research, including specific molecular mechanisms remaining unclear and differences between animal and human trials. Despite these limitations, more research into the related signal pathways may aid to develop therapeutic strategies for the treatment of diabetes.

2. Insulin signaling pathways

Insulin signal transduction pathways within pancreatic β-cells are a complex system, and are mainly composed of insulin

receptors (IR), including the insulin receptor (IR)-related receptor and insulin-like growth factor 1 (IGF-1) receptor, and substrates belonging to the insulin receptor substrates (IRS) family, including IRS, IR tyrosine kinase, phosphoinositide linositol-3-kinase (PI3K) and its downstream effectors such as protein kinase B [PKB; also known as serine/threonine kinase (AKT)], mitogen activated protein kinase (MAPK), MAPK kinase (MAPKK/MEK), raf protein and rat sarcomas (Ras) proteins (small G proteins) (6-8). Activated IR stimulates IRS, which is present in two major forms in β-cells; IRS-1 and IRS-2 (9). IRS-1 is generally distributed in islet β-cells, and closely regulates glucose-dependent insulin secretion (9). By contrast, IRS-2 is mainly located in the peripheral region of the pancreatic islets and at low levels in β-cells, and positively moderates the compensation mechanism of β-cells (9). In terms of regulatory mechanisms, IRS-1 is activated through the activation of PI3K and calcium channels, among others, while IRS-2 is activated by PI3K, MAPK, Ras and other pathways, and they ultimately modulate the growth, proliferation and mitosis of β-cells (10,11).

PI3K-AKT/PKB signaling pathway. The PI3K signaling pathway serves a dominant role in the regulation of β-cell function (12), which is orchestrated by an intricate network of mediators. AKT/PKB, acting as a downstream target of PI3K, regulates the proliferation of β-cells through modulation of its multiple downstream genes, which include Forkhead box protein O1 (FOXO1) (13), glycogen synthase kinase-3 (GSK3) (14) and mammalian target of rapamycin (mTOR) (8), among others.

FOXO1 is a member of the phosphorylase Fox gene family and its transcription activity is modulated through phosphorylation of PI3K/AKT signaling proteins (15). In β-cells, FOXO1 has been identified as a weak inhibitor of pancreatic and duodenal homeobox 1 (Pdx1) (15), which participated in the maintenance of common features of β-cells, including the regulation of target gene expression for genes such as glucose transporter 2 (GLUT2), insulin secretion and maintenance of appropriate cell function (16). This indicates the pivotal role of FOXO1 in the maintenance of β-cell function through modulation of Pdx1.

GSK3 has been demonstrated to be a downstream target of multiple signaling pathways and is associated with cell proliferation and cell cycle regulation (17). It has been reported that stimulation of GSK3 negatively regulates β-cell function by maintaining the sub-cellular localization and stability of Pdx1 (18). Furthermore, upon activation of mTOR, GSK3 is suppressed by FOXO1, which is activated through phosphorylated PI3K-AKT (Fig. 1) (19). mTOR, as a member of the serine/threonine protein kinase family, is a fundamental component within two mTOR complexes, mTORC1 and mTORC2 (20-22). The related signaling proteins of mTOR include PI3K-AKT, AMP activated protein kinase and growth factors, which influence multiple metabolic indices such as cellular metabolism, stem cell differentiation and dedifferentiation, pancreatic β-cell function, insulin secretion and resistance and cellular survival or death (21-23). Maiese (24) reported that downregulation of mTOR and mTORC1 activated PI3K-AKT through a feedback mechanism, which blocked all anticipated clinical benefits. PI3K-AKT suppressed activation of tuberous sclerosis complex 1/2 (TSC1/2), which was an upstream negative regulator of mTORC1, and then S6K1 and 4E-BPs promoted mRNA translation and synthesis of ribosomes, and eventually increased β-cell proliferation (Fig. 1) (7,8). Furthermore, P21cip1 and p27kip1 were inhibitors of the cell cycle (Fig. 1) (7). PI3K-AKT suppressed P21cip1 by activating MDM2/P53 gene, and increased β-cell proliferation, while it enhanced P27kip1 by activating FOXO1 gene, and hindered β-cell proliferation (Fig. 1) (7). A recent study demonstrated that the immortalized mouse β-cell line (exclusively expressing IR A isoform) was sensitive to the mitogenic response induced by IGF-1, which further activated β-cell proliferation, primarily through mTORC1 (Fig. 1) (25). Furthermore, in partial pancreatectomy (60%), mTORC1 exerted a compensatory effect on β-cell mass mainly through the cyclin D2 pathway in early stages (26).

Recently, studies have focused on the mechanism behind inulin-mediated fat and glucose metabolism, though few have investigated protein metabolism (13). For instance, it has been reported that hyperglycemia promoted compensatory β-cell proliferation to meet the insulin demand induced by hyperglycemia (27). Lipid metabolism has previously been investigated in pregnant female mice (10), whereby mice were randomly assigned to receive either a high-fat diet (MO-HF) or standard chow (MO-SC) without advance preparation. It was observed that MO-HF induced a failure in β-cell proliferation and survival by downregulating IRS1, PI3K and GLUT2 protein, while upregulating insulin protein and FOXO1 when compared with MO-SC mice (10,27). Furthermore, a high-fat diet has been demonstrated to negatively impact on β-cell proliferation, leading to the development of insulin resistance and D2M characteristics (28,29). Rhee *et al* (30) also suggested that preadipocyte factor 1 (Pref-1) may independently stimulate insulin secretion via AKT-Rab43 (Fig. 2). Finally, there has been dispute regarding the interplay between protein metabolism and the related signaling pathways of β-cell proliferation. Chen *et al* (13) argued that FOXO1 may inhibit the expression of albumin, while other proteins such as phycocyanin have been demonstrated to promote β-cell proliferation by regulating PI3K-AKT signaling and downstream FOXO1, and ameliorate diabetes mice by stimulating glucokinase expression and insulin signaling in the pancreas (11,31). It has also been reported that Exendin-4 may enhance β-cell proliferation in some instances by stimulating PI3K-AKT signaling, potentially via an intermediate ligand-binding activation step involving corresponding receptors (14).

Calcium-mediated signaling pathway. As an important second messenger, calcium participates in apoptosis and regulates the synthesis of enzymes and hormones, including that of insulin. The maintenance of normal Ca^{2+} concentration in the body is termed calcium homeostasis, and is critical to cell survival (32). Previous results have indicated that disruption of calcium homeostasis may accelerate β-cell death and lead to type 1 diabetes mellitus (D1M) (32). Furthermore, PI3K signaling stimulated the autocrine function of pancreatic β-cells to moderate β-cell proliferation by inhibiting endoplasmic reticulum Ca^{2+} ATPase, which increased the intracellular Ca^{2+} concentration and subsequently activated calcium-mediated signaling pathways (33,34). In calcium-mediated signaling, increases in intracellular calcium activate calmodulin (CaM), which has two substrates, namely carbohydrate response element-binding (CREB)-regulated transcription coactivator-2

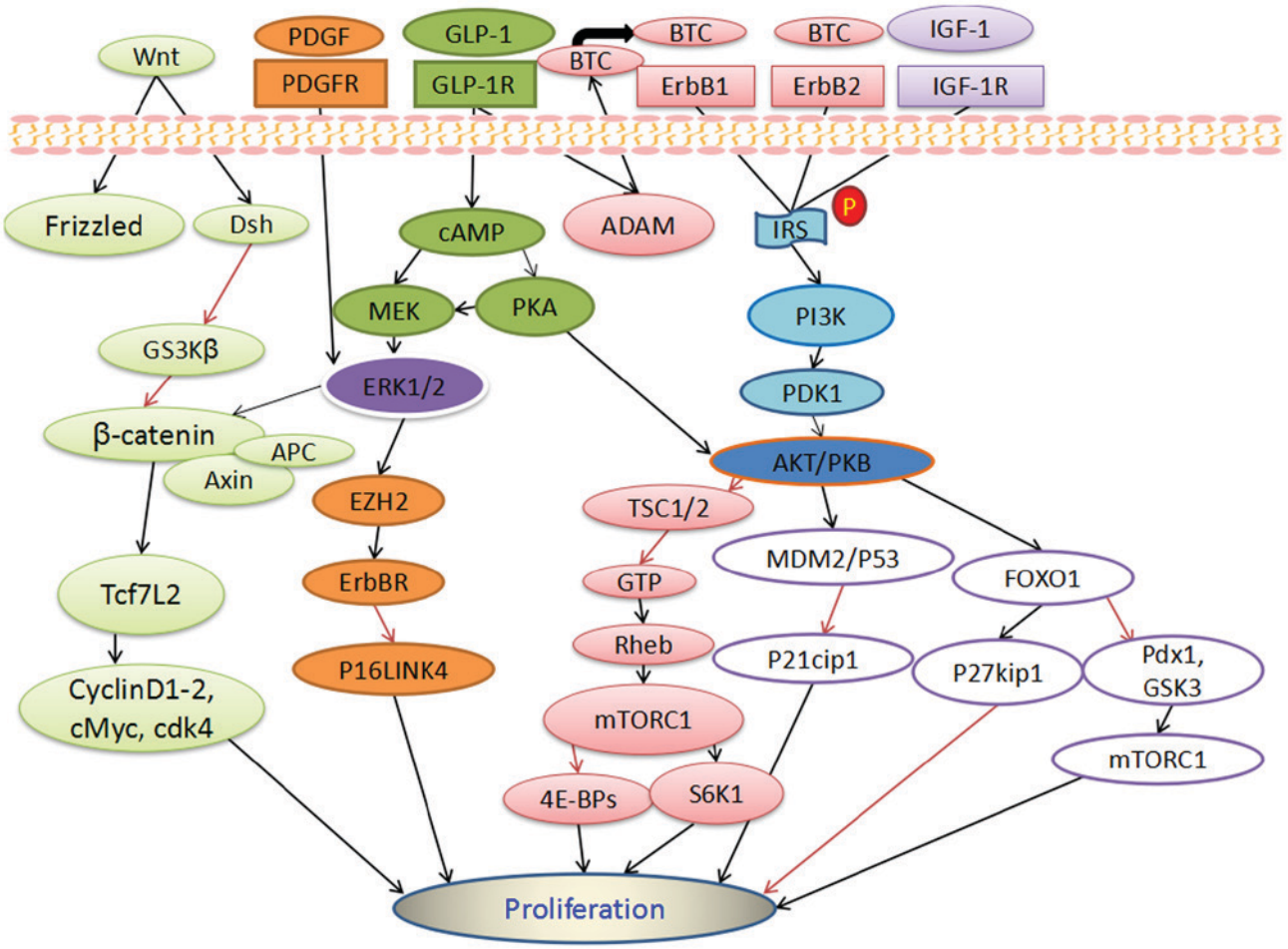

Figure 1. Binding of PDGF, GLP-1, IGF-1 and BTC to their respective receptors serves an important role in β-cell proliferation. The Wnt pathway regulates GSK3β to inhibit the phosphorylation of β-catenin and thus regulate the expression of Tcf7L2 and Cyclin D1-2, cMyc and cdk4, which ultimately modulates proliferation. PDGF binds to PDGFR and then activates the ERK1/2 pathway, increasing the expression of EZH2. IGF-1 binds to IGF-1R, and BTC binding to ErbB1 and ErbB2 also activates the IRS/PI3K pathway. GLP-1 binds to GLP-1R to activate cAMP-PKA, and it also acts via ADAM proteins to trigger the secretion of BTC that acts upon ErbB1/2. Circles of the same color represent signals within the same pathway. Red and black lines indicate inhibition and promotion, respectively. PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; GLP-1, glucagon like peptide 1; GLP-1R, glucagon like peptide 1 receptor; IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor 1 receptor; BTC, β-catenin; Dsh, disheveled; GSK3β, glycogen synthase kinase-3β; APC, adenomatous polyposis colis; cdk, cyclin-dependent kinase; PK, protein kinase; MEK, mitogen-activated protein kinase kinase; EZH2, enhancer of zeste homolog 2; EGFR, epidermal growth factor receptor; IRS, insulin receptor substrate; PI3K, phosphoinositide 3-kinase; PDK1, phosphoinositide-dependent kinase 1; TSC1/2, tuberous sclerosis complex 1/2; Rheb, Ras homolog enriched in brain; mTORC, mechanistic target of rapamycin complex; 4E-BP, eukaryotic translation initiation factor 4E-binding protein 1; S6K1, ribosomal S6 kinase 1; MDM2, mouse double minute 2 homolog; FOXO1, forkhead box protein O1; Pdx1, pancreatic and duodenal homeobox 1; P, phosphorylated.

(CRTC2) and transcription factors of the nuclear factor of activated T cells (NFAT) family (35-38). Notably, dephosphorylated NFAT translocated to the nucleus and combined with the promoters of cell-cycle activating agents, including cyclin A and D, cMyc, cyclin-dependent kinase (cdk) 2 and 4, FOX protein M1 (FOXM1; Fig. 2) and the promoter of IRS-2, which participated in PI3K-AKT and Ras-Raf-MAPK signaling to activate β-cell proliferation (35-37). By contrast, NFAT function may be improved by interaction with transcription factors, including CREB, cAMP-response element modulator and activator protein 1 (38). Changes in cytosolic Ca^{2+} concentration have been documented to exert a significant effect on insulin secretion by modulating gene expression from electrically excitable pancreatic β-cells (39). In pancreatic β-cells, intracellular high calcium concentration triggers exocytosis and leads to insulin secretion (40). In addition, previous data suggest that Ca^{2+} may be drawn into pancreatic islets either by the opening L-type voltage-dependent Ca^{2+} channels or crosstalk between intracellular Ca^{2+} concentration and protein kinase (PK) A/L/C to stimulate insulin secretion (40,41). Indeed, Ca^{2+}/CaM-dependent protein kinase 2 (CaMKK2) is considered to be a molecular regulator of insulin function, and Ca^{2+}/CaM/CaMKK2 has been documented to serve a crucial role in the modulation of holistic body metabolism (42,43). Collectively these observations indicate that calcium-mediated signaling pathways may be therapeutic targets for the modulation of β-cell proliferation in diabetes.

RAS-extracellular signal-regulated kinase (ERK)/MAPK signaling pathway. Three types of Ras protein are expressed in humans, namely H-Ras, K-Ras, and N-Ras. K-Ras is considered to be the most important form, acting as a downstream target of multiple cellular signaling pathways that regulate cell growth, proliferation and differentiation (44). Chamberlain *et al* (45)

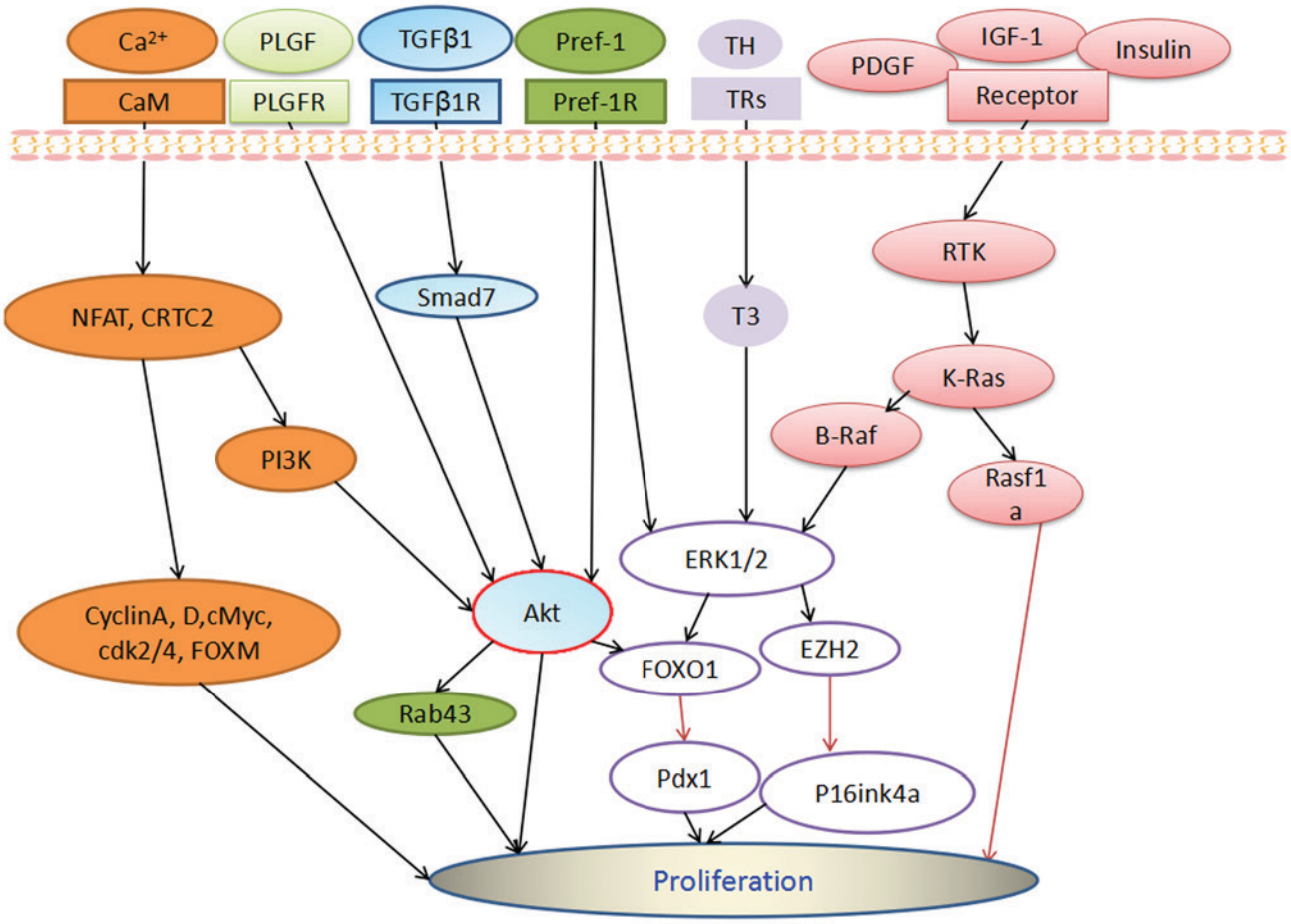

Figure 2. Binding of growth factors and hormones to their respective receptors or ligands serves a pivotal role in β-cell proliferation. K-Ras is a principal regulator of β-cell proliferation through its mediation of B-Raf-ERK and Rasf1a. CRTC2 and NFAT combine with the promoters of cell-cycle activating agents, including cyclins A and D, cMyc, cdk2/4 and FOXM (a member of the FOX family of transcription factors), and participate in AKT signaling to activate β-cell proliferation. Circles of the same color represent signals within the same pathway. Red and black lines indicate inhibition and promotion, respectively. CaM, calmodulin; NFAT, nuclear factor of activated T cells; CRTC2; carbohydrate response element-binding-regulated transcription coactivator-2; cdk, cyclin-dependent kinase; PI3K, phosphoinositide 3-kinase; PLGF, placental growth factor; PLGFR, placental growth factor receptor; TGFβ1; transforming growth factor β1; TGFβ1R; transforming growth factor β1 receptor; Pref1, preadipocyte factor 1; Pref1R, preadipocyte factor 1 receptor; TH, thyroid hormone; TRs, TH receptors; T3, 3,5,3'-Triidothyronine; FOXO1, forkhead box protein O1; Pdx1, pancreatic and duodenal homeobox 1; EZH2, enhancer of zeste homolog 2; PDGF, platelet-derived growth factor; IGF-1, insulin-like growth factor 1; RTK, receptor tyrosine kinase; Ras, rat sarcomas.

demonstrated that K-Ras stimulated the anti-proliferative ras association domain family 1A (Rasf1a) pathway, which diminished cell proliferation (Fig. 2). Therefore, K-Ras may serve a negative regulatory role in the proliferation of β-cells, and downregulation of the K-Ras gene may enhance proliferation by reducing Rassf1a activity.

ERKs (also known as classical MAPKs), are diffusely expressed cellular signaling molecules that participate in the modulation of cell proliferation (46). In pancreatic β-cells, ERK1 (MAPK3) and ERK2 (MAPK1) have been documented to be the major expressed forms of ERK (5). In general, the binding of a ligand to its cognate tyrosine kinase or G protein coupled receptor stimulates the small GTPase Ras, resulting in the formation of activated Ras-GTP, which phosphorylates c-Raf and subsequently activates MEK, and ultimately activates ERK1/2 (5). Furthermore, a number of growth factors and hormones have been reported to induce β-cell proliferation via the activation of ERK1/2. For instance, it was observed that stimulation of platelet derived growth factor receptor required activated ERK1/2, leading to upregulation of the polycomb group protein EZH2 (enhancer of zeste homolog 2, EZH2), inhibition of P16LINK4 tumor suppressor protein and ultimately adult β-cell expansion (Fig. 1) (47). ERK signaling was also demonstrated to serve a pivotal role in 3,5,3'-Triidothyronine (T_3)-induced β-cell proliferation (Fig. 2) (46). In addition, reactive oxygen species-facilitated β-cell differentiation by regulating the ERK1/2 pathway (48), and the anti-apoptotic function of visfatin was mediated by stimulation of the ERK1/2 signaling pathway (49). In a study by Ozaki *et al* (50), a mouse model of diabetes was established in high-fat diet KKAy mice and leptin receptor-deficient (db/db) mice. In these mice it was observed that obesity-associated insulin resistance could be treated with an inhibitor of MEK (50), indicating that regulation of ERK signaling may be an effective treatment for type 2 diabetes (D2M).

3. Growth factor signaling pathways

Several growth factors have been implicated in the modulation of B-cell proliferation, including IGF-1, members of the

epidermal growth factor (EGF) family, nerve growth factor (NGF), members of the transforming growth factor (TGF)-β superfamily, placental growth factor (PLGF) and their corresponding receptors (IGF-1R, EGFR, NGFR, TGFβR and PLGFR, respectively) (51). These mitogen signals have been associated with multiple downstream pathways, including PI3K-AKT-mTOR, ERK (Figs. 1 and 2) and janus kinase-signal transducers and activators of transcription (JAK-STAT), in the modulation of β-cell proliferation and survival (51).

EGF family signaling pathway. Multiple downstream proteins of the EGF family, including EGF, β-cellulin (BTC), TGF-α, heparin-binding (HB)-EGF and epiregnin, have been implicated in β-cell proliferation (52). For instance, BTC-dependent mitogenic signals were involved in the upregulation of IRS and activation of both EGF/ErbB1 and ErbB2 receptors in β-cells (Fig. 1) (53). BTC has also been linked to the IRS-PI3K signaling pathway, which signals through 3'-phosphoinositide-dependent protein kinase 1 (PDK1) to regulate AKT and FOXO1 (Fig. 1) (53). As members of the EGF superfamily, EGF and TGF-α have been reported to transiently activate ERK1/2, though the interaction was not strong enough to induce β-cell proliferation (53). Furthermore, constitutively active EGFR protected β-cells against damage and even death (54). It has also been reported that excessive nutrients may promote β-cell expansion via crosstalk between EGFR signaling, FOXM1-mediated cell proliferation and mTOR activation (55). Further study into the mechanism of β-cell survival has demonstrated that β-cell proliferation may be regulated via EGF and Raf-1/MEK/ERK signaling, which primarily increased the half-life of β-cells (51).

NGF signaling pathway. NGF regulates the development of neuronal cells and may control the function of non-neuronal cells (56,57). In islet β-cells, NGF is among the peptides stored by β-cells within secretary vesicles, and it may interact with β-cell receptors to trigger autocrine and paracrine effects in response to appropriate stimulation (57). NGF primarily acts via two membrane receptors, p75 neurotrophin receptor (P75 NTR) and tropomyosin receptor kinase A (trkA). trkA functions upon its phosphorylation, and mainly modulates the activation of signals involved in cell survival, differentiation and proliferation (58), while P75 NTR recruits specific intracellular effectors depending on its NGF-bound and unbound forms (59). A recent study suggested that islet NGF served a pivotal role in fine-tuning insulin secretion, to maintain both basal insulin secretion and biphasic secretion of glucose (60).

TGFβ superfamily signaling pathway. Various members of the TGFβ superfamily, including TGFβ, inhibins, activins, follistains, mullerian inhibitor substance and bone morphogenetic proteins, have been demonstrated to function in β-cells (5), though the exact underlying mechanisms remain unclear. The TGFβ superfamily, which has been implicated in numerous developmental processes, including proliferation, differentiation and growth arrest, served a crucial role in modulating pancreatic endocrine development and maturation (61-64). In particular, interplay between the inhibitor TGFβ signaling Smad7 and intracellular mediators of TGFβ signaling were involved in coordinating this process (61). A recent investigation into TGFβ signaling demonstrated that macrophages released TGFβ1 to trigger Smad7 expression, which then facilitated β-cell proliferation (65). Smad7 was also increased in β-cells after partial pancreatic duct ligation (PDL) (65). In general, the functions of TGFβ superfamily members affects downstream Smad proteins in β-cells, which typically suppresses proliferation (64). Therefore, suppression of TGFβ signaling may promote β-cell proliferation (65-70). In cultured human pancreatic duct cells, TGFβ1 induced the epithelial-mesenchymal transition and inhibited differentiation into β-cells, and bound with the downstream targets ERK1/2, AKT and Ras (71). The underlying mechanisms of pancreatic islet cell expansion may involve an upregulation in TGFβ signaling (68). Blockade of TGFβ signaling with short hairpin RNA (shRNA) against TGFβ1R, such as Alk5 shRNA, suppressed the differentiation and proliferation of β-cell-derived (BCD) cells, which may be associated with the AKT-FOXO1 pathway (Fig. 2) (72).

PLGF and Pref-1 signaling pathway. Finally, gestational PLGF may stimulate endothelial cells within the pancreatic islets to release growth factors that activate the PI3K-AKT pathway (Fig. 2), thus enhancing β-cell proliferation (73). A previous study demonstrated that Pref-1 independently facilitated the phosphorylation of AKT and ERK1/2, and triggered alterations in the expression of FOXO1 and Pdx1 (Fig. 2) (29).

4. Hormone signaling pathways

Hormones including thyroid hormone (TH), growth hormone (GH), glucagon like peptide 1 (GLP-1), IGF-1, and prolactin (PRL) and their cognate receptors (TR, GHR, GLP-1R, IGF-1R and PRLR, respectively) have been critically associated with β-cell survival, growth, proliferation, differentiation and insulin secretion, and may be involved in PI3K-AKT, JAK-STAT and ERK crosstalk (74). A stimulatory effect of T3 on cellular growth was observed on TRs in several cell lines. TR expression in the pancreas suggested that pancreatic β-cell proliferation might be induced by T3 (46). The study demonstrated that T3 induced pancreatic β-cell proliferation via the ERK signaling pathway (46). The current review has mainly focused on the incretin hormone GLP-1, which is primarily released from intestinal L-cells in response to hormones, nutrients and neurons, and may serve a significant role in β-cell proliferation and insulin secretion (75,76). In general, GLP-1 combined with its receptor (GLP-1R) may enhance insulin secretion. However, it has been reported that activation of GLP-1R requires a host of complex proteins interactions (77). Recent studies have identified multiple novel GLP-1R interactors, including the Ras superfamily proteins Rab5b and Rab5c, ATPase H^+-transporting lysosomal accessory protein 2 (ATO6Ap2) and progesterone receptor membrane component 1, which served dual roles by regulating both GLP-1R signaling and insulin secretion through EGF receptor and cAMP signaling (77,78). In β-cells, GLP-1 might activate various signaling pathways, including cAMP-PKA, PI3K-AKT, ERK1/2 and Wnt (Fig. 1) (79,80). In a study of the hyperglycemic response, GLP-1 reinforced glucose-stimulated insulin

secretion principally through activation of cAMP-PKA signaling in the β-cell line INS-1E (81). GLP-1 binding to GLP-1R has been reported to activate cAMP-PKA, and via ADAM proteins GLP-1 triggered the secretion of BTC, which acted upon ErbB1/2 (Fig. 1) (53). Furthermore, a recent report suggested that geniposide may enhance insulin secretion by activating GLP-1R in tandem with adenylyl cyclase (AC)/cAMP signaling (82). Yang *et al* (83) demonstrated that the peroxisome proliferator-activated receptor β/δ agonist, GW501516 (GW), in tandem with its transcriptional modulation of GLP-1R, may protect against lipotoxic apopotosis in β-cells. In addition, conditional chicken ovalbumin upstream promoter transcription factor II, as a novel mediator of GLP-1 signaling required for GLP-1 activation, depended on β-catenin signaling, and its expression was regulated by TCF7L2, which increased β-cell mass during the neonatal stage (84).

The present review has described a number of key hormone pathways implicated in β-cell proliferation, though further research is required to elucidate the full involvement of hormones in β-cell proliferation.

5. Wnt signaling pathways

The wnt signaling pathway is generally composed of extracellular wnt ligands, disheveled protein, Frizzled receptor, β-catenin, axin, GSK3β and adenomatous polyposis colis protein (Fig. 1) (85,86). The wnt pathway may be divided into three types: A canonical wnt/β-catenin pathway, a planar cell polarity (PCP) pathway and a non-canonical pathway, which includes wnt/Ca^{2+}, activated phospholipase C, PKC and small GTPase (87,88).

In terms of function, wnt signaling molecules have been demonstrated to influence pancreatic endocrine development and regulate the postnatal β-cell functions of insulin secretion, proliferation, survival and differentiation (89). Bader *et al* (90) concluded that wnt/PCP genes were responsible for functional β-cell heterogeneity and induced β-cell maturation. Fltp, as a wnt/PCP effector and firefly luciferase, is considered to be a marker gene that may aid to elucidate the molecular mechanisms of islet cell plasticity and heterogeneity, and may be a target in endocrine cells for functional β-cell regeneration in diabetes (91). Wnt4, a regulator of β-cell proliferation, has been documented to primarily regulate canonical wnt signaling (85,86). Krutzfeldt *et al* (91) demonstrated that the expression and upregulation of wnt4 was common in the β-cells of obese mice. Furthermore, stimulation with exendin-4 enhanced wnt4 expression in β-cells (87). It has also been reported that wnt3a modulated the proliferation of β-cells and enhanced β-cell function by activating the wnt/β-catenin pathway, indicating crosstalk with PI3K signaling (92). Rulifson *et al* (93) observed that wnt3a induced the expression of Cdk4 and cyclin D-1 and -2, and stimulated enhanced β-cell proliferation *in vitro*. Regarding stem cells, canonical wnt signaling facilitated stem cell proliferation and survival via the expression of β-catenin-related downstream targets, such as cMyc, which was conducive to the transplantation of pluripotent stem cells in D1M (94-96). Afelik *et al* (97) also documented that wnt7b was a modulator of pancreatic progenitor cell development. T cell factor 7-like 2 (TCF7L2) has been identified as a significant component of wnt/β-catenin signaling (Fig. 1), and a potent factor in the pathogenesis and progression of D2M (98). Notably, the dominant-negative form or 'at-risk' alleles of TCF7L2 served a deleterious role in β-cell proliferation and insulin secretion (99). Furthermore, the functional consequences of reduced high-mobility group protein B1 in BCD (INS1) and human colon cancer (HCT116) cells were reductions in TCF7L2 mRNA expression, TCF7L2 transcriptional regulatory activity and glucose triggered insulin secretion (100). A recent study also documented that geniposide promoted β-cell proliferation and survival by modulating the β-catenin/TCF7L2 signaling pathway (101).

6. JAK-STAT signaling pathways

JAK-STAT is a relatively novel signaling pathway, which has been associated with multiple cytokines, such as interleukin (IL)-1, -2 and -6, and hormones such as leptin, GH, placental lactogens, erythropoietin (EPO) and PRL (Fig. 3) (102-105). JAK-STAT participates in the regulation of key biological processes, including cell proliferation, differentiation and apoptosis (102). Furthermore, JAKs may serve as a fundamental switch that must be activated through a cytokine to trigger STAT proteins, which enables downstream target activation and subsequent regulation of target gene transcription (106). It has been reported that activated STAT proteins may also trigger suppressors of cytokine signaling (SOCS), protein repressors of activated STAT and transcription of cytokine-inducible SH2 domain-containing proteins (CISH; Fig. 3) (107,108). SOCS proteins are considered to be pivotal negative modulators of JAK-STAT signaling by terminating its upstream signals, of which four-SOC1, SOC2, SOC3 and CISH have been reported to serve as primary factors in the JAK-STAT pathway (106,109).

The progressive loss of pancreatic β-cells leads to D1M, which is closely associated with autoimmune assault (110). During the inflammatory progressive stage, overexpression of JAK-STAT molecules in pancreatic islets has been reported to contribute to β-cell dysfunction (111). A recent study documented that BRD0476, a novel inhibitor of β-cell apoptosis, impeded inteferon-γ-induced JAK2 and STAT1 signaling to facilitate β-cell survival (112). Unlike general JAK-STAT pathway suppressors, BRD0476 blocked JAK-STAT signaling pathways via ubiquitin-specific peptidase 9X (USP9X) without inhibiting the kinase function of any JAK (112). With regard to PRL, it has been observed that human β-cells failed to expand in response to PRL, potentially due to a deficiency of PRL receptors, among other explanations (5). Notably, a failure of β-cell expansion could be overcome by overexpression of murine STAT5a, due to the resulting upregulation and nuclear translocation of cdk4 and cyclins D1-3 (Fig. 3). This STAT5 signaling has been linked with β-cell cycle activity (113). Furthermore, EPO, acting via the EPO receptor, has been reported to stimulate β-cell proliferation through JAK2-STAT5 (Fig. 3) (114). De Groef *et al* (115) demonstrated that PDL stimulated the expression of multiple cytokines that served as positive ligands of STAT3 signaling in β-cells. In addition, β-cell cycling was enhanced by activating STAT3 with IL-6 (Fig. 3).

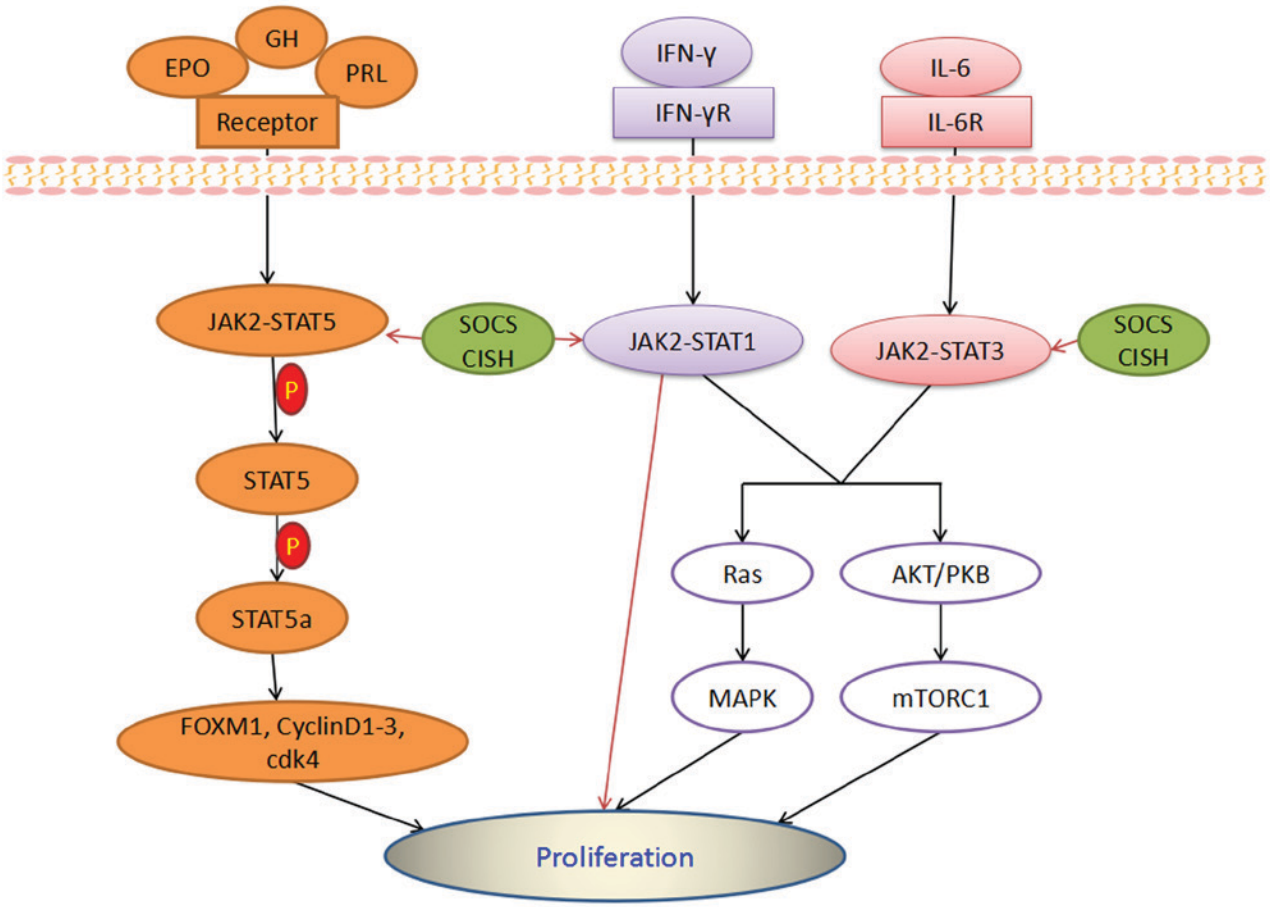

Figure 3. JAK-STAT signaling in tandem with multiple cytokines and hormones participates in the regulation of β-cells. Circles of the same color represent signals within the same pathway. Red and black lines indicate inhibition and promotion, respectively. JAK-STAT, janus kinase-signal transducers and activators of transcription; EPO, erythropoietin; GH, growth hormone; PRL, prolactin; FOXM1, forkhead box protein M1; cdk, cyclin-dependent kinase; SOCS, suppressor of cytokine signaling; CISH, cytokine-inducible SH2 domain-containing proteins; IFN-γ, interferon-γ; IFN-γR, interferon-γ receptor; IL-6, interleukin 6; IL-6R, interleukin 6 receptor; PKB, protein kinase B; MAPK, mitogen-activated protein kinase; mTORC1, mechanistic target of rapamycin complex 1; Ras, rat sarcomas; P, phosphorylated.

STAT3 played an important role in maintaining the stability of β-cells by regulating the cell cycle and protecting against DNA damage (115).

7. TLR4 signaling pathway

Toll like receptor 4 (TLR4) is principally expressed in the innate immune system, and is considered to be involved in DM (116). In D2M, the expression of TLR4 may increase due to activation of the nuclear factor-κB (NF-κB) signaling pathway. While NF-κB has not been associated with the inflammatory reaction in diabetes, it may have an important influence on glucose metabolism and insulin reaction. NF-kB binds to the promoters of innate immune genes, particularly those of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and IL-1β, which is considered to exert positive feedback on TLR4 expression (117-119). Sepehri *et al* (119) reported that TLR4 was upregulated in the peripheral blood mononuclear cells of patients with D2M patients, which was independent of sex, age, body mass index and blood sugar content. Furthermore, TLR4 is considered to be a significant candidate in the related complications of D2M, including nephropathy (120) and atherosclerosis (121).

8. Conclusions and perspectives

Cellular signaling pathways are substantial targets, and are capable of stimulating β-cell proliferation, as demonstrated in various islets and β-cell systems. As such, they may be useful in future treatment strategies for diabetes. Cellular signaling pathways involving interactions with ligands, receptors and the proliferative machinery of β-cells are complex systems. The present review evaluated the potential underlying mechanisms of insulin, growth factor, Wnt, JAK-STAT and TLR4 signaling. While various cellular signaling mechanisms were discussed, not all signaling pathways implicated in β-cell proliferation were included, such as those involving islet cell autoantigen-512, inhibin, activin, muscarinic and octeocalicn.

Cellular signaling molecules and their downstream targets form an intricate network, which may directly or indirectly regulate β-cell proliferation and survival. While an increased number of studies have investigated cellular signaling, difficulties remain in their applications. For instance, the expression of cellular signals in β-cells varies among different species, ages and tissues. Furthermore, various cellular signals have not been investigated, and their specific functions and mechanisms within β-cells remain unclear and disputed by

researchers. Though notably, excessive activation of signaling pathways may have negative impacts on β-cells.

In conclusion, multiple other therapeutic strategies may be used for the treatment of diabetes, including stem cell differentiation induction and islet transplantation. Cellular signaling pathways may have untapped potential in the induction of β-cell proliferation. Identification of appropriate molecular targets within these pathways may aid to develop novel strategies in the treatment of diabetes and improve the outcome for patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WJJ wrote the manuscript, collected images and analyzed the data; YCP processed the images; KMY analyzed the data, processed the images and revised the manuscript. All authors have read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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