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REVIEW

Transcription factor regulation of pancreatic organogenesis, differentiation and maturation

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ABSTRACT

Lineage tracing studies have revealed that transcription factors play a cardinal role in pancreatic development, differentiation and function. Three transitions define pancreatic organogenesis, differentiation and maturation. In the primary transition, when pancreatic organogenesis is initiated, there is active proliferation of pancreatic progenitor cells. During the secondary transition, defined by differentiation, there is growth, branching, differentiation and pancreatic cell lineage allocation. The tertiary transition is characterized by differentiated pancreatic cells that undergo further remodeling, including apoptosis, replication and neogenesis thereby establishing a mature organ. Transcription factors function at multiple levels and may regulate one another and auto-regulate. The interaction between extrinsic signals from non-pancreatic tissues and intrinsic transcription factors form a complex gene regulatory network ultimately culminating in the different cell lineages and tissue types in the developing pancreas. Mutations in these transcription factors clinically manifest as subtypes of diabetes mellitus. Current treatment for diabetes is not curative and thus, developmental biologists and stem cell researchers are utilizing knowledge of normal pancreatic development to explore novel therapeutic alternatives. This review summarizes current knowledge of transcription factors involved in pancreatic development and β-cell differentiation in rodents.

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Introduction

The mature pancreas is a mixed micro-organ comprising 3 major components: the exocrine, ductal and endocrine portions. The exocrine compartment is defined by acinar cells that produce digestive enzymes (e.g., lipases, proteases and nucleases) and is closely associated with ductal cells that secrete ions directed to the intestine by a branched ductal system. The endocrine pancreas is organized into functional units termed the islets of Langerhans with cells that produce the hormones glucagon (α-cells), insulin (β-cells), somatostatin (δ-cells), pancreatic polypeptide (PP-cells) and ghrelin (ε-cells).[1] The mature pancreas is mainly constituted by acinar cells (~98%) with islet cells (~2%) interspersed throughout the central regions of the organ. In mammals, each islet is a micro-organ with distinct cells (i.e., 20–30% α-cells, ~60% β-cells, ~10% δ-cells, <5% PP-cells and ~1% ε-cells) localized in the pancreas.[2] The anatomical arrangement of islet cells varies between species. Diabetes mellitus is marked by persistent hyperglycemia concomitant with altered carbohydrate, protein and fat metabolism. Type 1 diabetes (T1D) is an autoimmune disease induced by a combination of genetic and environmental stimuli leading to lymphocytic infiltration of islets and β-cell loss which results in absolute insulin deficiency. Type 2 diabetes (T2D) is caused by peripheral insulin resistance, impaired insulin secretion from β-cells, a deficiency in suppression of glucagon production and excess hepatic gluconeogenesis.[3]

In T1D, the administration of exogenous insulin via injection or pump remains the primary treatment. Therefore alternative therapeutic options such as transplantation of whole-organ pancreata or isolated islets[4,5] are being explored to limit insulin dependence. Both transplantation strategies are challenged by a shortage of donors to meet clinical demand and bear the risk of an immune response and organ rejection. Hence, alternate strategies to generate β-cells are under investigation. Currently, potential sources for generating β-cells are 1) human embryonic stem cells

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(hESCs),[6,7] 2) other endodermal tissue specifically the liver,[8] 3) existing β-cells by inducing proliferation and 4) reprogramming of other pancreatic exocrine and endocrine cells.[9,10] Recent examples of lineage reprogramming include the conversion of acinar cells,[11] α-cells[12] and gut cells[13] to β-cells. Although considerable research has been dedicated to seeking therapeutic alternatives, generating fully functional insulin-producing β-cells, remains elusive. Thus, a greater understanding of pancreatic organogenesis, differentiation and maturation is warranted. Transcription factors are critical in pancreatic organogenesis, differentiation and maintenance. This review therefore summarizes the current knowledge of transcription factors that govern development of the pancreas into a functional organ.

Overview of pancreatic development

In the developing mouse embryo, gastrulation (a process in which a single layered blastula is reorganized into a trilaminar structure/gastrula) at embryonic day (e) 7.5 leads to the generation of 3 germ layers, specifically the ectoderm, mesoderm and endoderm.[14] Pancreatic development has been characterized as a series of bifurcating lineage decisions: endoderm vs. mesoderm and ectoderm; pancreas vs. duodenum; exocrine vs. endocrine; and β-cell vs. other hormone-positive cell types.[15] At e9.5, the pancreas originates from the foregut endoderm as 2 independent pancreatic buds, along the dorsal and ventral axis.[16] The dorsal bud is first detected at e9.0 while its complement, the ventral bud, develops at e9.5.[16-18] Interestingly, this distinction arises due to diverse signals from neighboring mesoderm-derived tissues. The dorsal bud develops adjacent to the notochord and the splanchnic mesenchyme which later constitutes the dorsal aortae.[19] The complex signaling networks involved in the formation of the dorsal bud include activin, fibroblast growth factor (FGF), transforming growth factor-β (TGFβ), retinoic acid, vascular endothelial growth factor (VEGF), bone morphogenetic protein (BMP) inhibitors and hedgehog-type ligands.[19] Initially, the ventral bud evolves as 2 independent endodermal regions that grow adjacent to the liver and the bile duct epithelium and unifies at the time of the gut tube closing.[19] The ventral bud connects with the cardiac mesenchyme and the septum transversum[20,21] and intercellular signaling through TGFβ, Notch, FGF, Wnt and Hedgehog signaling; which are critical for pancreatic development.[19] The dorsal bud produces more endocrine cells than the ventral bud.[17] and further, these buds differ in their expression of transcription factors implicated in development.[20] Pancreatic organogenesis, differentiation and maturation is classified into 3 stages: the primary (e8.5–12.5), secondary (e12.5–16.5) and tertiary (e16.5-postnatal) transitions.[16]

The primary transition (e8.5–12.5)

The primary transition is a period of active proliferation of pancreatic progenitor cells which form a stratified epithelium accompanied by the formation of the multiple microlumen that later fuse.[16] Glucagon$^+$, insulin$^+$ and double-positive cells emerge from e9.0–13.5 in the dorsal bud[16,22-25] although these early cells do not commit to mature islets.[16,23] Further studies have revealed that these early endocrine cells form independently of transcription factors essential for early pancreatic development.[26-29] Additionally, glucagon, insulin, somatostatin, pancreatic polypeptide and ghrelin are expressed at transcriptional[30] and protein levels.[31] However, glucagon$^+$, insulin$^+$ and glucagon$^+$/insulin$^+$ cells remain the main cell subtype during the primary transition.[23] Gut rotation occurs which merges the 2 buds for fusion around e12–13.[16,32] At e12.5, the pancreatic epithelium evaginates into the neighboring mesenchyme and initiates compartmentalization into tip and trunk domains. Multipotent progenitor cells (MPCs) dominate the tip domain whereas endocrine/duct bi-potent precursors constitute the trunk domain.[33] This model reaffirms that the final size of the mature pancreas is determined by the number of progenitor cells assigned to the pancreas primordium between e8.5–12.5.[34]

The secondary transition (e12.5–16.5)

During the secondary transition, the pancreatic epithelium undergoes growth, branching, differentiation and pancreatic cell lineage allocation.[16,38] By e13.5, MPCs located at the tip of the branching epithelium may self-renew or differentiate into acinar progenitor cells; after e13.0 these cells become restricted to the exocrine cell fate.[33,35] Between e13–15, fully differentiated β- and α-cells arise from the epithelial trunk.[36] Early in development, the acinar and duct cells share some common transcription factors; however, later these cells acquire their own unique set of

transcription factors to orchestrate their differentiation and maturation.[37] Somatostatin-expressing δ-cells emerge within the next day and between e14–18 endocrine cells organize into small aggregates.[16] Thus there is an increase in endocrine and exocrine gene expression that coincides with a marked increase in cellular mass.

The tertiary transition (e16.5-Postnatal)

During the tertiary transition, differentiated pancreatic cells undergo additional remodelling and maturation.[16,38] From e18–18.5, differentiated PP-expressing cells emerge and persist into adulthood. The individual differentiated endocrine cells delaminate, migrate into the neighboring exocrine tissue and assemble into cell clusters to initiate the formation of mature islets.[15,39] In the mouse, β-cells form a central islet core with α-, δ- and PP-cells at the periphery and a small proportion of ε-cells scattered throughout the islet.[40,41]

Postnatal life

At birth, about 80% of the β-cell mass originates from the neogenesis of undifferentiated precursor cells and the remaining 20% arise from β-cell proliferation.[42] β-cell proliferation gradually declines from the first 4 weeks postnatally to after weaning.[42-44] Thereafter islet cell mass is maintained through self-replication. Thus, the adult β-cell mass is not maintained through neogenesis[7] but is capable of limited proliferation.[45] In rodents aged 30–40 days, the rate of β-cell replication is steady.[46] Under normal conditions, the adult β-cell has a long life span but proliferation decreases with age.[47-49] During adulthood, islet mass is unaltered, except in response to physiological (e.g., pregnancy) and pathological (e.g., obesity and insulin resistance) states.[50,51] Acinar differentiation, maturation and proliferation also continue after birth and dissipate until weaning.[52]

Transcription factors regulating pancreatic organogenesis

Pancreatic transcription factors are key factors that govern pancreatic organogenesis, differentiation and maturation. Pancreatic development is a dynamic process controlled by extrinsic signals from non-pancreatic tissues and intrinsic transcription factors.[53] Lineage-tracing studies and gain/loss-of-function analyses provided further insight into the molecular mechanisms involved in pancreatic development and pancreatic cell fate determination (Table 1).[20,32,54,55] Importantly, transcription factors are implicated at multiple levels of pancreatic development that include 1) the initiation of transcription, 2) organogenesis, 3) control mechanisms for cell differentiation and 4) maintenance of the functional cell phenotype (Fig. 1).[53]

Transcription factors involved in the primary transition (e8.5–12.5)

Homeobox gene product 9 (Hb9)

Hb9/Hlxb9 (also known as the motor neuron and pancreas homeobox protein, Mnx1), is expressed around e8.0 within the notochord and in the dorsal and ventral pancreatic buds during pancreatic development.[56,57] At e9.5, graded expression of Hb9 was observed along the dorsal-ventral axis.[58] Hb9 expression decreases at e12.5 and is subsequently confined to adult β-cells.[56] $Hb9^{-/-}$ mice showed dorsal bud agenesis and the ventral bud had small islets with few β-cells (Table 1).[56,57] Upon closer examination, the expression of Pdx1, Nkx6.1 and Glut2 in $Hb9^{-/-}$ β-cells was impaired.[57] The over-expression of Hb9 beyond e9–10 in Pdx1 promoter-driven transgenic mice impaired pancreatic development.[59] Additionally, endocrine and exocrine cell differentiation was hindered and the pancreatic mesenchyme adopted a stomach/intestinal mesenchyme identity.[59] Further research is warranted to explain the varied expression of Hb9 in both pancreatic buds and in the different stages of pancreatic development.

Islet 1 (Isl1)

The LIM homeodomain protein, Isl1 is expressed in the dorsal bud, the mesenchyme surrounding the dorsal bud, in post-mitotic islet cells and all adult islet cells.[26,60] Isl1 knock-out mice embryos revealed that expression of Isl1 in the dorsal mesenchyme and endoderm is critical for the formation of the dorsal bud and dorsal exocrine cell differentiation and differentiation of all endocrine cells respectively (Table 1).[26] The combination of Foxa1 and Foxa2 (also known as hepatocyte nuclear factor (Hnf)) were shown to regulate *Isl1* gene expression.[61]

Table 1. tiTranscription factors regulating the pancreatic transitions.

Transcription factor	Primary (e8.5–12.5) transition	Reference
	Role	
Hb9	Required for dorsal pancreatic development	56-57
Isl1	Involved in dorsal pancreatic mesenchyme development	26
Hnf1β	Required for ventral pancreatic bud development	66
Hnf3β/Foxa2	Expressed and maintained in the definitive endoderm	79-80
Hnf6/Onecut1	Required for ventral pancreatic bud development	65,68
Sox17	Regulates endoderm development	81,82
Pdx1	Involved in the development of pancreatic buds and expressed in pancreatic progenitor population	27,85,89
Ptf1a	Required for the development of the pancreatic buds and expressed in pancreatic progenitors	28,99
Sox9	Expressed in pancreatic progenitors and maintains Notch signaling	114
Gata4	Present in foregut endoderm, dorsal and ventral epithelium and later restricted to acinar cells	127-128
Gata6	Present in foregut endoderm, dorsal and ventral epithelium and later restricted to endocrine and ductal cells	127-128
	Secondary (e12.5–16.5) and tertiary (e16.5-postnatal) transitions	
Ngn3	Expressed in all endocrine progenitor cells	131
Hes1	Triggers differentiation of pancreatic precursors toward non-endocrine cell fate	70,136-137
Hnf6	Involved in duct cell differentiation and later maintained in duct cells	65,68
Sox9	Involved in differentiation of pancreatic precursors to their respective lineages and later confined to ductal cells	114-115
Pdx1	Involved in differentiation of endocrine progenitors and later expressed in β- and δ-cells; regulates β-cell function	86-88
Ptf1a	Controls exocrine cell differentiation	99
NeuroD1	Involved in the development and maturation of β-cells	145
Rfx3	Required for islet cell development	159
Rfx6	Required for islet cell development	146
Isl1	Involved in dorsal exocrine and all endocrine cell development	26,163
Arx	Expressed in endocrine progenitors, required for α- and PP-cell maturation	181-182
Pax4	Expressed in endocrine progenitors, required for β- and δ-cell maturation	186
Pax6	Expressed in endocrine cells and required for differentiation of α- and β-cells	195
Nkx2.2	Expressed in endocrine progenitors and later confined to α-, β- and PP-cells; maintains β-cell function	40,167
Nkx6.1	Expressed in Ngn3$^+$ endocrine precursors, later restricted to β-cells; required for β-cell differentiation	175
MafB	Expressed in α- and β-cells, later confined to α-cells; required for development and terminal differentiation of β-cells	210
MafA	Switch from MafB to MafA expression critical for β-cell maturation; required for normal embryonic insulin concentrations	219-221
Glis3	Involved in β-cell development and insulin expression	200-202

Hepatocyte nuclear factor (Hnf) family of transcription factors

Several Hnf members have been implicated in the formation of the foregut endoderm from which the pancreas arises including Hnf1β, Hnf3β (hereafter called Foxa2) and Hnf6 (also called Onecut-1).[62-65] At e9.5, Hnf1β mutant mice lacked the ventral bud but a transient dorsal bud was present with temporal expression of Pdx1 and Hb9 (Table 1).[66] Later by e13.5, pancreatic agenesis presented with a phenotype similar to Ptf1a deficiency.[66] Additionally, Hnf1β binding sites were identified on the Ptf1a promoter, suggesting a direct regulatory relationship.[66] Between e11.5–13.5, Hnf1β^+cells in the trunk compartment were precursors of acinar, duct and endocrine cells.[67] By e13.5–16.5, Hnf1β^+cells formed the embryonic duct epithelium and generated both ductal and endocrine cell lineages; later, Hnf1β expression was confined to ductal cells.[67]

Hnf6 is expressed in the foregut-midgut region of the endoderm[65,68] and pancreatic epithelium;[65] later in fetal life, Hnf6 is localized in ductal and acinar cells (Table 1).[65,68] Additionally, Hnf6 has been shown to regulate Hnf3β,[65,68] Pdx1 promoter regulatory regions (i.e., Areas I-III),[69] and is an upstream activator of Ngn3.[70-72] Hnf6$^{-/-}$ mice had islets with disrupted architecture attributed to near total loss in Ngn3 expression.[72] In addition, Hnf6$^{-/-}$ mice developed cysts in inter- and intralobular ducts.[73] Further, 2 binding sites for Hnf6 were located in the distal region of the Ngn3 gene.[72] Recently, Hnf6 was identified as a negative regulator of MafA.[74] Cre-mediated conditional gene inactivation confirmed that Hnf6 functions during early and late pancreatic development and is required for maintenance of Ngn3 expression and pancreatic duct morphology.[75] Overexpression of Hnf6 in transgenic mice leads to hyperplastic islets near the pancreatic ducts with disrupted spatial organization of endocrine cell types and a lack of Glut2 in β-cells.[76]

The winged helix/forkhead members, Foxa1 and Foxa2, are expressed in the foregut endoderm prior to pancreatic development [63,64] and persist in all islet and acinar cells into adulthood.[77,78] The knockout of Foxa1 and Foxa2 in mice caused reduced Pdx1 expression and extreme pancreatic hypoplasia.[79] The mutant mice displayed hyperglycemia and impaired acinar and islet cell content, and subsequently died (Table 1).[79] Foxa1 and Foxa2 bind to the distal Pdx1

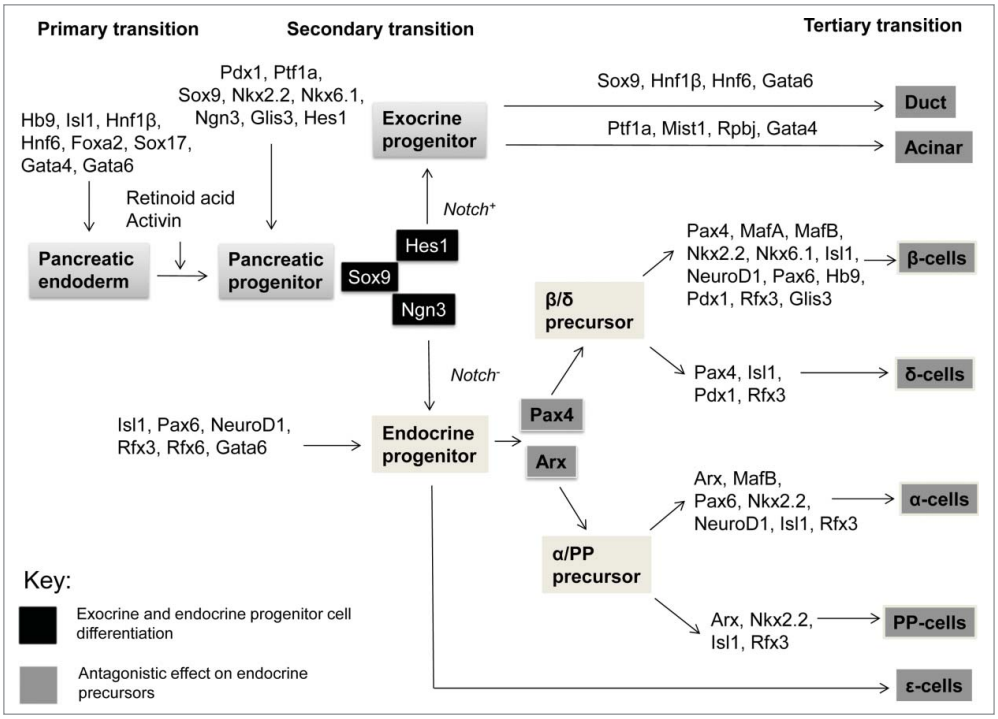

Figure 1. Transcription factors regulating pancreatic organogenesis, differentiation and maturation. Key pancreatic transcription factors, in concert with extrinsic signals from non-pancreatic organs, form an intricate regulatory network orchestrating pancreatic development. Pancreatic development is classified into 3 different stages: the primary, secondary and tertiary transitions. In mice, at e7.5 prior to the primary transition (e8.5–12.5), the formation of the pancreatic endoderm is initiated and pre-differentiated cells shift to proto-differentiated cells. Several transcription factors involved in early pancreatic development are also observed in later transitions. During the secondary transition (e12.5–16.5), proto-differentiated tissue yield fully differentiated cells. A critical regulatory system, involving Sox9, Notch signaling, Hes1 and Ngn3, is required for exocrine and endocrine progenitor cell differentiation. Subsequently, endocrine precursors are further differentiated via the antagonistic relationship between Pax4 and Arx. There are several dynamic interrelationships between transcription factors that lead to cell lineage decisions. Finally, during the tertiary transition (e16.5-postnatal), differentiated endocrine cells organize into cell aggregates to undergo further maturation postnatally. These specialized islet cells are plastic during early neonatal life; throughout life they are dynamic and can compensate in response to fluctuating metabolic demand; and with aging their proliferative and compensatory abilities diminish. These specific transcription factors are thus integral for pancreatic development, cellular differentiation and maturation into a functional organ.

enhancer.[79] Endoderm-specific ablation of Foxa2 in mice induced extreme hypoglycemia and early death (Table 1).[80] Further, the differentiation of α-cells was impaired; however, the expression of the key α-cell transcription factors Arx, Pax6 and Brn4 was unaltered by Foxa2 ablation.[80]

Sex determining region Y box 17 (Sox 17)

Sox17 is a Sry-related HMG box factor that regulates endoderm development (Table 1) in concert with Foxa1 and Foxa2.[81] Sox17 is a common progenitor in the biliary system and ventral pancreas (Table 1).[82] Additionally, Sox17 regulates the segregation of the biliary system, liver and pancreas.[82] Down-regulation of Pdx1 expressing cells is critical for normal pancreatic development.[82] Sox17 and Hes1 may operate in a feedback loop to separate the biliary and pancreatic lineages.[82] Sox17 has been recently implicated in the regulation of insulin trafficking and secretion in adult β-cells both in normal and diabetic states.[83]

Pancreatic duodenal homeobox gene 1 (Pdx1)

Pdx1 (also known as Ipf1) is expressed in both the dorsal and ventral buds from e8.5 and is therefore required for pancreatic development beyond initial bud formation.[27,84] Early hormone producing cells, which comprise insulin$^+$ and glucagon$^+$/insulin$^+$ cells, form independently of Pdx1.[27,85] Subsequently, all cells originating from endoderm-endocrine, exocrine and ductal cells expressed Pdx1.[84] Importantly, Pdx1 is co-expressed with Ptf1a in this pancreatic progenitor population.[28] Downstream Pdx1 expression is

limited to differentiated β- and δ-cells and mature β-cells.[86] Further, reduced expression of Pdx1 is required for acinar cell differentiation and maturation.[87,88] Pdx1 deficiency leads to pancreatic agenesis due to failed growth of the pancreatic primordium (Table 1),[27,85,89] and mutations result in maturity onset diabetes of the young (MODY) 4,[90] or irreversible neonatal diabetes.[91]

The spatiotemporal expression of Pdx1 is essential for endocrine and exocrine development.[92] Forced expression of Pdx1 in Ngn3$^+$ cells altered the ratio of α- and β-cells in embryos and adults.[93] The Pdx1 gene has 4 highly conserved regions viz., Areas I-II-III (the proximal enhancer region)[94] and Area IV (the distal enhancer).[95] Hnf1α,[96] Foxa2,[94] Hnf6,[69] Pax6,[97] and MafA[98] have binding sites within Areas I-II-III whereas Foxa1 and Foxa2 regulate Pdx1 expression via Area IV.[79] Pdx1 regulates β-cell identity by repressing the α-cell program via a shift in transcription profiles.[95]

Pancreas specific transcription factor 1a (Ptf1a)

At e9.5, a subset of cells co-express Pdx1 and the bHLH factor Ptf1a that give rise to the pancreatic anlagen.[29] However, by e13.5 Ptf1a is confined to acinar progenitor cells.[99] Ptf1a$^{-/-}$ mice display an extremely hypoplastic dorsal bud with a lack of total acinar cells (Table 1).[28,99] Hence, Ptf1a is critical for the development of the dorsal pancreatic endoderm and exocrine gene transcription.[99-101] The presence of a pancreatic rudiment in both Pdx1 and Ptf1a phenotypes suggest that the pancreatic genetic program can continue in transcription factor deficiency.[102] The transcriptional activity of Ptf1a is dependent on a third DNA binding subunit, i.e., the recombination signal binding protein kappa J (Rbpj) region,[103] an effector of the Notch signaling pathway.[104] This Ptf1a-Rbpj complex is required for pancreatic development.[103] A study demonstrated that mutations in one of the motifs of Ptf1a prevents the formation of the Ptf1a-Rbpj complex and resembles the Ptf1a$^{-/-}$ mice pancreatic phenotype.[105] The Ptf1a-Rbpj complex activates the expression of Rbpjl (pancreas-restricted paralog of Rbpj), a shift in the expression of Ptf1a-Rbpj to Ptf1a-Rbpjl initiates the differentiation of acinar cells.[106] Further, the expression of Ptf1a is autoregulated.[107] Interestingly in the developing pancreas, low expression of Ptf1a triggers endocrine cell fate whereas high expression inhibits endocrine and promotes exocrine cell fate.[108,109]

The regulation of delta-like ligand (Dll1) expression by Ptf1a is important for Notch mediated control of early pancreas development.[110] Ptf1a controls Dll1 to inhibit Ngn3 expression.[110] Further, Ptf1a is a direct target of Hb9, Pdx1, Hnf6 and Nkx6.1.[111,112] Recently, a study described the expression of Ptf1a$^+$ MPCs during pancreatic organogenesis.[113] Limited Ptf1a$^+$ cells were identified during the secondary transition and later Ptf1a$^+$ cells were confined to acinar cells.[113] Subsequently, pancreatic duct ligation (PDL) triggered facultative reactivation of multipotent factors that comprised Sox9 and Hnf1β in Ptf1a$^+$ acini and reprogrammed acinar cells to duct and endocrine cells.[113] Upon streptozotocin (Stz) administration, acinar trans-differentiation to endocrine/β-cells was enhanced.[113]

Sex determining region Y Box 9 (Sox 9)

The HMG box transcription factor, Sox9, is co-expressed with Pdx1 in MPCs between e9.5–12.5.[114] Sox9 maintains pancreatic progenitors by triggering their proliferation, survival and persistence in an undifferentiated state.[114] During the secondary transition, Sox9 is restricted to ductal/endocrine cells of the trunk domain and later it is maintained in ductal cells.[114,115] Pancreas-specific ablation of Sox9 depleted the progenitor cell pool and caused pancreatic hypoplasia (Table 1).[114] Additionally, Sox9 maintains MPC identity via a process associated with mesenchymal FGF signaling.[116] Sox9 also maintains multipotent progenitors through the regulation of Hnf1β, Hnf6 and Foxa2.[115] Hence, Sox9 may have a central role in the regulation of MPC formation and maintenance.

Gata binding protein 4 (Gata4) and gata binding protein 6 (Gata6)

Two zinc finger transcription factor family members, Gata4 and Gata6, have been associated with pancreatic development.[117-119] Both proteins are co-expressed in the early foregut endoderm, later the dorsal and ventral pancreatic bud epithelia and thereafter Gata4 expression is restricted to acinar cells and Gata6 to endocrine and ductal cells.[117,120-123] Gata4 and Gata6 null mice undergo early embryonic demise.[124-126] In mice, 2 genetic studies that inactivated Gata4 or Gata6 in embryonic MPCs using Cre/LoxP technology

induced minor derangements in pancreatic cell morphology that resolved postnatally whereas the loss of both Gata4 and Gata6 led to pancreatic agenesis at birth (Table 1).[127,128] Further, mice with pancreatic ablation of both Gata4 alleles and one Gata6 allele had less acinar cells. Pdx1 was identified as a direct target of Gata proteins.[128] During early endoderm formation, Gata4 is directly regulated by Foxa2.[129] Recently, Gata6 was reported to complete acinar differentiation via multiple transcriptional regulators including Rbpjl and Mist1.[130] Additionally, Gata6 was required for the maintenance of mature acinar cells.[130]

Transcription factors involved in the secondary and tertiary transitions

Neurogenin 3 (Ngn3)

During the secondary transition, the pro-endocrine bHLH transcription factor Ngn3 initiates the genesis of all endocrine cells in the pancreatic epithelium.[131-134] Ngn3 expression is observed from e9.5–15.5 but is nearly undetectable at birth.[131] Ngn3-deficient mice lacked endocrine cells but the exocrine and ductal portions appeared intact; shortly after birth these mice succumbed to diabetes (Table 1).[131] Additionally, overexpression of Ngn3 under the influence of the Pdx1 promoter caused early differentiation of MPCs and expansion of endocrine cells, mostly glucagon-producing cells.[70,133]

The Notch signaling pathway is implicated in the segregation of cells within the trunk domain via lateral inhibition.[70,71] Notch signaling activates Hes1 which inhibits Ngn3 and promotes the exocrine cell lineage.[71] Further ablation of Dll1 or Rbpj or over-expression of Ngn3 increases endocrine differentiation.[70] Ptf1a controls Dll1 to suppress Ngn3 expression.[110] The misexpression of Notch in Pdx1$^+$ progenitor cells arrests the differentiation of endocrine and exocrine cells and enhances the maintenance of progenitor cells.[135]

Another important regulatory system involving Sox9, Notch signaling, hairy and enhancer of split 1 (Hes1) and Ngn3 was implicated in pancreatic endocrine differentiation (Fig. 1).[136] In this system, the gradient of Notch activity regulates the proliferation and differentiation of the pancreatic endocrine and ductal progenitors.[136] Within the primitive epithelium, Notch signaling activates Sox9 expression. Subsequently, Sox9 triggers the expression of Ngn3. However, Ngn3 is simultaneously adversely regulated by the Notch effector, Hes1 (Table 1).[70,136,137] Hence, Ngn3 expression is counter regulated by the expression of Sox9 and Hes1.[136]

When Notch signaling is elevated, Hes1 activity impairs the activation of Ngn3 by Sox9.[136] During intermediate Notch activity, Hes1 expression is decreased or absent, triggering the activation of Ngn3 by Sox9.[136] When Sox9 activity is silenced, endocrine and ductal cells fail to develop leading to polycystic ducts that lack primary cilia.[136] Later, cell autonomous repression of Sox9 by Ngn3 occurs to permit endocrine cell differentiation.[136] If Notch activity remains elevated, endocrine progenitors will conserve Sox9 and convert to ductal progenitors.[136] Meanwhile Sox9 regulates Hes1 and with diminished Sox9 activity there is a decline in the expression of Hes1$^+$ cells.[114]

The competence of Ngn3 expression is altered with time as early Ngn3$^+$ cells develop exclusively into α-cells, but late Ngn3$^+$ cells develop into β-, PP- (after e11.5) and δ-cells (after e14.5).[133] The biphasic expression of Ngn3 in relation to the primary and secondary transitions of endocrine cell differentiation was recently described.[39] Additionally, the threshold of Ngn3 expression is critical for determining endocrine cell fate.[138] High Ngn3 protein expression levels are required to direct pancreatic cell progenitors into the endocrine cell fate whereas low levels of Ngn3 prompt the formation of acinar and duct cells.[138] Hence, endocrine cell fate determination is dependent on the developmental stage and dosage of Ngn3.[138] Interestingly, a recent study supported the hypothesis that Ngn3$^+$ cells constitute a heterogeneous population of unipotent cells each limited to a specific endocrine lineage.[139] Ngn3 has been shown to either positively or negatively auto-regulate its own expression.[140-142] Also, Ngn3 expression activates several transcription factors including NeuroD1, Pax4, Arx, Pax6, Isl1, Nkx2.2, Nkx6.1 and Rfx6 which are involved in further differentiation and subtype specification of pancreatic endocrine hormones.[20,140,143-146]

Ngn3 triggers the epithelial-to-mesenchymal transition (EMT), later inhibiting the expression of E-cadherin which initiates delamination of endocrine cells from the pancreatic epithelium.[147] At e11.5, pancreatic inhibition of Ngn3 led to a reduction in insulin$^+$ cells whereas glucagon$^+$ cells remained unaffected.[148] Also, an increase in markers of undifferentiated progenitors and embryonic ductal cells was observed.[148] Later in

development, upon Ngn3 expression, undifferentiated progenitors and embryonic ductal cells differentiated into endocrine cells; thus endocrine-committed cells preserve their ability to differentiate into endocrine cells.[148] Further, Ngn3-labeled progenitors were also required for controlling the fate and morphogenesis of the pancreatic duct epithelium.[149]

A p21 protein-activated kinase 3, Pak3, is expressed in Ngn3^{+} progenitors, maintained in mature hormone-expressing cells and later confined to adult islets.[150] Pak3 regulates 1) endocrine cell differentiation via its role in cell cycle exit and 2) glucose homeostasis in mice fed a high fat diet.[150] Insulinoma associated 1 (Insm1) has also been identified as a regulator of a network of genes involved in endocrine differentiation including *Ngn3*.[151]

Neurogenic differentiation 1 (Neurod1)

During the secondary transition, the bHLH transcription factor, NeuroD1, is expressed in all major endocrine cell types, i.e., α-, β- and δ-cells.[145] NeuroD1 is detected at ~e9.5 in a subset of pancreatic epithelial cells proximal to glucagon expression.[152] and at e14.5 alongside the ductal epithelium but by e17.5 its expression is confined to islets.[145] Also, NeuroD1 is required for β-cell maturation and maintenance of glucose-responsive β-cells.[153] Mice lacking NeuroD1 are diabetic due to a reduction in all endocrine subtypes and succumb perinatally (Table 1).[145] The pancreatic epithelium ectopic expression of either Ngn3 or NeuroD1 resulted in substantial premature differentiation of endocrine cells specifically α-cells leading to a hypoplastic pancreas (Table 1).[70,132] In combination with other factors, NeuroD1 can drive β-cell differentiation.[154,155] Additionally, the combination of NeuroD1, Pdx1 and MafA in non-β-cells induced insulin production.[156]

Regulatory factor X 3 and 6 (Rfx3 and Rfx6)

Rfx3 and Rfx6 are members of the regulatory factor X family of winged-helix transcription factors and are implicated in islet development.[157-159] Rfx3 is expressed in Ngn3^{+} progenitors, developing and mature endocrine cells.[159] In perinatal Rfx3$^{-/-}$ mice islets, a small number of cells express insulin, glucagon and ghrelin whereas PP-producing cells increased (Table 1).[159] Adult Rfx3$^{-/-}$ mice exhibited small, disorganized islets with diminished insulin production and impaired glucose tolerance.[159] Thus, Rfx3 is required for the differentiation and function of mature β-cells.

Rfx6 is expressed at e7.5 in the definitive endoderm, then co-expressed with Ngn3 and Nkx2.2; after e9 it becomes restricted to the pancreatic buds and is later confined and maintained in all adult endocrine cells.[146,160] In Arx, Pax4 and NeuroD1 deficient mice, Rfx6 expression is unaltered therefore Rfx6 acts downstream of Ngn3 and upstream of Arx, Pax4 and NeuroD1.[146,160] If either Ngn3 or Rfx6 genes are knocked out, mice experience loss of the hormone producing islet cells; however, Rfx6$^{-/-}$ mice still have PP-cells (Table 1).[146] The ablation of Rfx6 in adult β-cells results in loss of functionality of mature β-cells attributed to reduced expression of glucokinase, the ATP-binding cassette subfamily C member 8/sulfonylurea receptor 1 (Abcc8/SUR1) subunit of K_{ATP} channels and voltage gated Ca^{2+} channels.[161] In humans, Rfx6 regulates insulin expression and secretion via modulation of Ca^{2+} channel expression.[162]

Islet 1 (Isl1)

In pancreas-specific Isl1 deficient mice, a decline in islet cell proliferation and progressive loss of islet mass was observed (Table 1).[163] Additionally, MafA was shown to be a direct target of Isl1.[163,164] Isl1 deficient embryos displayed a diminished number of Arx^{+} cells, confirmed by a reduction in Arx mRNA levels; further, Isl1 activator binding sites were identified within the Arx locus.[165] LIM-domain-binding co-regulator, Ldb1, is a transcriptional co-regulator of α-, β- and δ-cell development and produces a phenotype similar to Isl1 conditional mutants.[166] Also, Ldb1 co-regulates Isl1-activated genes including *MafA, Arx, Insulin* and *Glucagon-like peptide 1 receptor* (Glp1r).[166]

Nk class of homeodomain-encoding genes 2.2 and 6.1 (Nkx 2.2 and Nkx 6.1)

Nkx2.2 has a major role in β-cell lineage differentiation. In early pancreatic development, Nkx2.2 expression is observed from e9.5 in the dorsal pancreatic epithelium and Ngn3-expressing endocrine cells; later Nkx2.2 resides in α-, β- and PP-cell subtypes.[132,167] In Nkx2.2$^{-/-}$ embryos, δ-cells remain intact but α-, β- and PP-cells are displaced by ε-cells (Table 1).[40,167] Therefore, Nkx2.2 has been implicated in the late differentiation of β-cells and the development of α- and

PP-cells. Nkx2.2 interacts with other transcription factors to regulate endocrine cell differentiation. Further, Nkx2.2 activates NeuroD1 leading to β-cell generation; however, Nkx2.2 needs to repress NeuroD1 for α-cell formation.[40,168] Further, concomitant inactivation of Nkx2.2 and NeuroD1 enhances α- and PP-cells and reduces the ε-cell number without altering β-cells.[169] In committed β-cell precursors, Nkx2.2 and Pax 4 control Arx activity.[170] Nkx2.2 also interacts with Arx in defining the PP-cell lineage.[171] Despite Pax4 mutant mice exhibiting a similar phenotype to Nkx2.2 mutant mice, a genetic interaction has yet to be identified.[40] Nkx2.2 also activates the *MafA*[172] and Insulin genes.[173]

Nkx6.1 is observed at e9.5 in both pancreatic buds until e13 and is then confined to the developing β-cells.[174,175] Although Nkx6.1 deficient mice do not exhibit β-cells, the other cell subtypes develop normally (Table 1).[175] In the β-cells, Nkx6.1 inhibits glucagon promoter activity.[176,177] In β-cell development, Nkx6.1 is expressed in Pdx1$^+$ progenitors prior to Ngn3 activation.[178]

Nkx6.2 is expressed in the endoderm domain similar to Pdx1.[178] In Nkx6.1 single mutant embryos, β-cell numbers were impaired; however, a further reduction in β-cells was observed in Nkx6.1/Nkx6.2 double mutants (Table 1).[179] Additionally, in the Nkx6.1 single and Nkx6.1/Nkx6.2 double mutant embryos the mature β-cell markers MafA and Glut2 were deficient.[179] Also, Nkx6.1/Nkx6.2 double mutant embryos had α-cell hypoplasia, a phenotype absent in Nkx6.1 and Nkx6.2 single mutants. Hence in Nkx6.1 deficiency, Nkx6.2 completely compensates for α-cell development.[179] However, Nkx6.2 only partially compensates for β-cell development.[179] Additionally, Myt1 was identified as a downstream target of Nkx6 genes.[179] Genetic gain/loss-of-function studies identified a cross-repressive interaction (before e14) between Nkx6.1/Nkx6.2 (Nkx6) and Ptf1a leading to MPCs differentiating to either the endocrine or acinar cell lineages respectively.[112] There is a repressive relationship between Nkx6.1 and Arx which results in either β- or α-cell lineages respectively.[180]

Aristaless paired-class homeobox gene (Arx) and paired homeodomain factor 4 (Pax4)

An important antagonistic relationship exists between Arx and Pax4 in the specification of the endocrine precursors (Fig. 1).[181,182] Arx and Pax4 reciprocate repression via direct physical interaction with the pertinent promoter.[181,182] Hence, Arx mutant mice upregulate Pax4 mRNA and Pax4 mutant mice demonstrate elevated expression of Arx mRNA. Arx is expressed at around e9.5 and is confined to α- and PP-cells[183] operating downstream of Ngn3.[182] Arx-deficient mice exhibit severe hypoglycemia, weakness and dehydration concomitant with an absolute loss of α-cells and augmentation of β- and δ-cells (Table 1).[181,182] The overexpression of Arx in Pdx1$^+$ progenitor cells converted β- and δ-cell precursors to α- and PP-cell precursors with unaltered total endocrine cell number concomitant with persistent Pax4 expression.[54]

Pax4 is expressed at e9.5 in the dorsal and ventral buds but is limited to the first and second wave β-cells; however, it is down-regulated shortly after birth and undetectable in adult islets.[184-186] Additionally, lineage tracing revealed that Pax4$^+$ cells represent specified endocrine progenitors that may commit to endocrine cell fate.[187,188] Pax4 is expressed downstream of Ngn3 and its expression is lost in Ngn3$^{-/-}$ mice but not *vice versa*.[131,138] Ngn3 and Hnf1α bind to the Pax4 regulatory region and may thus activate expression of Pax4 in endocrine progenitor cells.[143] Pancreata from Pax4$^{-/-}$ embryos display normal islet morphology but are devoid of β- and δ-cells and exhibit elevated levels of α- and ε-cells (Table 1).[186] Also, Pax4 is a repressor of both ghrelin expression and Pax6-mediated glucagon expression; hence there is elevated expression of these 2 cell types in Pax4 mutants.[185,188,189] A loss in Pax4 expression inhibits Pdx1, Hb9 and insulin mRNA in β-cell precursors.[190] Ectopic expression of Pax4 and Arx prompts the formation of β- and α-cell lineage respectively.[54,191] In early pancreatic development, inactive forms of Pax4 and Arx are co-expressed later due to either selective conformational changes or post-translational modification, with either Pax4 or Arx dominating to prompt the allocation of their respective cell lineages.[181,182]

Paired homeodomain factor 6 (Pax6)

Pax6 is expressed at e9.5–10.5 in a subset of cells in both dorsal and ventral pancreatic buds; later its expression is confined to cells of the endocrine lineage.[192,193] Despite expression in glucagon$^+$ and insulin$^+$ cells, Pax6 is only essential for α-cells.[193]

Pax6 mutant mice display abnormal islet organization with marked α-cell reduction relative to other cells types.[194] Pax6$^{-/-}$ mice die shortly after birth as their islets fail to form.[193] Conditional inactivation of Pax6 in mice resulted in reduced glucagon^{+} and insulin^{+} cells but unaffected PP- and δ-cells with these mice failing to form islets (Table 1).[195] Thus, Pax6 may be critical for the full expansion of islet cells.[196,197] Also, Pax6 mutant mice have increased ghrelin-expressing cells (independent of cell proliferation) suggesting that Pax6 directs endocrine progenitors toward the ε-cell fate.[197]

Gli-Similar 3 (Glis3)

Glis3 is a Kruppel-like zinc finger transcription factor essential for the development of β-cells.[198,199] Glis3 knockout mice produce pups with neonatal diabetes presenting with hyperglycemia and hypoinsulinemia that die shortly after birth (Table 1).[200-202] These pups have diminished β-cells. Glis3 has also been shown to regulate insulin expression in mature β-cells.[201,203-205] Glis3 binding sites were located near the distal promoter region of Ngn3 and Glis3 also interacts with Hnf6.[206] The Glis3/Hnf6 protein complex may operate in conjunction with a larger transcription factor network to regulate Ngn3 expression and thus activate endocrine cell specification.[206]

V-Maf musculoaponeuroticfibrosarcoma oncogene family protein A and B (Mafa and Mafb)

During β-cell maturation, the bZIP family members MafA and MafB, shift from a MafB^{+} immature state to MafA^{+}/MafB^{+} and lastly to a MafA^{+} mature state.[207,208] This process may be triggered by Pdx1 upregulation.[208] Both MafA and MafB developmental expression patterns are remarkably delayed relative to all other islet-enriched transcription factors: Pdx1 at e8.5; Pax6 and Ngn3 at e9.0; and Isl1 and Nkx2.2 at e9.5.[209] MafB mutant mice have reduced α- and β-cells although the endocrine cell number is unaltered and these mice die shortly after birth (Table 1).[210] Further, a comparison between wild type and MafB mutant mice revealed no difference in the endocrine cell numbers.[210] MafA$^{-/-}$ mice are viable but undergo β-cell dysfunction ultimately leading to glucose intolerance and diabetes.[211] Additionally, the expression of key β-cell genes including Ins1, Ins2, NeuroD1 and Glut2 was impaired. Later it was identified that MafA together with Pdx1 and NeuroD1 control the level of insulin gene expression.[211] Postnatally, MafA is expressed exclusively in mature β-cells and serves as a marker of terminally differentiated β-cells.[207] Pancreatic ablation of MafA leads to impaired β-cell mass, β-cell dysfunction and disrupted islet organization in 3-week-old mice.[207] Earlier in pancreatic development, Maf-regulated gene expression in β-cells was altered.[207] MafA is important for glucose-stimulated insulin secretion (GSIS), particularly in glucose metabolism, insulin production and insulin granule docking.[212] Premature induction of MafA in Ngn3^{+} endocrine progenitors inhibited differentiation and formation of hormone^{+} cells.[213] This effect occurred after progenitors committed to a specific endocrine cell type.[213] However, upon removal of MafA, these cells reverted to hormone^{+} cells that led to an increase in immature insulin^{+}MafB^{+} cells at postnatal day (p) 5.[213] Thus, for normal pancreatic organogenesis, MafA expression needs to follow insulin.[213] Also, MafB expression in mature insulin^{+} cells is dependent on cell-autonomous mechanisms.[213]

Emerging pancreatic transcription factors

In the embryonic mouse endoderm, misexpression of Ptf1a (Ptf1a^{EDD}) expanded the pancreatic gene regulatory network.[214] Additionally at an early stage, pancreas-proximal organ switch occurred producing all pancreatic lineages.[214] The endogenous endodermal Pdx1^{+} domain expanded and triggered other pancreatic progenitor genes.[214] Thus there is a developmental window during which the endoderm can be re-specified.[214] Nuclear receptor subfamily 5 group A member 2 (NR5A2) is a member of the nuclear hormone receptor family and has been identified as a regulator of pancreatic organogenesis.[215] NR5A2 is required for the expansion of the nascent pancreatic epithelium and subsequently in the genesis of MPCs. NR5A2 deficient mice display impairment in all 3 pancreatic epithelial tissue types evident by partial loss of endocrine cells, >90% deficit of acinar cells and a disrupted ductal tree.[215] Additionally, NR5A2, Ptf1a and Rbpjl control additional regulatory genes including Foxa2, Gata4 and myelocytomatosis oncogene (MYC).[215] The novel transcription factors, Ets variant 1 (Etv1), PR domain containing 16 (Prdm16), runt-related transcription factor 1 translocated to 1 (Runx1t1) and

B-cell lymphoma/leukemia 11A (Bcl11a) were identified as regulators of pancreas organogenesis.[216] The R spondin receptor, Lgr5, is implicated with an organoid-forming epithelial progenitor population, but little is known about this organoid-initiating epithelial progenitor population. Recently, the origin of the organoid-forming epithelial cells have been identified, i.e., $MIC^{-}1C3^{+}/CD133^{+}/CD26^{-}$ in the adult mouse pancreas and liver.[217] $MIC^{-}1C3^{+}/CD133^{+}/CD26$ cells are phenotypically similar in both organs and are rich in Sox9 and forkhead box protein J1 (FoxJ1).[217] Later, when organoids were transplanted to $Fah^{-/-}$ mice, hepatocyte-like cell grafts were generated in half of the recipients.[217] This demonstrated a differentiation capacity similar to hepatic organoids. Later, the adenoviral delivery of Pdx1, Ngn3 and MafA induced insulin expression.[217] Hence the organoid-initiating cells have the capacity to differentiate.[217] Wingless-type MMTV integration site family member 7b (Wnt7b) is expressed in the epithelium and is required for pancreatic progenitor cell growth.[218] Pancreatic ablation of Wnt7b prior to and during the secondary transition inhibited proliferation of pancreatic progenitors and prompted pancreatic hypoplasia.[218] Surprisingly, over-expression of Wnt7b under the Pdx1 promoter did not increase progenitor mass but instead suppressed pro-endocrine and pro-acinar cells.[218] This was followed by arrested morphogenesis and loss of differentiated endocrine and acinar cells leading to polycystic duct-like epithelial complexes and increased pancreatic mesenchymal mass.[218]

Perspectives

Developmental biology has enhanced our understanding of normal pancreatic development, differentiation and function through the extensive use of rodent models. The decoding of these dynamic processes serves as a pillar for novel diabetic therapies. Pancreatic transcription factors and extrinsic signals from non-pancreatic tissue form a complex gene regulatory network that orchestrates pancreatic development. Extrinsic signals are important for gut tube patterning and these intrinsic transcription factors differentiate pancreatic progenitor cells to their specific cell lineages, viz., endocrine, exocrine and ductal. The regulatory roles of transcription factors in pancreatic development, β-cell differentiation and function are complex. Despite the extensive progress, further investigation is warranted which include defining the precise functional relationship between transcription factors and extrinsic signals and the molecular mechanisms that drive pancreatic differentiation. Collective research efforts will therefore generate a comprehensive understanding of pancreatic processes which can be translated into novel therapies.

Abbreviations

Abcc8	ATP-binding cassette, sub-family C, member 8
Arx	aristaless paired-class homeobox gene
BMP	bone morphogenetic protein
Dll1	delta-like ligand
Etv1	Ets variant 1
Foxa1	forkhead box protein a 1
Foxa2	forkhead box protein a 2
FoxJ1	forkhead box protein J 1
FGF	fibroblast growth factor
Gata4	gata binding protein 4
Gata6	gata binding protein 6
Glis3	Gli-similar 3
Glut2	glucose transporter 2
GSIS	Glucose-stimulated insulin secretion
Hb9	homeobox gene product 9
hESCs	human embryonic stem cells
Hnf	hepatocyte nuclear factor
Hnf1β	hepatocyte nuclear factor 1 β
Hnf3β	hepatocyte nuclear factor 3 β
Hnf6	hepatocyte nuclear factor 6
Isl1	islet 1
Lgr5	R spondin receptor
MafA	V-maf musculoaponeurotic fibrosarcoma oncogene family protein A
MafB	V-maf musculoaponeurotic fibrosarcoma oncogene family protein B
MPCs	multipotent progenitor cells
MYC	myelocytomatosis oncogene
NeuroD1	neurogenic differentiation 1
Ngn3	neurogenin 3
Nkx2.2	NK class of homeodomain-encoding genes 2.2
Nkx 6.1	NK class of homeodomain-encoding genes 6.1
Nkx 6.2	NK class of homeodomain-encoding genes 6.2
NR5A2	Nuclear receptor subfamily 5, group A, member 2
Pak3	p21 protein-activated kinase 3

Pax4	paired homeodomain factor 4
Pax6	paired homeodomain factor 6
Pdx1	pancreatic duodenal homeobox gene 1
Prdm16	PR domain containing 16
Ptf1a	pancreas specific transcription factor 1 a
$Ptf1a^{EDD}$	misexpression of Ptf1a in the embryonic mouse endoderm
Rbpj	recombination signal binding protein kappa J
Rbpjl	pancreas-restricted paralog of Rbpj
Rfx3	regulatory factor x 3
Rfx6	regulatory factor x 6
Runx1t1	runt-related transcription factor 1 translocated to 1
Sox 9	sex determining region Y box 9
Sox 17	sex determining region Y box 17
Stz	streptozotocin
SUR1	sulfonylurea receptor 1
T1D	type 1 diabetes
T2D	type 2 diabetes
TGFβ	transforming growth factor β
VEGF	vascular endothelial growth factor
Wnt	wingless-type MMTV integration site family
Wnt7b	wingless-type MMTV integration site family member 7b.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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