Chapter 17
Wnt Signaling in Pancreatic Islets

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Abstract The Wnt signaling pathway is critically important not only for stem cell amplification, differentiation, and migration, but also is important for organogenesis and the development of the body plan. Beta-catenin/TCF7L2-dependent Wnt signaling (the canonical pathway) is involved in pancreas development, islet function, and insulin production and secretion. The glucoincretin hormone glucagon-like peptide-1 and the chemokine stromal cell-derived factor-1 modulate canonical Wnt signaling in β-cells which is obligatory for their mitogenic and cytoprotective actions. Genome-wide association studies have uncovered 19 gene loci that confer susceptibility for the development of type 2 diabetes. At least 14 of these diabetes risk alleles encode proteins that are implicated in islet growth and functioning. Seven of them are either components of, or known target genes for, Wnt signaling. The transcription factor TCF7L2 is particularly strongly associated with risk for diabetes and appears to be fundamentally important in both canonical Wnt signaling and β-cell functioning. Experimental loss of TCF7L2 function in islets and polymorphisms in TCF7L2 alleles in humans impair glucose-stimulated insulin secretion, suggesting that perturbations in the Wnt signaling pathway may contribute substantially to the susceptibility for, and pathogenesis of, type 2 diabetes. This review focuses on considerations of the hormonal regulation of Wnt signaling in islets and implications for mutations in components of the Wnt signaling pathway as a source for risk-associated alleles for type 2 diabetes.

17.1 The Diabetes Problem

The prevalence of diabetes mellitus and its accompanying complications is increasing in populations throughout the world [1]. Diabetes results from a deficiency of the β-cells of the islets of Langerhans to produce insulin in amounts sufficient to meet

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the body's needs, either absolute deficiency (type 1 diabetes) or relative deficiency (type 2 diabetes). In type 2 diabetes the remaining β-cells are placed under stress by (1) being forced to overproduce insulin to compensate for the lost β-cells, (2) insulin resistance, and (3) by the glucotoxic effects of prolonged, sustained hyperglycemia. In the USA, 20 million individuals are currently afflicted with some form of diabetes, while an estimated 12 million additional people in the USA have diabetes but do not know it yet [2]. Worldwide, an estimated 190 million people have the disease and this global figure is expected to skyrocket to 366 million by 2030 [3]. Type 2 diabetes is the most prevalent form of diabetes comprising >90% of all diabetes. Most individuals who develop type 2 diabetes do so in association with obesity [4]. Because a common feature of both type 1 and type 2 diabetes is a reduction in β-cell mass, understanding the factors and the cellular mechanisms that govern β-cell growth and survival may lead to new effective treatments for diabetes.

In adult rats and mice the entire mass of the β-cells in the pancreas turns over approximately every 50 days (2–3% per day) by processes of apoptosis counterbalanced by replication from existing β-cells and neogenesis from progenitor cells believed to be located in the pancreatic ducts and possibly within the islets [5–7]. The adult pancreas of rodents, including the endocrine islets, has a substantial capacity for regeneration [8]. Rodent models of pancreatic injuries are followed by partial to nearly complete regeneration of the exocrine and endocrine pancreas. Such models of pancreas regeneration include partial pancreatectomy [9], streptozotocin-mediated ablation of the β-cells [10, 11], duct ligation, and caerulein treatments [12]. However, it remains controversial whether progenitors exist in the adult pancreas. A slow cycling, multi-potent stem cell in the pancreas has not yet been identified convincingly. Compelling evidence found that the majority of new β-cells derive from preexisting insulin-expressing cells after partial pancreatectomy [13], but recent evidence suggested that another form of surgical injury duct ligation activates Ngn3-positive β-cell precursors in the ductal epithelium [14]. Therefore, the activation of adult pancreatic progenitors might depend on the specific experimental model.

Genome-wide scans of several large populations of diabetic cohorts have begun to uncover some of the genes associated with type 2 diabetes [15–20]. Of note, the majority of the candidate genes identified thus far appear to be involved in islet functions, and most notably, the insulin-producing β-cells in the islets [19, 20]. Furthermore, as discussed later in this chapter, several of these genes appear to be involved in the Wnt signaling pathway; either components of the Wnt signaling system itself or target genes for downstream Wnt signaling by beta-catenin and TCF7L2. The Wnt signaling pathway may be involved in the dysfunction of β-cells in type 2 diabetes [21]. Attention is directed to recent reviews on the role of Wnt signaling in pancreas development and function [18–20] and the importance of the transcription factor TCF7L2 in pancreatic islet function and diabetes [20, 25–36]. In this review evidence is considered for the regulation of islet β-cell functions by beta-catenin/TCF7L2 induced by glucagons-like peptide-1 and stromal cell-derived factor-1. Speculations are presented on the potential involvement of the Wnt signaling pathway in the genetic predisposition to type 2 diabetes.

17.2 Wnt Signaling Pathways

The Wnt signaling cascade controls several cellular functions, including differentiation, proliferation, and migration [37–43]. Useful brief summaries of the Wnt signaling pathways are provided in [44] and [45]. The Wnt proteins form a large family of cell-secreted factors that control diverse aspects of development and organogenesis. Wnt proteins exert their effect by binding to cell surface G protein-coupled Frizzled (Fz) receptors and the lipoprotein receptor-like proteins, LRP5/6 co-receptors, and modulate the expression of various target genes through a series of intracellular processes ultimately leading to the regulation of transcription. There are currently several recognized Wnt signaling pathways: the beta-catenin-dependent, so-called canonical Wnt pathway that is dependent on the activation of the transcriptional complex of proteins consisting of beta-catenin and TCF/LEF (Fig. 17.1) and several (at least nine) distinct and complex beta-catenin, TCF/LEF-independent, noncanonical pathways (Fig. 17.2, Ref. [41]).

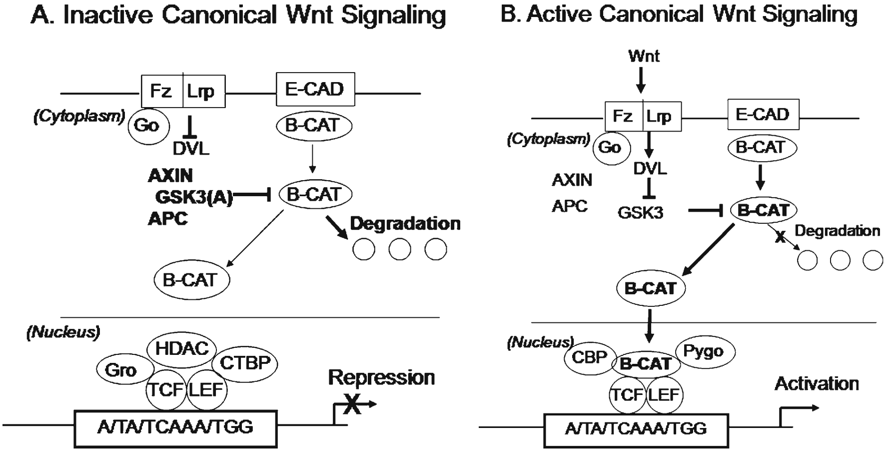

Fig. 17.1 Models depicting the canonical, beta-catenin/TCF/LEF-dependent Wnt signaling pathway in inactive and active states. **A**. Inactive Wnt signaling. In the absence of Wnt ligand-mediated activation of its receptor frizzled (Fz), beta-catenin in the cytoplasm is phosphorylated by the protein kinases glycogen synthase kinase-3beta (GSK3beta) and casein kinase Ialpha (CKIa) leading to its degradation by proteasome complexes. GSK3beta and CKIalpha are constitutively activated by the cofactors adenomatous polyposis coli (APC) and Axin that along with GSK3beta and CKIalpha are known as the destruction complex. In the absence of sufficient levels of cytosolic beta-catenin, nuclear levels are depleted and the DNA-binding transcription factors TCF and LEF act as repressors of gene transcription by the recruitment of corepressors such as Groucho and CtBP. **B**. Active Wnt signaling. In the presence of Wnt ligands Fz is activated via G protein G alpha i/o and small GTPases leading to the activation of disheveled (DVL) that disrupts the destruction complex composed of GSK3, CKI, APC, and Axin, thereby inhibiting the activities of GSK3 and CKI. In the absence of phosphorylation, unphosphorylated beta-catenin is stabilized, translocated to the nucleus where it non-covalently associates with TCF/LEF DNA-binding proteins, recruits coactivators such as CBP and Pygo resulting in the activation of gene transcription

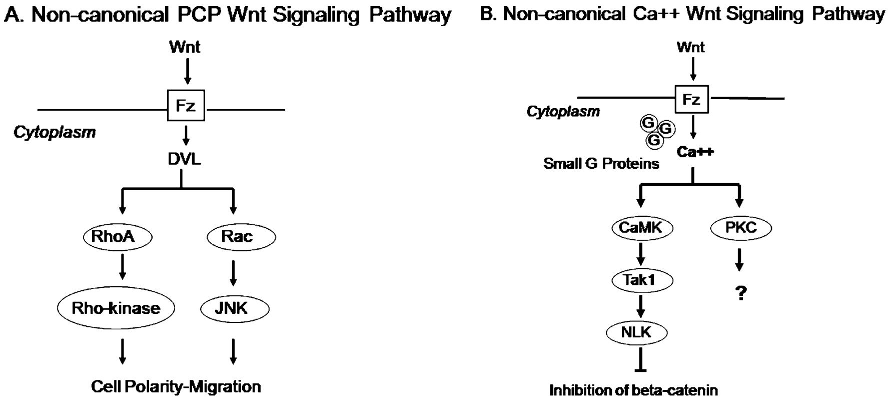

Fig. 17.2 Models depicting noncanonical beta-catenin-independent Wnt signaling pathways. **A**. The planar cell polarity (PCP) pathway. The activation of Fz by Wnts leads to the activation of DVL and small G proteins such as rhoA and Rac and the kinases Rho-kinase and Jun kinase (JNK). Through as yet undefined pathways Rho-kinase and JNK modulate changes in the cytoskeleton involved in cell migration and polarity. **B**. The Ca^{2+} pathway. Wnt ligands such as Wnt 5a activate Ca^{2+}-activated calmodulin kinases. CaMK and downstream kinases TAK1 and NLK. This pathway inhibits the canonical beta-catenin-dependent Wnt signaling pathway and is active during gastrulation. The Ca^{2+} pathway also activates protein kinase C (PKC)

17.2.1 The Canonical Wnt Signaling Pathway

The downstream canonical Wnt signaling pathway is defined as the pathway that ends in the formation of active, productive transcriptional transactivation complexes composed of beta-catenin and the DNA-binding proteins TCF (T-cell factor) and LEF (lymphocyte enhancer factor) (Fig. 17.1). It involves beta-catenin that when stabilized translocates to the nucleus where it associates with the TCF/LEF family of transcription factors to regulate the expression of canonical Wnt target genes. In the absence of a Wnt signal, beta-catenin is efficiently captured by the scaffold protein Axin, which is present within a protein complex (referred to as the destruction complex) that also harbors adenomatous polyposis coli (APC), glycogen synthase kinase (GSK)-3, and casein kinase 1 (CSNK1) (Fig. 17.1a). The resident CSNK1 and GSK3 protein kinases sequentially phosphorylate conserved serine and threonine residues in the N-terminus of beta-catenin subsequently targeting it for ubiquitination and degradation. The efficient suppression of beta-catenin levels ensures that Groucho proteins are free to bind members of the lymphocyte enhancer factor (LEF)/T cell factor (TCF) family of transcription factors occupying the promoters and enhancers of Wnt target genes in the nucleus. These transcriptionally repressive complexes actively suppress the Wnt target genes such as c-Myc and cyclin D1, thereby silencing an array of biological responses, including cell proliferation. Rapid activation of the canonical pathway occurs when Wnt proteins interact with specific receptor complexes comprising members of the Frizzled family of proteins and the low-density lipid co-receptor LRP5 or LRP6 (Fig. 17.1b). The ligand-receptor binding activates the intracellular protein, Disheveled (Dvl), which inhibits APC-GSK3beta-axin activity and subsequently blocks degradation of beta-catenin. This stabilization of beta-catenin allows it to accumulate and translocate to the nucleus where it forms a transcriptionally active complex with the DNA-binding TCF transcription factors to activate the expression of Wnt signaling target genes. In pancreatic β-cells TCF7L2 is a major form of TCF involved in downstream Wnt signaling responsible for the activation of growth-promoting genes in response to glucagon-like peptide-1 (GLP-1) agonists [46, 47]. Notably, TCF7L2 has recently been found to be a major susceptibility factor for the development of T2D manifested by diminished insulin production [24, 25, 30, 32, 33, 48].

17.2.2 Noncanonical Wnt Signaling

Wnt signaling via frizzled receptors can also lead to the activation of noncanonical pathways that are independent of beta-catenin and TCF/LEF complexes [45]. Two of the several recognized [45] beta-catenin-independent pathways are considered (Fig. 17.2). One such noncanonical pathway consists of the release of intracellular calcium. Other intracellular second messengers associated with this pathway include heterotrimeric G proteins, phospholipase C (PLC), and protein kinase C (PKC). The Wnt/Ca^{2+} pathway is important for cell adhesion and cell movements during gastrulation [49]. The Wnt/Ca^{2+} pathway is also known to control cell migration and is involved in regulating endothelial cell migration. Interestingly, the Wnt/Ca^{2+} pathway may antagonize the canonical Wnt/beta-catenin pathway. The canonical and noncanonical Wnt pathways are likely to have opposing effect on endothelial cells and probably antagonize each other in order to finely balance endothelial cell growth.

The WNT/planar cell polarity (PCP) signaling pathway is a second noncanonical Wnt signaling pathway [49, 50, 51]. PCP controls tissue polarity and cell movement through the activation of RHOA, c-Jun N-terminal kinase (JNK), and nemo-like kinase (NLK) signaling cascades. In the planar cell polarity pathway Wnt signaling through frizzled receptors mediates asymmetric cytoskeletal organization and the polarization of cells by inducing modifications to the actin cytoskeleton.

17.3 Wnt Signaling in Pancreas Development and Regeneration

Expression of components of the Wnt signaling pathway, including Wnt ligand family members and various frizzled receptors, is well documented in the developing mouse, rat, chick, fish, and human pancreas [52–56]. A description of the subsets of the dozen or so Wnt ligands, Frizzled receptors, and the Wnt/FZ regulators, secreted frizzle-related proteins, and dickkopfs is provided in Heller et al. [52]. Endogenous Wnt signaling also occurs in mouse and rat β-cell lines [46]. Detailed information on the cellular distributions of expression of the various Wnt ligands, receptors, and regulators is not available. From the findings of Heller et al. [52] it is clear that Wnt signaling factors are expressed both in epithelium and in mesenchyme. Several studies confirm that functional Wnt signaling is active in islets throughout development. A Wnt reporter strain of mice, in which lacZ was inserted into the locus of the Wnt target gene conductin/axin2, expressed beta-galactosidase, the product of the LacZ gene, throughout the islets [57]. Expression of the conductin gene is transcriptionally activated by the canonical Wnt pathway via TCF binding sites in its promoter. Furthermore, the beta-galactosidase (LacZ) reporter activity is maintained in islets of mice up to 6 weeks after birth. A monoclonal antibody specific for the non-phosphorylated form of beta-catenin revealed a strong immunoreactivity in the pancreatic epithelium of the mouse at embryonic day 13 [58]. Taken together, human and rodent islets and rodent β-cell lines are known to express members of the Wnt ligand and frizzled receptors families, along with modulators of Wnt signaling, the LRP co-receptors, and secreted Dkk (dickkopf) proteins.

Another source of Wnt ligands is adipose tissue [59]. Adipocytes secrete a wide range of signaling molecules including Wnt proteins. Fat cell-conditioned media from human adipocytes increases the proliferation of INS-1 β-cell and induces Wnt signaling, which could contribute to the β-cell hyperplasia that occurs in humans and rodents in response to obesity. Interestingly, inhibitory noncanonical Wnt ligand Wnt5b gene is associated strongly with obesity and type 2 diabetes [59]. Expression of Wnt5b in preadipocytes increases adipogenesis and the expression of adipokine genes through the inhibition of canonical Wnt signaling [59]. Thus, alterations in Wnt5b levels in humans could alter adipogenesis and, consequently, affect the risk of diabetes onset.

17.3.1 Wnt Signaling Loss-of-Function Studies

Following early pancreas specification, Wnt signaling appears to be indispensable for pancreas development, although its precise role remains controversial. The majority of studies have shown that Wnt signaling is essential in the development of the exocrine pancreas. Disruption of the Wnt signaling pathway results in an almost complete lack of exocrine cells [57, 58, 60, 61]. However, its role in endocrine cell development is still uncertain. Several studies in which Wnt signaling is abolished by conditional beta-catenin knockout in the developing mouse pancreas have revealed that the endocrine component of the pancreas develops normally and is functionally intact in the studies of Murtaugh et al. [60] and Wells et al. [61] in which the beta-catenin gene in the epithelium of the pancreas and duodenum was specifically deleted, pancreatic islets are intact and contain all lineages of endocrine cells. In contrast, using a different beta-catenin knockout approach Dessimoz et al. [57] found a reduction in endocrine islet numbers. It is worth noting that knockout studies should be interpreted with some caution because of the potential occurrence of adaptive compensatory mechanisms that could alter the phenotype. Furthermore, the use of different strains of mice expressing PDX-Cre, which have different recombination efficiencies, are expressed at different stages of development and are shown to have mosaic expression in the pancreata of transgenic mice [62]. It seems possible that beta-catenin and Wnt signaling have several different roles throughout the development of the pancreas. Since the timing of the activation or inactivation of Wnt signaling is crucial for its effects on pancreas development, the currently available Cre-based recombinant technology might not be adequate to fully explore the role of Wnt signaling. Collectively, the loss-of-function studies have not yet provided a definitive role for beta-catenin in the development and/or maintenance of function of adult islets. Nonetheless, these results underscore the possible dual nature of Wnt signaling in pancreas growth and development. Excessive Wnt signaling activation prevents proper differentiation and expansion of early pancreatic progenitor cells during early, first transition specification. During the second transition, beta-catenin acts as a pro-proliferative cue that induces gross enlargement of the exocrine and/or endocrine pancreas.

17.3.2 Wnt Signaling Gain-of-Function Studies

Gain-of-function experiments suggest an inhibitory role for Wnt pathway in pancreas specification, a stage when cells at the appropriate regions of the foregut begin to form a bud. Heller et al. [52] showed that forced misexpression of Wnt1 driven by PDX-1 promoter in mice induces a block in the expansion and differentiation of PDX-1-positive cells and causes ensuing reduction in endocrine cell number and a lack of organized islet formation. Excessive Wnt signaling in the epithelia limits the expansion of both the mesenchyme and the epithelium and inhibits growth of the pancreas and islets. Using a different approach, Heiser et al.'s [62] study reached a similar conclusion. The conditional knock-in of stable beta-catenin in early pancreatic development of mice using PDX-1-driven Cre recombinase efficiently targets all three pancreatic lineages – endocrine, exocrine, and duct – and results in up-regulation of Hedgehog and leads to a loss of PDX1 expression in early pancreatic progenitor cells [62]. This genetic model of forced over-expression of beta-catenin prevents normal formation of the exocrine and endocrine compartments of the pancreas. Using a Xenopus model, McLin et al. [63] found that forced Wnt/beta-catenin signaling in the anterior endoderm, between gastrula and early somite stages, inhibits foregut development. By contrast, blocking beta-catenin activity in the posterior endoderm is sufficient to initiate ectopic pancreas development [62]. These genetic manipulations of Wnt signaling in mice suggest a contribution of both inhibitory and facilitating roles of Wnt signaling during pancreas development. The gain-of function studies by Dessimoz et al. [57] show a distinctive role of Wnt signaling in endocrine development. Wnt3A induces the proliferation of islet and MIN-6 cells [64]. The addition of the soluble Wnt inhibitor, Fz 8-cysteine-rich domain (Fz8-CRD), eliminated this stimulatory effect of Wnt3a on cell proliferation [64]. The treatment of islets with Wnt3a significantly increased mRNA levels of cyclin D1, cyclin D2, and CDK4, all of which have Wnt-responsive elements in the promoter regions of their genes [56]. Conditional knock-in of active beta-catenin in mice promotes the expansion of functional β-cells [62] whereas the conditional knock-in of the Wnt inhibitor Axin impaired proliferation of neonatal β-cells [64].

Surprisingly, recent studies found that Wnt signaling may play a role in regulating the secretory function of mature β-cells [65]. The Wnt co-receptor, LRP5, is required for glucose-induced insulin secretion from the pancreatic islets. The knockout of LRP5 in mice resulted in glucose intolerance [65]. Treatment of isolated mouse islets with purified Wnt3a and Wnt5a ligands causes potentiation of glucose-stimulated insulin secretion. Thus, LRP5 together with Wnt proteins appear to modulate glucose-induced insulin secretion. Furthermore, Schinner et al. [59] reported that activating Wnt signaling increases insulin secretion in primary mouse islets and activates transcription of the glucokinase gene in both islets and INS-1 cells. The consummate evidence came in isolated mouse and human islets, in which reducing levels of TCF7L2 by siRNA decreases glucose-stimulated insulin secretion, expression of insulin and PDX-1, and insulin content [47, 66, 67].

17.4 Role of Wnt Signaling in β-Cell Growth and Survival

In addition to its potential role in regulating glucose-stimulated insulin secretion, the Wnt pathway is involved in β-cell growth and survival. The activation of Wnt signaling in β-cell lines or primary mouse islets results in an expansion of the functional β-cell mass, findings consistent with the up-regulation of pro-proliferative genes including cyclin D1 and D2 [46]. Furthermore, the misexpression of a negative regulator of Wnt signaling, axin, impairs the proliferation of neonatal β-cells, demonstrating a requirement for Wnt signaling during β-cell expansion [64]. Axin expression impaired normal expression of islet cyclin D2 and pitx2, a transcriptional activator that directly associates with promoter regions of the cyclin D2 gene. Shu et al. [47] provide further evidence in support of a role for Wnt signaling in β-cell growth and survival in both mouse and human islets. Depletion of TCF7L2 in human islets causes a decrease in β-cell proliferation, an increase in levels of apoptosis, and a decline in levels of active Akt, an important β-cell survival factor [46]. Similarly, in INS-1 cells, expression of dominant-negative TCF7L2 decreases proliferation rates [46]. Furthermore, over-expression of TCF7L2 in both mouse and human islets protects β-cells against glucotoxicity or cytokine-induced apoptosis [47].

17.5 Roles of Non-Wnt Hormonal Ligands in the Activation of the Wnt Signaling Pathway in Islets

Several hormones and growth factors, such as insulin, insulin-like growth factor-1, platelet-derived growth factor, parathyroid hormone, and prostaglandins, are known to activate the canonical and noncanonical Wnt signaling pathways. However, these observations have been made in non-islet tissues such as intestine, cancer cell lines, osteoblasts, and fibroblasts [68]. It has been proposed that a primary function of Wnt signaling is to maintain stem cells in a pluripotent state and that growth factors such as FGF and EGF augment their proliferation [69]. Very little is known, however, about the hormonal activation of Wnt signaling in pancreatic islets. Recent studies of glucagon-like peptide-1 (GLP-1) and stromal cell-derived factor-1 (SDF-1) actions on islet β-cell demonstrate that both hormones activate downstream Wnt signaling via beta-catenin/TCF7L2-regulated gene transcription and that downstream Wnt signaling is required for the pro-proliferative actions of GLP-1 [46] and the anti-apoptotic actions of SDF-1 [70].

17.5.1 Downstream Wnt Signaling Requirement for GLP-1-Induced Stimulation of β-Cell Proliferation

Glucagon-like peptide-1 (GLP-1) is a glucoincretin hormone released from the intestines in response to meals and stimulates glucose-dependent insulin secretion from pancreatic β-cells [71, 72]. GLP-1 also stimulates both the growth and the survival of β-cells. GLP-1 is produced in the enteroendocrine L-cells that reside within the crypts of the intestinal mucosa by selective posttranslational enzymatic cleavages of the prohormonal polypeptide, proglucagon, the protein product of the expression of the glucagon gene (Gcg). Notably, the same proglucagon expressed from Gcg in the α-cells of the pancreas is alternatively cleaved to yield the hormone glucagon, rather than GLP-1. Glucagon functions as an insulin counter-regulatory hormone to stimulate hepatic glucose production and thereby to maintain blood glucose levels in the postabsorptive, fasted state.

Genes expressed in Wnt signaling in β-cells were examined using a focused Wnt signaling gene microarray and the clonal β-cell line INS-1 [46]. Of the 118 probes represented on the Wnt signaling gene array, 37 were expressed above background in cultured INS-1 cells. Exposure of the cells to GLP-1 enhanced the expression of 14 of the genes, including cyclinD1 and c-myc, strongly suggesting that GLP-1 agonists activate components and target genes of the Wnt signaling pathway. GLP-1 agonists activate beta-catenin and TCF7L2-dependent Wnt signaling in isolated mouse islets and INS-1 β-cells and antagonism of beta-catenin by siRNAs and of TCF7L2 by a dominant negative form of TCF7L2-inhibited GLP-1-induced proliferation [46]. These findings suggest that Wnt signaling is required for GLP-1-stimulated proliferation of β-cells. Although INS-1 cells maintain high basal levels of Wnt signaling via Wnt ligands and Frizzled receptors, GLP-1 agonists specifically enhance Wnt signaling through their binding to the GLP-1 receptor (GLP-1R), a G protein-coupled receptor coupled to GalphaS and the activation of cAMP-dependent protein kinase A (PKA). Although PKA is not involved in maintaining basal levels of Wnt signaling, it is essential for the enhancement of Wnt signaling by GLP-1 [46]. In addition, the pro-survival protein kinase Akt, along with active MEK/ERK signaling, is required for maintaining both basal- and GLP-1-induced

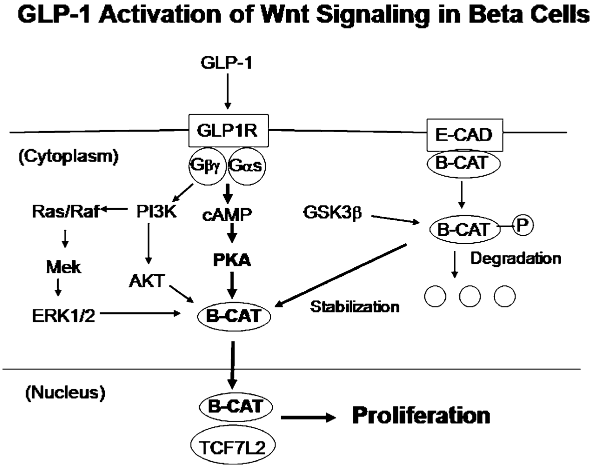

Fig. 17.3 Diagram summarizing the signaling pathway in pancreatic β-cells by which GLP-1 actions couple to the downstream Wnt signaling pathway [37]. The interaction of GLP-1 with the GLP-1 receptor (GLP-1R) activates G protein alpha S (GalphaS) resulting in cAMP formation and activation of the cAMP-dependent protein kinase A (PKA). Remarkably, by the GLP-1-activated pathway beta-catenin is stabilized by direct phosphorylation by PKA, rendering it resistant to degradation in response to phosphorylations by GSK3beta. This stabilization of beta-catenin by PKA-mediated phosphorylation is a distinct departure from the canonical Wnt pathway in which phosphorylation of beta-catenin by GSK3beta results in its degradation. Beta-catenin thus stabilized by PKA-mediated phosphorylation is resistant to degradation in response to phosphorylation by GSK3beta, accumulates in the cytoplasm, and is translocated to the nucleus where it associates with TCF7L2 to form a productive transcriptional activation complex. Beta-catenin/TCF7L2 complexes activate the expression of target genes involved in β-cell proliferation

Wnt signaling [46] (Fig. 17.3). In summary, both beta-catenin and TCF7L2 appear to be required for GLP-1-mediated transcriptional responses and cell proliferation.

17.5.2 Downstream Wnt Signaling Requirement for SDF-1-Induced Promotion of β-Cells Survival

SDF-1 is a chemokine originally identified as a bone marrow (BM) stromal cell-secreted factor and now recognized to be expressed in stromal tissues in multiple organs [73–76]. The most extensively studied function of the SDF-1/receptor CXCR4 axis is that of chemoattraction involved in leukocyte trafficking and stem cell homing in which local tissue gradients of SDF-1 attract circulating stem/progenitor cells. SDF-1/CXCR4 signaling in the pancreas remains relatively unexplored. Kayali and coworkers reported expression of SDF-1 and CXCR4 in the fetal mouse pancreas and CXCR4 in the proliferating duct epithelium of the regenerating pancreas of the nonobese diabetic mouse [77]. The cross talk between the

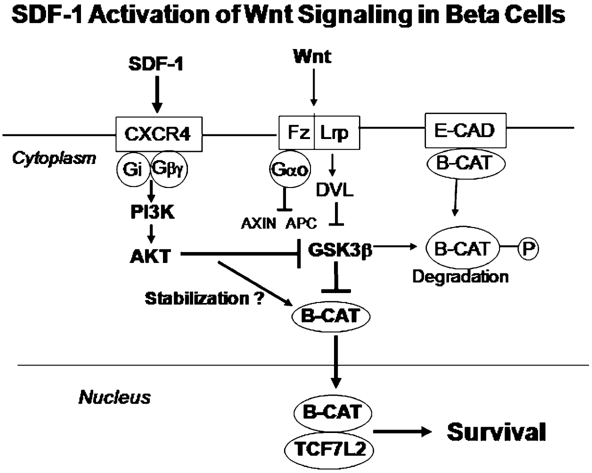

Fig. 17.4 Schematic model of signaling pathways utilized by SDF-1/CXCR4 in the activation of beta catenin/TCF7L2-mediated transcriptional expression of genes involved in β-cell survival. Interactions of SDF-1 with its G protein-coupled receptor CXCR4 activates G protein i/o that activates the phosphoinositol kinase 3 (PI3K) and the downstream pro-survival kinase Akt. Akt is a potent inhibitor of the Wnt signaling destruction complex composed of Axin, APC, and GSK3beta. Inhibition of GSK3beta by Akt results in the inhibition of phosphorylation of beta-catenin by GSK3, prevents the degradation of beta-catenin, and thereby results in the stabilization of beta-catenin which accumulates in the cytoplasm, enters the nucleus, where it associates with TCF7L2. The beta-catenin/TCF7L2 forms a transcriptional activation complex that activates the expression of genes that promote β-cell survival. A direct action of Akt on the stabilization of beta-catenin remains conjectural

SDF-1-CXCR4 axis and the Wnt signaling pathway was first demonstrated by Luo et al. [78] in studies of rat neural progenitor cells. Transgenic mice expressing SDF-1 in their β-cells (RIP-SDF-1 mice) are protected against streptozotocin-induced diabetes through activation of the pro-survival protein kinase Akt and resulting downstream pro-survival, anti-apoptotic signaling pathways [79]. An examination of SDF-1-activated Wnt signaling in both isolated islets and INS-1 cells using a beta-catenin/TCF-activated reporter gene assay revealed enhanced Wnt signaling through the Galphai/o-PI3K-Akt axis, suppression of GSK3beta, and stabilization of beta-catenin [70] (Fig. 17.4). Phosphorylation of GSK3 by Akt represses its phosphorylating activities on beta-catenin and thereby to reduce the degradation of beta-catenin. Moreover, SDF-1 signaling in INS-1 β-cells stimulates the accumulation of beta-catenin mRNA, likely due to an enhancement the transcription of the beta-catenin gene [70]. Recent evidence also suggests that active Wnt signaling mediates, and is required for, the cytoprotective, survival actions of SDF-1 on β-cells [70].

17.5.3 Potential Mechanisms by Which GLP-1 and SDF-1 May Act Cooperatively on Wnt Signaling to Enhance β-Cell Growth and Survival

There appear to be differences in the mechanisms of the interactions of SDF-1/CXCR4 signaling and GLP-1/GLP-1R signaling with the Wnt signaling pathway in β-cells. Although both SDF-1 and GLP-1 activate the downstream pathway of Wnt signaling, consisting of beta-catenin/TCF7L2-mediated gene expression, they do so by way of different pathways of interactions with the more upstream components of the Wnt signaling pathway. These proposed different upstream pathways of signaling utilized by GLP-1 and SDF-1 raises the possibility of additive or synergistic effects on downstream Wnt signaling in the promotion of β-cell growth and survival. SDF-1 inhibits the destruction complex of the canonical Wnt signaling pathway consisting of Axin, APC, and the protein kinases, glycogen synthase kinase-3 (GSK3) and casein kinase-1 (CSNK1). This inhibition of GSK3 and CSNK1 by SDF-1 is likely mediated by the well-known actions of Akt to inhibit these kinases, resulting in the stabilization and accumulation of beta-catenin. In marked contrast to the actions of SDF-1 on β-cells, GLP-1 activates beta-catenin/TCF7L2 complexes via the stabilization of beta-catenin by a different mechanism involving the phosphorylation and stabilization of beta-catenin by the cAMP-dependent protein kinase A (PKA). PKA activated by GLP-1/GLP-1R phosphorylates beta-catenin on Serine-675, resulting in its stabilization and accumulation. Thus, unlike SDF-1, GLP-1-induced activation of gene expression by beta-catenin/TCF7L2 in β-cells occurs independently of the destruction box and the activities of GSK3. It also remains possible that beta-catenin may be stabilized by its direct phosphorylation by Akt.

Beta-catenin is the activation domain and TCF7L2 is the DNA-binding domain of the transactivator. It is tempting to speculate that different phosphorylations of beta-catenin provided by SDF-1 signaling versus GLP-1 signaling result in different conformations of beta-catenin. When different conformers of beta-catenin interact with TCF7L2 they confer different conformations to the DNA-binding domains of TCF7L2, resulting in differing affinities of TCF7L2 for its cognate enhancer binding sites on the promoters of various Wnt signaling target genes. Such a combinatorial mechanism could account for the difference in genes regulated by beta-catenin/TCF7L2 in β-cells in response to SDF-1 compared to GLP-1. Wnt signaling may be a final downstream pathway for both SDF-1 and GLP-1 signaling in β-cells. However, gene expression targets diverge so that SDF-1 predominately regulates genes involved in cell survival, whereas GLP-1 regulates genes involved in cell cycle control (proliferation). If this circumstance proves to be valid, our findings raise the possibility of a dual therapeutic approach for increasing β-cell mass. GLP-1 is predominantly pro-growth and SDF-1 is predominantly pro-survival. Thereby the two peptides may act synergistically to promote both the growth and the survival of β-cells and to conserve, or even enhance, β-cell mass in response to injury.

17.6 Type 2 Diabetes Genes

Genome-wide scans in several large populations have uncovered associations of specific genetic loci with the development of type 2 diabetes [15–20, 27, 80–91]. At least 19 genes have associations with diabetes that are consistent among various population studies (Table 17.1). Of note, the majority of these genes (14 of 19) are expressed in pancreatic β-cells. Furthermore, several of the genes (seven) appear to be involved in the Wnt signaling pathway. TCF7L2, the DNA-binding component of the downstream transcription factor complex, appears to have a particularly strong association with type 2 diabetes.

17.6.1 Genes Associated with Islet Development/Function and Wnt Signaling

17.6.1.1 TCF7L2 (Transcription Factor 7-Like 2)

Grant and coworkers provided the index report on an association of polymorphisms in TCF7L2 with type 2 diabetes [92]. Epidemiology studies from Icelandic, Danish, and US cohorts reported that the inheritance of a specific single nucleotide polymorphism (SNPs), at the region DG10S478, within the intron 3 region of TCF7L2 gene is related to an increased risk of type 2 diabetes [25–36]. Then two other SNPs within introns 4 and 5 of TCF7L2, namely rs12255372 and rs7903146, were found in strong linkage disequilibrium with DG10S478 and showed similarly robust associations with type 2 diabetes patients with glucose intolerance. In Asian populations, the frequencies of SNPs rs7903146 and rs12255372 are quite low, but two novel SNPs-rs290487 and rs11196218 are associated with the risk of type 2 diabetes in a Chinese population. The most likely candidate is the rs7903146 single nucleotide polymorphism that has a strong association with type 2 diabetes [93]. This polymorphism resides in a noncoding region of the gene and no clear mechanism for its effects on TCF7L2 expression is apparent. It has been reported that nondiabetic carriers of the risk-associated TCF7L2 SNPs do not have defects in GLP-1 secretion. The risk alleles are associated with impaired insulin secretion, incretin effects, and an enhanced rate of hepatic glucose production. As mentioned previously, knockdown of TCF7L2 with small interfering RNAs reduces glucose-stimulated insulin secretion from β-cells [66, 67]. However, a study from Lyssenko et al. [25] demonstrates that TCF7L2 mRNA transcripts are more abundant in the islets of diabetic patients and the level of TCF7L2 expression in islets negatively correlates with insulin secretion. This finding indicates that increased levels of TCF7L2 in islets would increase the risk of diabetes onset by the inhibition of insulin secretion. However, it has not yet been determined whether the increase in TCF7L2 mRNA levels in human islets translates to an increase in protein levels of TCF7L2.

The glucoincretin hormone GLP-1 appears to be involved in the pathogenesis of diabetes in individuals who carry TCF7L2 risk alleles. These carriers of TCF7L2 risk alleles have impaired insulin secretion as a major contributor to impaired

Table 17.1 Type 2 diabetes genes identified by Genome-Wide Association Studies

Gene symbol	Functions	β-cell functions	Wnt signaling
Genes associated with islet development function and Wnt signaling			
TCF7L2	HMG transcription factor-7L2	β-cell proliferation and survival Insulin secretion	Canonical Wnt signaling regulates target genes in association with beta-catenin
FTO	Fatso. Fused toes locus includes FTS, FTM	Pancreas development obesity	FTS, a target gene for Wnt signaling
NOTCH 2	Delta/Notch signaling	Pancreas development	Wnt signaling interaction via phosphorylation by GSK3
IGF2BP2	Insulin growth factor 2 mRNA-binding protein 2	Islet growth	Expression induced by beta-catenin and TCF7L2
HHEX	Homeodomain transcription factor	Early pancreas development	Repressed by beta-catenin and TCF7L2
TCF2	Hepatocyte nuclear factor 1 beta (MODY 5)	Early islet progenitor cell specification. T2D pancreas development	Regulates beta-catenin
CDKN2A/N2B	Cyclin-dependent kinase Inhibitor, P16, INK4A	Islet regeneration regulates CDK4 in β-cells	Cross talk with Wnt signaling induced by beta-catenin
Genes associated with islet development/function, Wnt signaling unknown			
PPARgamma	Peroxisome proliferator activating receptor gamma	Insulin resistance insulin secretion	PPARdelta, Wnt target gene
KCJN11	Inward rectifying K+ channel	Regulates insulin secretion along with Sur1 (ABCC8)	Not known
WFS1	Wolfram syndrome 1 transmembrane protein	Insulin secretion, endoplasmic reticulum protein trafficking	Not known
CDKAL1	Cyclin-dependent kinase 5 homolog inhibitor	Islet glucotoxicity inhibitor, impaired insulin secretion	Not known
SLC30a8	Solute carrier 38a8 zinc transporter	Insulin granules, secretion	Not known
KCNQ1	Potassium channel	Insulin secretion	Not known
MTNR1B	Melatonin receptor 1b	Insulin secretion	Not known

Table 17.1 (continued)

Gene symbol	Functions	β-cell functions	Wnt signaling
Genes not known to be involved in either islet development/function or Wnt signaling			
TSPAN8/LGR5/GPR 49	Tetraspanin 8. Leucine-rich G protein-coupled receptor 5. G protein-coupled receptor 49	Unknown	Wnt signaling target gene in intestinal crypt stem cells
JAZF1	Nuclear zinc finger transcriptional repressor	β-cell apoptosis?	Not known
CDC123/CAMK1D	Calcium-dependent calmodulin kinase	β-cell apoptosis?	Not known, planar cell polarity, noncanonical Wnt signaling?
THADA	Thyroid adenoma associated	Unknown	Not known
ADAMTS9	Metallopeptidase with thrombospondin 9	Unknown	Not known

glucose tolerance or diabetes [25–36]. Glucose clamp studies on a large cohort of carriers of TCF7L2 polymorphisms revealed both reduced insulin secretion in response to oral glucose tolerance tests and impaired GLP-1-induced insulin secretion [48]. However, in these studies plasma GLP-1 levels were not influenced by the TCF7L2 variants [48]. These findings are of interest because two pathogenetic mechanisms involving GLP-1 have been proposed: impaired GLP-1 production in the intestine [29, 68] and impaired GLP-1 actions on pancreatic β-cells [46]. The studies of Schafer et al. [48] suggest that the defect in the enteroinsular axis in individuals with defective TCF7L2 functions lies at the level of impaired actions of GLP-1 on insulin secretion from pancreatic β-cells, rather than the level of impaired production of GLP-1 by intestinal L-cells. Evidence is reported from studies in vitro that support an important role for beta-catenin/TCF7L2-mediated Wnt signaling in both the expression of the proglucagon gene in intestinal cells [94] and in the regulation of insulin secretion [47, 66, 67] and β-cell proliferation [46]. Interestingly, there is some reported evidence that TCF7L2 may be expressed at low levels [94, 95], or not at all [96] in β-cells. These reports conflict with those of the Rutter [67] and Maeder [47] laboratories, and our own observations [46]. Based on the findings currently available, the contributions of TCF7L2 functions to the enteroinsular axis may occur at the levels of both the production of GLP-1 by intestinal L-cells and the actions of GLP-1 on pancreatic β-cells. The two levels of involvement of TCF7L2 actions are not necessarily mutually exclusive.

17.6.1.2 FTO (Fat Mass and Obesity-Associated Protein)

FTO encodes a protein that is homologous to the DNA repair AlkB family of proteins that are involved in the repair of alkylated nucleobases in DNA and RNA [97]. The FTO gene is up-regulated in orexigenic neurons in the feeding center of the hypothalamus [98]. Genetic variants in FTO result in excessive adiposity and insulin resistance, as well as a markedly increased predisposition to the development of diabetes [99]. A 1.6 Mb deletion mutation in the mouse results in the deletion of a locus containing FTO, FTS (fused toes), FTM, and three members of the Iroquois gene family, Irx3, Irx5, and Irx6 [100], resulting in multiple defects in the patterning of the body plan during development [100, 101]. The Irx (Iroquois) proteins are homeodomain transcription factors. The FTO, FTS, and IRX locus is implicated in Wnt signaling. FTS is a small ubiquitin-like protein with conjugating protein ligase activity that is known to interact with the protein kinase Akt, a potent inhibitor of GSK3beta activity in the Wnt signaling pathway. Moreover, Wnt signaling is reported to induce the expression of Irx3 [102]. Irx1 and Irx2 are expressed in the endocrine pancreas of the mouse under the control of Neurogenin-3 (Ngn3) expression [103].

17.6.1.3 NOTCH2

The delta/notch signaling pathway is an important cell–cell interactive signaling pathway (lateral inhibition) involved in embryonic stem cell amplification, differentiation, and in determination of organogenesis. Notch2 is expressed in pancreatic ductal progenitor cells and may be involved in early branching morphogenesis of the pancreas [104]. The conditional ablation of Notch2 signaling in mice moderately disturbed the proliferation of epithelial cells during early pancreas development [105]. Evidence is presented linking Notch2 to Wnt signaling [106]. GSK3beta phosphorylates Notch2, thereby inhibiting the activation of Notch target genes.

17.6.1.4 IGF2BP2 (Insulin-Like Growth Factor 2 Binding Protein 2)

IGF2BP2 is a paralog of IGF2BP1, which binds to the 5' UTR of the insulin-like growth factor 2 (IGF2) mRNA and regulates IGF2 translation [107]. IGF2 is a member of the insulin family of polypeptide growth factors involved in the development, growth, and stimulation of insulin action.

Wnt1 is reported to induce the expression of IGF2 in preadipocytes [108].

17.6.1.5 HHEX (Hematopoietically Expressed Homeobox)

HHEX is a homeodomain protein that regulates cell proliferation and tissue specification underlying vascular, pancreatic, and hepatic differentiation [109–111]. Variants in the Hhex gene manifest in impaired β-cell function [112]. Hhex is associated with Wnt signaling during pancreas development, as it acts with beta-catenin to serve as a corepressor of Wnt signaling [113, 114].

17.6.1.6 TCF2 (Hepatocyte Nuclear Factor 1 Beta, HNF1beta, MODY 5 Gene)

Tcf2 is a critical regulator of a transcriptional network that controls the specification, growth, and differentiation of the embryonic pancreas [115]. Mutations in the TCF2 gene result in hypoplasia of the pancreas, resulting in exocrine pancreas dysfunction to varying degrees [115–117]. Some mutations manifest as a form of Maturity Onset Diabetes of the Young (MODY 5).

17.6.1.7 CDKN2A/B (Cyclin-Dependent Kinase Inhibitor 2A/B, ARF, p16INK4a)

The CDKN2A/B gene generates several transcript variants which differ in their first exons. CDKN2A is a known tumor suppressor and its product, p16 INK4a, inhibits CDK4 (cyclin-dependent kinase 4), a powerful regulator of pancreatic β-cell replication [118–120]. Over-expression of Cdkn2a leads to decreased islet proliferation in ageing mice [121]. Cdkn2b over-expression is also causally related to islet hypoplasia and diabetes in murine models [122]. P16(Ink4a) is linked to the Wnt signaling pathway as stabilized beta-catenin silences the p16(Ink4a) promoter in melanoma cells [123].

17.6.2 Genes Associated with Islet Development/Function, Wnt Signaling Unknown

17.6.2.1 PPARgamma (Peroxisome Proliferator-Activated Receptor Gamma)

PPARgamma is involved in insulin signaling in insulin-responsive target tissues [124] and is implicated in β-cell growth and survival. PPARgamma mediates growth arrest and survival of β-cells [125]. Islets of mice in which PPARgamma is specifically ablated display a marked reduction in the expression of the transcription factor PDX-1 and develop glucose intolerance, impaired glucose-stimulated insulin secretion, and a loss of actions of PPARgamma agonists to enhance PDX-1 expression [125]. PPARgamma is not yet linked to the Wnt signaling pathway, although PPARdelta is a known target gene for activation by Wnt signaling [126].

17.6.2.2 KCNJ11 (Inward Rectifying Potassium Channel)

KCNJ11 is an important component of the ATP-sensitive potassium channel on β-cells responsible for the regulation of insulin secretion [127]. KCNJ11 exists in a complex with the sulfonylurea-regulated receptor SUR1. In response to elevated glucose and other insulin secretagogues, the ATP-sensitive potassium channel closes and allows for a decrease in the resting potential (depolarization) of β-cells resulting in the opening of voltage-sensitive calcium channels. The inward flux of Ca^{2+} into β-cells is believed to be an important stimulus for the exocytosis of insulin. A deficiency of the numbers and/or functions of ATP-sensitive channels, either KCNJ11 or SUR-1, due to genetic mutations results in a chronic depolarized state of β-cells and unregulated excessive insulin secretion [128]. As of now no direct evidence implicates Wnt signaling with KCNJ11.

17.6.2.3 WFS1 (Wolfram Syndrome 1)

WFS1 encodes a transmembrane protein of 890 amino acids that is highly expressed in the endoplasmic reticulum of neurons and pancreatic β-cells [129]. Mutations in WFS1 result in Wolfram syndrome, an autosomal recessive neurodegenerative disorder. Disruption of the WFS1 gene in mice causes progressive β-cell loss and impaired stimulus-secretion coupling in insulin secretion [130]. The reduction in β-cell mass is likely a consequence of enhanced endoplasmic reticulum stress resulting in the apoptosis of β-cells [131–133]. Impaired proinsulin processing to insulin and insulin transport through the secretory pathway may also be involved in the impaired insulin secretion. To date no information is available on the mechanisms that regulate WFS1 expression or of an involvement of Wnt signaling in its expression.

17.6.2.4 CDKAL1 (CDK5 Regulatory Subunit-Associated Protein-1-Like 1)

CDKAL1 encodes a protein of unknown functions. However, the protein is similar to CDK5 regulatory subunit-associated protein 1 (encoded by CDK5RAP1), expressed in neuronal tissues. CDKAL1 inhibits cyclin-dependent kinase 5 (CDK5) activity by binding to the CDK5 regulatory subunit p35 [134]. Variants in the CDKAL1 gene in humans are associated with decreased pancreatic β-cell functioning. [112]. CDK5 has a role in the loss of β-cell function in response to glucotoxicity as the inhibition of the CDK5/p35 complex prevents a decrease of insulin gene expression that results from glucotoxicity [135]. Therefore, it seems possible that CDKAL1 may have a role in the inhibition of the CDK5/p35 complex in pancreatic β-cells similar to that of CDK5RAP1 in neuronal tissue. One may conjecture that a reduced expression and inhibitory function of CDKAL1 or reduced inhibitory function could exacerbate β-cell impairment in response to glucotoxicity.

17.6.2.5 SLC30a8 (Solute Carrier 30a8)

SLC30A8 transports zinc from the cytoplasm into insulin secretary vesicles [136, 137] where insulin is stored as a hexamer bound with two Zn^{2+} ions prior to secretion [138]. Variation in SLC30A8 may affect zinc accumulation in insulin granules, affecting insulin stability, storage, or secretion. In high-glucose conditions, over-expression of SLC30A8 in INS-1E cells enhanced glucose-induced insulin secretion. SLC30A8 is specific to the pancreas and is expressed in β-cells, where it facilitates accumulation of zinc from the cytoplasm into intracellular vesicles [139].

17.6.2.6 KCNQ1 (Potassium Channel Q1)

KCNQ1 encodes the pore-forming alpha subunit of the voltage-gated potassium channel KvLQT1 [140]. It is expressed in pancreatic islets and blockade of the channel stimulates insulin secretion [141].

17.6.2.7 MTNR1B (Melatonin Receptor 1B)

The melatonin receptor 1b is expressed throughout the nervous system and in the β-cells of the pancreatic islets [142]. Melatonin is secreted in a circadian pattern from the pineal gland with high nocturnal levels of secretion. Since melatonin suppresses insulin secretion from β-cells it is suggested that it may suppress insulin secretion during the night [143]. The risk allele for diabetes results in an increase of the receptor in β-cells perhaps leading to an inappropriate inhibition of insulin secretion [143]. It has been suggested that melatonin receptor antagonists may be an effective therapy for patients with diabetes linked to defects in MTNR1B [143].

17.6.3 Genes Not Known to be Involved in Either Islet Development/Function or Wnt Signaling

17.6.3.1 TSPAN8/LGR5/GPR49

The protein encoded by this gene is a member of the transmembrane 4 superfamily, also known as the tetraspanin family. Most of these members are cell surface proteins that have a role in the regulation of cell development, activation, growth, and motility. LGR5/GPR49 is a leucine-rich repeat-containing G protein-coupled receptor. A role for TSPAN8 in the pancreas is as yet unknown. However, Tspan8/Lrg5 is a recognized Wnt signaling target gene in small intestinal and colonic stem cells [144].

17.6.3.2 JAZF1 (Zinc Finger 1, TIP27)

JAZF1 is a zinc finger transcriptional repressor, corepressor [145]. The gene is susceptible to chromosomal recombination in endometrial stromal tumors with resultant transcription of chimeric mRNAs encoding fusion proteins of JAZF1 with JJAZF1 and SUZ12 (suppressor of zeste 12) [146]. Remarkably, the RNA transcripts from the JAZF1 and SUZ12 genes in noncancerous tissues undergo trans-splicing resulting in the translation of an identical protein [147]. This protein exerts strong both pro-proliferative and anti-apoptotic actions in cells. It remains unknown whether JAZF1 proteins are expressed in the pancreatic islets, but if they are, it seems likely that they may contribute to their growth and survival.

17.6.3.3 CDC123/CAMK1D

The CAMK1D gene encodes a member of the Ca^{2+}/calmodulin-dependent protein kinase 1 subfamily of serine/threonine kinases [148]. The encoded protein may be involved in the regulation of granulocyte function through the chemokine signal transduction pathway. Alternatively spliced transcript variants encoding different isoforms of this gene have been described [149]. Camk1d is implicated in the apoptosis of cells [150]. No information is available about a possible role of CAMK1D in the pancreas or any connections with Wnt signaling. It is tempting to speculate, however, that it may be a competent of the noncanonical Ca^{2+} Wnt signaling pathway.

17.6.3.4 THADA (Thyroid Adenoma Associated)

THADA is identified as the target gene of 2p21 aberrations in thyroid adenomas. The gene spans roughly 365 kb, and based on preliminary results, it encodes a death receptor-interacting protein [151]. Chromosomal rearrangements lead to alterations in the gene and encoded protein, one of which consists of a fusion of an intronic sequence of PPARgamma to exon 28 of THADA [152]. Associations of THADA with islets and/or Wnt signaling are unknown.

17.6.3.5 ADAMTS9

The ADAMTS9 gene encodes a member of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) protein family [153]. Members of the ADAMTS family have been implicated in the cleavage of proteoglycans, the control of organ shape during development, and the inhibition of angiogenesis. ADAMTS8 is widely expressed during mouse embryo development [154]. Functions for ADAMTS9 in pancreas or in Wnt signaling are heretofore unrecognized.

17.7 Future Directions

Continued studies of the involvement of the Wnt signaling pathway in islet development and function may reveal novel factors important in β-cell growth and survival. A prerequisite for understanding the potential importance of Wnt signaling in islets is the identification of the specific Wnt signaling factors that are expressed in islets. Identification of these factors may provide opportunities for development of small molecules that target specific components of the pathways to promote growth and survival. Ongoing high-throughput screening studies of hundreds of thousands of compounds using islet tissues containing fluorescence reporter genes and growth or apoptosis-responsive promoters may uncover such small molecules.

Anti-diabetogenic therapies consisting of combinations of GLP-1 and SDF-1 agonists may provide additive benefits in promoting both the growth and the survival of β-cell, thereby preserving or enhancing β-cell mass. Recent findings suggest that both the pro-proliferative actions of GLP-1 and the anti-apoptosis actions of SDF-1 are mediated by the activation of beta-catenin and TCF7L2 in β-cells. Although both the GLP-1/GLP-1R and the SDF-1/CXCR4 axes converge on downstream Wnt signaling at the level of the formation of transcriptionally productive complexes of beta-catenin/TCF7L2, the target genes activated by GLP-1 and by SDF-1 differ. GLP-1-mediated activation of beta-catenin/TCF7L2 results in the expression of genes involved in the cell division cycle, whereas SDF-1 actions result in the activation of the expression of genes engaged in cell survival. Furthermore, downstream beta-catenin/TCF7L2 activation is a requisite for the pro-proliferative actions of GLP-1 and the anti-apoptotic actions of SDF-1. The two hormones, GLP-1 and SDF-1, acting together may provide additive benefits in promoting the regeneration and maintenance of β-cell mass in diabetes.

Genome-wide association studies in search of risk alleles for type 2 diabetes are just beginning. It is estimated that 80–90% of the human genome remains yet to be explored for the existence of diabetes-associated genes in the population. Predictably, further genome-wide scans in the future will uncover even more than the current 19 genes, many will likely be involved in islet and β-cell development and functions. It is tempting to speculate that the additional risk genes for type 2 diabetes that remain to be discovered in the future will include genes encoding components of the Wnt signaling pathway.

Intriguing current evidence warrants further investigations of Wnt ligands and Wnt signaling in the cross talk between adipose tissue and islets. Possibilities arise suggesting that Wnt ligands produced and secreted by adipocytes act on β-cells to stimulate Wnt signaling.

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