

REVIEW

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Bridging pancreatic and hepatic development: overlapping genes and their role in diabetes

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Abstract

Diabetes mellitus is a complex metabolic disorder characterized by hyperglycemia due to impaired insulin production, action, or both. The Pancreas and Liver play central roles in glucose regulation, and their dysfunction is critical to the onset and progression of specific types of diabetes, including type 2 diabetes and certain forms of monogenic diabetes. While these organs have distinct physiological roles, they originate from the foregut endoderm and share key developmental regulators and signaling pathways. This review explores the overlapping transcription factors and genes that are essential for both pancreatic and hepatic development and function. These dual-role genes not only govern early organogenesis but are also implicated in diabetes pathogenesis, underscoring their significance in metabolic homeostasis. We highlight how interorgan signaling, particularly between hepatokines and pancreatic islet cells, contributes to the maintenance or disruption of glucose metabolism. Furthermore, we discuss the clinical implications of these shared pathways, emphasizing how insights from developmental biology can inform precision diagnostics and therapeutic strategies for diabetes. Finally, we consider how emerging tools, such as pluripotent stem cell-based disease models and gene editing and multi-omics approaches, are transforming our understanding of gene function and disease progression. By bridging the developmental and metabolic landscapes of the pancreas and liver, this review provides a comprehensive framework for uncovering novel regulators of diabetes and paves the way toward targeted, personalized treatment strategies.

Keywords: Embryonic development, Diabetes, Hepatic–pancreatic signaling, Glucose homeostasis, Therapeutic targets

Introduction

Diabetes mellitus is one of the most common chronic metabolic disorders, characterized by hyperglycemia resulting from the loss of pancreatic β -cells, insufficient insulin action, or both [1]. The effect of this metabolic dysregulation of glucose homeostasis in the body leads to the development of diabetes. The pancreas and liver serve as vital organs with critical functions in glucose metabolism and regulation, the dysfunction of which causes an imbalance in glucose homeostasis, allowing the pancreas and liver to be targets for



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diabetes. The pancreas consists of the exocrine component, which includes acinar and ductal cells, as well as a distinct endocrine portion, known as the islet of Langerhans. This endocrine component is the main source of the key metabolic hormones in regulating glucose homeostasis, insulin (β -cells) and glucagon (α -cells) [2]. In type 1 diabetes (T1D), the selective destruction of pancreatic β -cells by an autoimmune mechanism leads to impairment of insulin production and insulin deficiency, resulting in hyperglycemia [3–5]. On the other Hand, in type 2 diabetes (T2D), pancreatic dysfunction is attributed through a combination of insulin resistance in peripheral tissues (liver, fat, and muscle) and progressive β -cell failure. In addition to this direct link between insulin production dysfunction of the pancreas and diabetes, the liver has an important role in glucose metabolism and homeostasis through regulating many pathways of glucose metabolism, including glycogenesis, glycogenolysis, glycolysis and gluconeogenesis [6]. In most cases of T2D, hepatic insulin resistance and dysregulated glucose metabolism is the key driver of the pathogenesis of this disease. In monogenic diabetes, characterized by mutations in a single gene, many of these affected genes are crucial for the proper development and function of both the pancreas and liver [7, 8]. These are regulatory genes involved in several pathways related to early embryonic development, differentiation, and metabolic regulation, emphasizing the shared molecular and developmental pathways between these two organs.

The pancreas and liver are interconnected organs that share significant molecular and developmental pathways and initially develop from a shared multipotent population of foregut endoderm cells [9, 10]. Despite these similarities, each tissue originates from various regions of the endoderm, influenced by a network of distinct genes and signaling pathways [11, 12] (Fig. 1). The interplay between these factors govern cell proliferation and specifies the hepatic and pancreatic fate. Exploring the signaling pathways and shared genes that govern the differentiation of the liver and pancreas during embryonic development is crucial for producing highly functional hepatic and pancreatic β -cells. This will enhance our ability to model various types of diabetes and deepen our understanding of these distinct forms. Thus, the aim of this review is to explore shared pathways between pancreas and liver development and their link in the context of diabetes, highlighting the potential of this work to bridge developmental biology and metabolic disease.

Embryonic development of the pancreas and liver

During early embryogenesis, the liver and pancreas both begin to form from the endoderm layer. In the process of gastrulation, cellular movements within the blastula lead to the creation of the endoderm. As development continues, targeted signaling pathways guide the differentiation of the endoderm into various progenitor cells that eventually give rise to organs such as the pancreas, liver, intestine, and lungs [13–15]. For both the pancreas and liver, this differentiation is regulated by a series of signaling pathways, including those from the fibroblast growth factor (FGF), bone morphogenic protein (BMP), NOTCH, Hedgehog, Wnt, and transforming growth factor beta (TGF- β) pathways.

The first indication of pancreas and liver development appears as two distinct regions within the endoderm, known as the pancreatic and hepatic buds, respectively

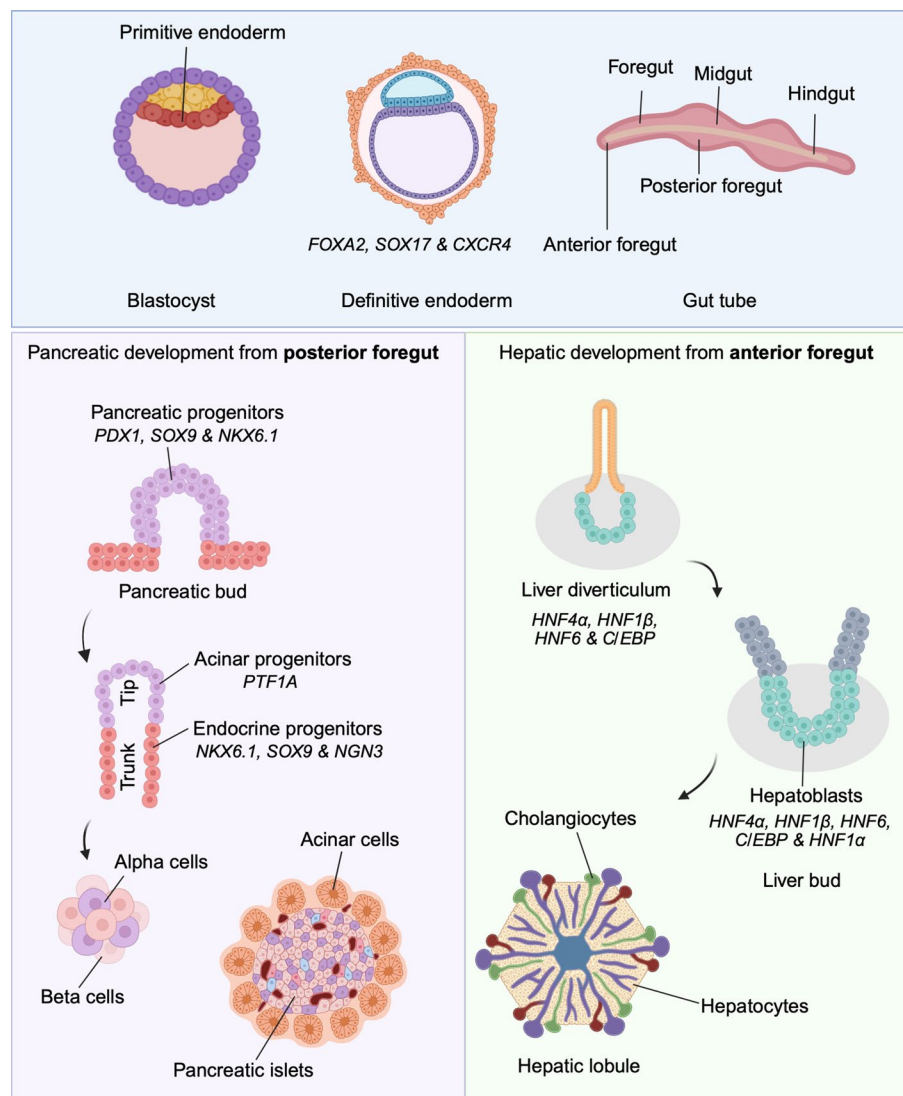


Fig. 1 Pancreatic and hepatic embryonic development. Schematic representation of the key developmental stages of the pancreas and liver. Both organs develop from the foregut endoderm. The transcription factors such as *FOXA2*, *SOX17*, and *CXCR4* are broadly expressed in the definitive endoderm where overlapping expression of *HHEX* and *PDX1* defines a common hepatic-pancreatic progenitor region later on. *HHEX*+ cells specify the liver bud, while *PDX1*+ progenitors give rise to the dorsal and ventral pancreatic buds. Early expression of transcription factors such as *PDX1*, *SOX9*, and *NKX6.1* marks the pancreatic progenitor domain. Afterwards, epithelial branching and expansion of multipotent progenitors begin where the tip and trunk domains are specified: *PTF1A* expression marks tip progenitors that give rise to acinar cells, while *NKX6.1*, *SOX9*, and *NGN3* are enriched in trunk regions, leading to endocrine cells. Furthermore, endocrine progenitors form islet cell types, including insulin-producing β -cells, while exocrine and ductal cells organize into mature structures. On the other hand, liver bud cells expressing *PROX1* and *HNF4a* migrate and begin hepatoblast proliferation to eventually differentiate into hepatocytes and cholangiocytes. Cholangiocytes are the epithelial cells lining the bile ducts. The figure was created using BioRender

[16]. These regions undergo significant morphogenic changes as the cells proliferate and differentiate into specialized progenitor cells, which will eventually form the mature organs [17, 18]. Although the development of the liver and pancreas follows separate pathways, they share some common regulatory mechanisms [10, 11, 16]. In

the case of the Liver, hepatic progenitors arise from the anterior foregut endoderm around day 16 of human embryonic development (Fig. 1). The liver bud expands rapidly, and its cells differentiate into hepatocytes and cholangiocytes, which form the liver parenchyma and bile ducts [19, 20]. The pancreas develops shortly thereafter, beginning with the formation of two distinct buds: the dorsal and ventral pancreatic buds. These buds appear at different times during embryogenesis and later fuse to form the fully developed pancreas [17, 18] (Fig. 1). As the pancreas develops, progenitor cells differentiate into both exocrine cells, which produce digestive enzymes, and endocrine cells, which form the hormone-producing islets of Langerhans. Fetal pancreatic β -cells first appear around 8 weeks post-conception (wpc), followed by glucagon (GCG)-expressing cells at 9 wpc [20–22]. Endocrine cell clustering begins at 10 wpc, and by 12–13 wpc, all endocrine cell types are present [21, 23]. Human islet morphology changes during development: at 14 wpc, β -cells are in the core and α -cells at the periphery, as seen in mice and small human islets. By 21 wpc, both cell types are intermingled, a change not observed in mice, possibly essential for the final maturation of human endocrine cells [20].

The development of both organs is tightly regulated by a complex network of signaling pathways and transcription factors (TFs), which control the precise timing and coordination of cellular differentiation, ensuring proper organ formation and function. In the following sections, we focus on key genes and TFs that play a critical role in the development and/or function of both pancreas and liver.

Genes linked to the development and function of the pancreas and liver

Given the shared developmental origins of the pancreas and liver, it is foreseen that they are governed by common transcriptional regulators and genes. Thus, members of the following families Forkhead box A (FOXA), SRY-related HMG box (SOX), and hepatocyte nuclear factor (HNF) are very crucial in the development of both adult liver and pancreas [10, 24–27] (Table 1).

Transcription factors

The SRY-related HMG box family (SOX)

Transcription factor networks including those from the sex-determining region Y-box (SOX) family drive liver and Pancreas development. This family consists of 30 known members in mammals, all sharing a highly conserved HMG domain responsible for DNA binding [28, 29]. They are categorized into nine distinct subgroups, with members within the same subgroup sharing structural similarities and often performing overlapping functions. On the other hand, members from different subgroups typically differ significantly except for the conserved HMG domain.

SOX17

SOX17, a member of the SOXF subgroup, is expressed in the endoderm starting from the onset of gastrulation and plays a crucial role as an intrinsic regulator of endoderm formation across vertebrate species [30–33]. As endodermal development progresses, Sox17 is involved in directing the differentiation and segregation of key organs derived from the foregut, including the liver, biliary system, and ventral pancreas [34, 35]. In

Table 1 Genes linked to the development and function of the pancreas and liver

Gene family	Gene name	Function	Required for development	Required for adult function	Animal model	Human model
SOX family	SOX17	Regulates proper specification of the pancreatic lineage and foregut endoderm patterning; promotes the development of the liver and biliary system	Pancreas and liver	Not well established	Mouse models (Sox17 ^{-/-} and ventral foregut specific Sox17 ^{-/-}) [33–35]	hESC-derived ventral foregut progenitors [34]
	SOX9	Maintains pancreatic progenitors, promotes endocrine and ductal cell differentiation; in adults, regulates β -cell insulin secretion; essential for hepatobiliary development, cell fate decisions, and for maintaining liver homeostasis in adults	Pancreas and liver	Pancreas and liver	Mouse models (Sox9 ^{-/-} , Sox9 ^{-/-} , β -cell-specific Sox9 ^{-/-} , and liver specific Sox9 ^{-/-}) (Sox9 ^{-/-} ; Pdx1 ^{+/-} and Sox9 ^{-/-} ; Pdx1 ^{-/-}) [25, 36, 37, 40, 43, 44]; Ectopic expression [39]	hESC-derived pancreatic progenitors [40]; hPSC-derived islets [44]
	SOX4	Essential for late pancreatic endocrine differentiation and islet cell expansion; critical for cholangiocyte and bile duct differentiation; regulates lipid and triglyceride metabolism in the mature liver	Pancreas and liver	Pancreas and liver	Mouse models (Sox4 ^{-/-} , β -cell specific Sox4 ^{-/-} and liver-specific Sox4 ^{-/-}) [45, 47, 51–53]	-

Table 1 (continued)

Gene family	Gene name	Function	Required for development	Required for adult function	Animal model	Human model
HNF family	<i>HNF1A</i>	Promotes islet cell maturation; regulates insulin secretion, β -cell number, liver metabolism and regulates hepatocyte differentiation	Pancreas and liver	Pancreas and liver	Mouse models (<i>Hnf1a</i> ^{+/−} and <i>Hnf1a</i> ^{−/−}) [59, 61–64]	Primary human islets iPSC-derived pancreatic cells iPSC-derived hepatic cells [7, 65, 66, 74]
	<i>HNF1B</i>	Directs pancreatic progenitor and endocrine differentiation; essential in adult pancreas for maintaining ductal integrity and preventing chronic pancreatitis; controls bile duct morphogenesis during development	Pancreas and liver	Pancreas and liver	Mouse models (<i>Hnf1b</i> ^{+/−} , <i>Hnf1b</i> ^{−/−} , β -cell specific <i>Hnf1b</i> ^{−/−} pancreatic duct-specific <i>Hnf1b</i> ^{−/−}) [57, 112–114, 119]	iPSC-derived pancreatic cells hESC-derived pancreatic cells [113, 115–118, 362]
	<i>HNF4A</i>	Promotes islet cell maturation; regulates insulin secretion, glucose/lipid metabolism, bile acid synthesis and establishes hepatic identity	Pancreas and liver	Pancreas and liver	Mouse models (<i>Hnf4a</i> ^{+/−} , β -cell specific <i>Hnf4a</i> ^{−/−}) [7, 77–81]	iPSC-derived pancreatic cells iPSC-derived hepatic cells [8, 66, 86–88]
	<i>HNF6</i>	Regulates endocrine lineage differentiation, bile duct formation, and hepatocyte maturation	Pancreas and liver	Liver	Mouse models (<i>Hnf6</i> ^{+/−}) [90, 91, 94, 97–100]	iPSC-derived pancreatic cells iPSC-derived hepatic cells [90, 101, 102]

Table 1 (continued)

Gene family	Gene name	Function	Required for development	Required for adult function	Animal model	Human model
FOX family	<i>FOXA1</i>	Activates key pancreatic genes; regulates early pancreatic progenitor differentiation, promotes liver specification and regulates hepatic metabolic homeostasis	Pancreas and liver	Pancreas and liver	Mouse models (<i>Foxa1</i> ^{-/-} and <i>Foxa1</i> ^{-/-} ; <i>Foxa2</i> ^{-/-}) [140–143]	iPSC-derived pancreatic cells iPSC-derived hepatic cells [136, 150]
	<i>FOXA2</i>	Regulates islet formation, β-cell function, hepatic specification, and lipid/bile acid metabolism	Pancreas and liver	Pancreas and liver	Mouse models (<i>Foxa2</i> ^{-/-} , <i>Foxa1</i> ^{-/-} ; <i>Foxa2</i> ^{-/-} , β-cell specific <i>Foxa2</i> ^{-/-} , hepatocyte specific <i>Foxa2</i> ^{-/-}) [27, 142, 155–159, 169, 172]	hESC-derived pancreatic progenitors iPSC-derived pancreatic cells [163–167, 173]
	<i>FOXO1</i>	Maintains β-cell identity; controls gluconeogenesis, hepatic lipid metabolism, and autophagy	Pancreas	Pancreas and liver	Mouse models (liver specific <i>Foxo1</i> ^{-/-} , <i>Foxo1</i> ^{-/-} db/db and <i>Foxo1</i> ^{-/-} ; <i>Akt</i> ^{-/-}) [180, 181, 183]	iPSC-derived pancreatic cells; iPSC-derived hepatic cells [193–195]
GATA factors	<i>GATA4/GATA6</i>	Regulates pancreatic and hepatic lineage allocation; essential for pancreas formation, with GATA4 linked to exocrine and GATA6 to endocrine differentiation	Pancreas and liver	Not well established	Mouse models (<i>Gata4</i> ^{-/-} , <i>Gata4</i> ^{+/-} ; <i>Gata6</i> ^{-/-} , <i>Gata6</i> ^{+/-} ; <i>Gata6</i> ^{+/-}) [205–209, 211]	iPSC-derived pancreatic cells [212–214]
Homeobox family	<i>HHEX</i>	Regulates liver and ventral pancreas development; induces liver bud and hepatoblast proliferation	Pancreas and liver	Not well established	Mouse model (<i>Hhex</i> ^{-/-}) [121, 124–126]	hESC-derived pancreatic cells; hiPSC-derived pancreatic cells [127–129]
	<i>PROX1</i>	Regulates organ morphogenesis, progenitor identity, β-cell maturation, hepatocyte migration, and identity maintenance	Pancreas and liver	Not well established	Mouse models (Pancreas specific <i>Prox1</i> ^{-/-} , liver-specific <i>Prox1</i> ^{-/-} , and <i>Prox1</i> ^{+/-}) [226, 227, 233]	-

Table 1 (continued)

Gene family	Gene name	Function	Required for development	Required for adult function	Animal model	Human model
Glucose sensing genes	(<i>GLUT 1, 2, 3</i>)	Mediates glucose homeostasis and glucose transport in liver and β -cells	Not required	Pancreas and liver	Mouse models (<i>Slc2a2</i> ^{-/-}) [242–244]	Human pancreatic islets [245–254]
	<i>GCK</i>	Regulates insulin secretion in pancreatic β -cells and promotes hepatic glycogen synthesis	Not required	Pancreas and liver	Mouse models (Pancreas specific <i>GCK</i> ^{-/-} , liver specific <i>GCK</i> ^{-/-}) [307]	Human fetal pancreatic tissue iPSC-derived pancreatic cells [280, 287–289, 308]

Sox17^{-/-} mutant mice, a significant deficiency in gut endoderm development is observed [33] (Table 1). During the early stages of hepatopancreatic specification, Sox17 is co-expressed with hematopoietically expressed homeobox (Hhex) and pancreas/duodenum homeobox protein 1 (Pdx1) in the ventral foregut endoderm [35]. The initial segregation of these Lineages begins around embryonic day 8.5 (E8.5), when the prospective liver primordium downregulates Sox17 expression but retains Hhex expression. By E9.5, the co-expression domain of Sox17 and Pdx1 in the posterior ventral foregut separates, with the Sox17-positive region giving rise to the extrahepatobiliary system, while the Pdx1-positive region differentiates into the ventral pancreas. Both global and ventral foregut-specific deletion of Sox17 leads to the complete absence of the gallbladder and cystic duct, highlighting its essential role in the development of the extrahepatobiliary system [34, 35]. When Sox17 is removed from the ventral foregut starting at embryonic day 8.5 (E8.5), Pdx1 expression expands abnormally throughout the ventral foregut. As a result, Pdx1-positive cells are mislocalized within the liver bud, and pancreatic tissue appears ectopically in the common bile duct. On the other hand, if Sox17 expression is sustained in the Pdx1-positive region, pancreatic development is suppressed, leading to the formation of ectopic ductal structures in the stomach and duodenum [34].

SOX9

SOX9, is also a member of the Sox TFs. During liver development in mice, the expression of *Sox9* is initially in the endodermal cells Lining the Liver diverticulum at embryonic day 10.5 (E10.5) [36]. This expression temporarily disappears as hepatoblasts migrate into the septum transversum but reappears near the portal vein by E11.5. Influenced by signals from the surrounding portal mesenchyme, *Sox9*-positive hepatoblasts form a single-cell layer around the portal vein branches, creating a structure known as the ductal plate by E15.5. The early ductal structures exhibit asymmetry, with *Sox9*-positive biliary cells on the portal side and *Sox9*-negative hepatoblasts on the parenchymal side. This imbalance resolves as some of the parenchymal hepatoblasts differentiate into biliary cells, contributing to the mature bile ducts. Cells from the ductal plate that do not form bile ducts become periportal hepatocytes [36]. While SOX9 is the earliest marker of intrahepatic bile duct cells, it is not essential for their differentiation. In mice lacking liver-specific *Sox9*, bile duct development is delayed, indicating *Sox9* regulates the timing of this process (Table 1). *Sox9* is also expressed in the extrahepatic biliary tract of mouse embryos starting at embryonic day 13.5 (E13.5), and this expression continues into adulthood [37]. However, studying SOX9 function in this region is challenging because mice lacking both copies of *Sox9* die early, around E11.5 [36].

In the adult liver, SOX9 is continuously expressed and plays a key role in maintaining liver homeostasis [38]. It regulates fibrotic extracellular matrix components by promoting collagen production in activated hepatic stellate cells (HSCs) in response to profibrotic signals, such as TGF- β , contributing to liver fibrosis (reviewed in [39]).

Moreover, this TF plays pivotal roles throughout pancreatic organogenesis as illustrated in conditional deletion of *Sox9* in mice. *Sox9* expression begins around embryonic day 8.75 (E8.75) in regions destined to become the pancreas and proximal duodenum, before the formation of pancreatic buds [40]. In this early pre-pancreatic domain, *Sox9* expression overlaps with Pdx1, another critical TF. Importantly, SOX9 and PDX1 appear

to mutually reinforce each other's expression, with each factor binding to regulatory regions of the other's gene [41, 42]. In mice with individual Sox9 or Pdx1 mutations, some pancreatic development still occurs, suggesting partial compensation. However, in compound mutants, which carry different combinations of null and gut-specific alleles for Sox9 and Pdx1, a range of pancreatic malformations are observed. These include a reduced ventral pancreatic bud in compound heterozygous mice and complete absence of both dorsal and ventral buds in compound homozygous mutants [25, 43]. This highlights the synergistic and essential role of SOX9 and PDX1 in the initiation and progression of pancreatic development. SOX9, beyond its developmental role, is critical in mature β -cells for proper insulin secretion. In rodents, Sox9 deficiency leads to impaired insulin release and age-related glucose intolerance, resembling T2D progression [44]. Similarly, loss of SOX9 in hPSC-derived β -cells reduces first-phase insulin secretion. This effect is mediated through SOX9's regulation of alternative splicing, particularly by maintaining expression of key splicing factors such as SRSF5. Disruption of SOX9 alters splicing patterns, resulting in accumulation of non-functional isoforms critical for β -cell function, underscoring its essential role in β -cell gene regulation and insulin secretion [44].

SOX4

Another member of the SOX family is SOX4, which exhibits the highest expression among all Sox genes in the mouse endocrine pancreas [45, 46]. Additional studies have also shown that SOX4 is expressed in the embryonic pancreas of humans, mice, and zebrafish [46, 47] with an initial broad distribution that later becomes restricted to mature islet cells, suggesting that its main role occurs during the late stages of endocrine cell differentiation [45]. In mammals, Sox4 expression has also been reported in multiple developing and adult tissues, including the central nervous system, thymus, heart, lung, gonads [48], and gut [49]. In the pancreas, data from pancreatic explants indicate that Sox4 is essential for the adequate expansion of the endocrine cell population, particularly β -cells [45]. Moreover, SOX4 drives endocrine differentiation downstream of its primary role in activating NEUROG3 protein expression [50]. Complete loss of Sox4 leads to cardiac defects, impaired blood flow, and embryonic death by E14.5, before most endocrine cell differentiation is completed, in addition to significant decrease in insulin and glucagon [45, 47] (Table 1). Embryos lacking Sox4 display normal Pancreatic bud development and endocrine cell differentiation up to 12.5 dpc [45]. Beyond this point, however, they fail to develop normal islets, with impaired expansion of the endocrine cell population, especially β -cells [45]. Using an inducible β -cell-specific knockout mouse model, deletion of Sox4 at 6 weeks of age led to progressive deterioration of glucose tolerance, reduced insulin secretion, and the onset of diabetes by 30 weeks of age [51].

Additionally, SOX4 has also been shown to have an important role in the liver, primarily during embryonic development. Liver-specific deletion of SOX4, either alone or in combination with SOX9 loss, disrupts cholangiocyte differentiation, impairs apico-basal polarity, and hinders bile duct formation [52]. Sox4 expression is significantly elevated in the livers of both obese rodents and humans. Experimental adenovirus-mediated over-expression of Sox4 in lean mouse livers induces hepatic steatosis, while liver-specific

Sox4 knockdown reduces triglyceride accumulation and alleviates insulin resistance in obese mice [53], highlighting an important role in hepatic triglyceride metabolism.

The hepatocyte nuclear factor (HNF) family

Hepatocyte nuclear factor 1 alpha (*HNF1α* or *HNF1A*), *HNF1B*, and *HNF4α* encode TFs essential for the proper development and function of the pancreas and liver. Mutations in these genes are strongly associated with maturity onset diabetes of the young (MODY) and an increased risk of T2D [54–56].

HNF1α

HNF1A or *HNF1α* is a critical TF that plays a pivotal role in the development and function of the pancreas and liver [7, 57, 58]. In the pancreas, *HNF1A* is essential for the regulation of insulin and other islet-specific genes such as *GCK*, *SLC2A2* (GLUT2), and *ABCC8*, contributing to the maintenance of β -cell number and insulin secretion [57, 59]. Heterozygous mutations in *HNF1A* cause MODY3, which is the most common form of monogenic diabetes [60]. Studies using mouse models have found that heterozygous deletion of *HNF1α* (*HNF1α*^{+/-}) does not result in pancreatic defects, and these mice appear normal. However, *HNF1α*^{-/-} mice develop diabetes [61]. *HNF1α*^{-/-} mice display growth retardation and impaired insulin secretion, resulting in abnormal glucose levels and diabetes development [59, 61, 62]. Furthermore, *Hnf1α*^{-/-} mice showed reduced expression of Glut2, amino acid transporter, liver pyruvate kinase (L-Pk), insulin, and key islet-enriched transcription factors such as *Pdx-1*, *Hnf4α*, and *NeuroD1/Beta-2* [59, 63], while another group showed *HNF1α* KO mice to exhibit hepatomegaly and fatty liver [64] (Table 1). Knockdown studies in primary human islets have demonstrated that the acute loss of *HNF1α* leads to multiple defects in hormone secretion, including reduced insulin secretion, excessive glucagon output during hyperglycemia, and blunted glucagon secretion during hypoglycemia [65], while KO studies from human iPSC models differentiated toward pancreatic lineage showed downregulation of foregut genes and several markers of pancreatic and β -cell development, as well as changes in the expression of β -cell stress and cellular respiration genes [7, 65]. Interestingly, a study on the effect of brief intraperitoneal xenotransplantation using encapsulated pancreatic progenitor cells demonstrated that optimal induction of *HNF1A* and *HNF4A* enhances the islet profile toward single hormonal expression [66], highlighting the function of these regulators to restrict multipotent hormone expression.

Beyond its role in the pancreas, *HNF1α* is also a key regulator of hepatic development and function. Hepatocyte-specific KO studies in rodents have shown that *HNF1α* is necessary for normal liver development and function, with *Hnf1α*-deficient mice exhibiting impaired glucose homeostasis and the development of diabetes [59] and fatty liver-related hepatocellular carcinoma [67]. The broad transcriptional programs regulated by *HNF1α* in both the pancreas and the liver underscore its importance in maintaining tissue-specific functions in these organs. KO studies from iPSC models differentiated toward the hepatic lineage show similar phenotypes, with downregulation of hepatic genes *ALB* and *CYP3A4* and altered metabolic pathways [7, 65].

HNF1A-MODY3 accounts for approximately 50% of all MODY cases [68, 69]. MODY3 patients typically have early-onset diabetes characterized by impaired glucose-stimulated

insulin secretion, high insulin sensitivity, and a progressive decline in β -cell function. Furthermore, variants in *HNF1 α* are associated with lipid metabolism disorders in several genome-wide association studies (GWAS), including hypercholesterolemia (rs1169288-A), hyperlipidemia (rs1169288-A), and dyslipidemia (rs2649999-C) [70, 71]. Single-nucleotide polymorphisms (SNPs) in *HNF1A* have also been associated with disrupted levels of liver enzymes such as GGT (rs2650000-A), ALT (rs1169306), and ALP (rs7305618-T) [72, 73]. To investigate the pathophysiology of MODY3 in humans, hPSC models have been used in multiple studies. Differentiation of *HNF1A*^{+/-} and *HNF1A*^{-/-} hPSC lines into pancreatic β -cells revealed that *HNF1A* is crucial for suppressing alpha cell genes, maintaining beta cell function, and regulating the expression of LINC01139, a long noncoding RNA essential for mitochondrial respiration [74]. Differentiating *HNF1A*^{-/-} hESCs into β -cells showed defects in endocrine β -cell development, though pancreatic progenitors remained unaffected. The loss of *HNF1A* resulted in decreased expression of β -cell TFs and genes linked to insulin synthesis and β -cell stress, along with impaired mitochondrial function and glycolysis [74]. These changes lead to a significant reduction in insulin-secreting cells and an increase in glucagon-secreting cells owing to reduced *PAX4* expression [74], which aligns with the increase in alpha cell mass observed in pancreatic islets from MODY3 patients compared with nondiabetic islets [75]. Furthermore, in a MODY3 patient, LINC01139 expression is reduced in alpha cells but not β -cells, suggesting that LINC01139 downregulation may contribute to the increased alpha cell mass [74]. Although an increase in alpha cells is not observed in mouse *HNF1 α* models, mice lacking *Pax4* exhibit a rise in glucagon+ and ghrelin+ cells along with a significant decrease in insulin+ cells [76], highlighting differences in phenotypes between humans and mice.

HNF4A

HNF4A (*HNF4 α*), a member of the nuclear receptor superfamily, plays a crucial role in the development and function of both the pancreas and the liver. In the pancreas, *HNF4 α* is essential for the maintenance of β -cell identity and function, as well as the regulation of insulin secretion [7]. Complete loss of *HNF4 α* (*HNF4 α* ^{-/-}) in mice is embryonically lethal due to dysfunction of the visceral endoderm [77, 78]. However, β -cell-specific *HNF4 α* ^{-/-} mice show impaired glucose-stimulated insulin secretion (GSIS), leading to glucose intolerance [7, 79, 80]. Conditional KO studies show that *HNF4 α* deletion in hepatoblasts results in hepatomegaly and steatosis, while acute loss of *HNF4 α* in the adult murine liver recruits a proliferative response in normal hepatocytes [81] (Table 1).

In the liver, *HNF4A* is a master regulator of hepatocyte differentiation and a key player in metabolic processes, including gluconeogenesis and bile acid, cholesterol, fatty acid oxidation and lipid metabolism [82]. *HNF4A* regulates the hepatic transcriptional network, including interactions with other liver-enriched factors such as *HNF1A* and *C/EBPs* [82]. The expression of *HNF4 α* is tightly regulated in both the pancreas and the liver, and it interacts with a network of other TFs to control the expression of genes involved in cell identity, metabolism, and insulin secretion [7]. Several studies have demonstrated that *HNF4 α* directly regulates the expression of genes essential for glucose sensing, insulin production, and β -cell function in the pancreas including *ABCC8* (*SUR1*), *KCNJ11* (*Kir6.2*), and glucokinase (*GCK*) [79, 83]. In the hepatic progenitor

stage, *HNF4A* plays a crucial role in establishing hepatic identity, it collaborates with five other TFs (*HNF1A*, *HNF1B*, *FOXA2*, *HNF6*, and *LRH-1*) to form a core transcription factor network that drives hepatoblast differentiation into hepatocytes [84, 85]. Shortly after, *HNF4A* becomes expressed in hepatic progenitors promoting the differentiation into hepatoblasts during a stage known as liver bud formation from the foregut endoderm [85].

Several recent studies have explored the role of *HNF4A* in pancreatic and hepatic development, as well as its involvement in diabetes, using hPSC models. However, some of these studies reported discrepancies in their results [8, 86, 87]. These differences may be attributed to the fact that certain studies did not use isogenic hPSC models, which could have helped account for variations in differentiation efficiencies caused by differences in the genetic backgrounds of the iPSC lines. Vethe et al. demonstrated that iPSCs derived from patients with *HNF4A* heterozygous mutations (p.Ile271fs) generate β -cells comparable to those produced from healthy iPSC controls [86]. Another study showed that Pancreatic differentiation of iPSCs derived from patients with nonsense mutations in exon 7 of *HNF4A* (Q268X) showed an upregulation of TFs associated with the pancreatic progenitor stage, compared with healthy controls [87]. Furthermore, the expression levels of islet hormones, including *INS*, *GCG*, and *SST*, are higher in pancreatic progenitors derived from MODY1-iPSCs than in controls, suggesting a compensatory response [87]. In contrast, a more recent study using iPSCs derived from patients with the *HNF4A* heterozygous mutation (p.Ile271fs) (*HNF4A*^{p.Ile271fs/+}) revealed that *HNF4A* mutations lead to defects in the development of the foregut, β -cells, and hepatocytes [8]. The study found that *HNF4A*, *PDX1*, and *GATA4* are significantly downregulated in foregut endoderm derived from *HNF4A*^{p.Ile271fs/+} iPSCs [8]. Interestingly, β -cells derived from MODY1-iPSCs also showed reduced expression of *HNF4A* and *HNF1A* [8]. This aligns with previous studies indicating that *HNF4A* directly regulates *HNF1A* expression, suggesting that mutations in *HNF4A* could contribute to diabetes by reducing *HNF1A* expression. Additionally, a study examining short-term intraperitoneal xenotransplantation of encapsulated pancreatic progenitor cells from MODY patients showed that sufficient induction of *HNF1A* and *HNF4A* promotes islet cell maturation characterized by a shift toward monohormonal identity [66]. These findings suggest the function of these two key regulatory factors to maintain commitment to a monohormonal endocrine cell fate.

HNF4 α plays a role in regulating cellular stress responses in both pancreatic β -cells and liver cells by controlling genes involved in stress-related pathways. In human beta-like cells derived from stem cells, *HNF4 α* target genes are enriched in pathways related to stress-activated protein kinase signaling and reactive oxygen species (ROS) metabolism—key processes for managing oxidative stress and maintaining proper glucose sensing [7, 88]. *HAAO* and *USH1C* emerged as novel, directly regulated targets of *HNF4A* in β -cells, with their expression rising during differentiation—hinting at specialized roles in mature β -cell function. Silencing either gene impaired GSIS without affecting total insulin content, suggesting that their influence lies in the secretion process rather than insulin synthesis. While *HAAO* demonstrated clear transcriptional activation by *HNF4A*, *USH1C* showed more modest regulation. Together, these findings position *HAAO* and *USH1C* as intriguing new players in the fine-tuned orchestration of insulin release and

glucose homeostasis [7]. In liver cells, *HNF4α* similarly influences cytoskeletal organization but uniquely regulates amine catabolism and peptidase activity, reflecting its metabolic role. While both cell types share pathways such as actin filament regulation and GTPase activity, β -cells show stronger enrichment in insulin secretion and cAMP signaling, whereas liver cells are more linked to PI3K–Akt signaling [7]. These findings highlight *HNF4α*'s dual function in maintaining shared structural features and directing distinct functional specializations in pancreatic and hepatic tissues [7].

HNF6

HNF6, also known as *ONECUT1*, is a TF that plays a crucial role in the development and function of the pancreas and liver. In humans, *HNF6* has been found to be expressed in the Pancreas at 7–12 weeks of gestation [20, 22]. In the liver, *HNF6* is expressed in hepatoblasts (bipotent progenitor cells of the liver) during liver development and later in hepatocytes and biliary epithelial cells [89]. It regulates genes involved in bile duct formation and hepatocyte maturation, including *HNF1B* and *FOXA2*. *HNF6* coordinates signaling pathways, including those involving FGF and BMP, which are essential for liver bud growth and proliferation [84], while in the pancreas, *HNF6* is expressed in early pancreatic progenitors and later in the developing islets of Langerhans [90]. It controls the expression of key genes, including *NEUROG3* and *INS*, which are crucial for endocrine pancreas development [90]. Inactivation of the *HNF6* gene in mouse embryos resulted in impaired endocrine cell differentiation, with the expression of *NEUROG3* being almost abolished [91].

During mouse embryonic development, *HNF6* is present in the developing liver, Pancreas, and nervous system. It is initially expressed in the Liver around embryonic day 9 and continues until day 12.5, at which point expression decreases significantly. Around embryonic day 15, *HNF6* expressions reappear in both the liver and the extrahepatic biliary system [89, 92, 93]. *HNF6* continues to be highly expressed in the adult liver [89]. *Hnf6* and *Pdx1* interact during murine pancreas endocrine development, and the combined function of both TFs has proven vital for β -cell maturation and adaptation [90, 94–96]

Hnf6 knockout mice exhibit impaired liver development with defective bile duct morphogenesis, abnormal hepatocyte differentiation, and dysfunctional gluconeogenesis by a delayed expression of glucose-6-phosphatase (g6pc) [97–99]. Meanwhile, mice lacking *Hnf6* display significant defects in pancreatic development such as impaired formation of endocrine progenitors due to downregulation of *Neurog3* and *Pdx-1* [90, 91, 94, 100], a hypoplastic pancreas, and reduced insulin production, leading to glucose intolerance and diabetes-like symptoms [90, 91, 94, 100] (Table 1).

During hepatic differentiation of stem cells, the overexpression of *HNF6* enhances the expression of hepatic markers such as *HNF1B*, *ALB*, and *CYP3A4* [101]. On the other hand, *HNF6* is required during the early stages of hPSC pancreatic differentiation into pancreatic progenitors. Loss of *HNF6* disrupts the transition from multipotent pancreatic progenitors to endocrine progenitors, leading to reduced expression of *NEUROG3*, *PDX1*, *NKX6.1*, *NKX6.2*, *NKX2.2*, and *INS* [90, 102]. Computational analysis of transcriptional and open chromatin data from hPSC pancreatic differentiation revealed *HNF6* expression at the PE and PP stages alongside key pancreatic TFs [90].

HNF6-bound genes were enriched for pancreatic and endocrine development. It likely primes enhancers with *FOXA2*, *GATA6*, *PDX1*, and *NKX6.1* to activate pancreatic regulators [90].

Variants in *HNF6* are associated with an increased risk of T2D [102, 103]. GWAS have identified polymorphisms in the *HNF6* locus that affect β -cell function and insulin secretion [102, 104]. Rare homozygous loss-of-function mutations in *HNF6* have been linked to neonatal diabetes and pancreatic hypoplasia in humans [102, 103]. Further studies on human liver tissue indicate that *HNF6* is essential for the differentiation and function of cholangiocytes (bile duct cells) and hepatocytes such that abnormal *HNF6* expression has been implicated in cholestatic liver diseases, such as Alagille syndrome, due to defective bile duct morphogenesis in mice models [105].

HNF1B

HNF1B (*HNF1 β*), also known as transcription factor 2 (*TCF2*), is highly expressed during development in the foregut endoderm. *HNF1B* acts at two levels during organogenesis: first, in the early acquisition of hepatic and pancreatic fates from multipotent endoderm, and second, in the morphogenesis of tubular structures such as the biliary duct and gut epithelium [57, 106, 107]. A sequential cascade of *HNF1B*, *HNF6*, and *PDX1* was found to direct the differentiation of endodermal cells into pancreatic progenitors in mice [108]. From E14.5 until adulthood, *HNF1B* expression is confined to the embryonic ductal cords that later develop into the adult ductal cells [107, 109]. In humans, heterozygous mutations in *HNF1B* lead to MODY5 associated with pancreatic hypoplasia [56, 110, 111].

Mice models with heterozygous mutations develop normal pancreases [57]. *Hnf1b* null mice, on the other hand, have died in utero, proving a vital role for *Hnf1b* for normal visceral endoderm differentiation [112] and indicating a vital role for *hnf1b* during development. To model MODY5 in mice, conditional deletion in β -cells specifically exhibited an impaired glucose tolerance as early as 2 months of age with reduced insulin secretion compared with wild-type mice but upheld a normal insulin secretory response to arginine [113]. The β/β H1-KO islets also exhibited increased *Hnf1 α* and *Pdx-1*, decreased *Hnf4 α* mRNA levels, and a reduced glucose-stimulated insulin release. These results indicate that loss of *Hnf1b* disrupts the regulatory pathways necessary for glucose signaling in-cells and is necessary for glucose sensing or glycolytic signaling [113]. Further, β/β H1-KO model were normoglycemic and normoinsulinemic in both the fed and fasted states, which is different from human MODY5 patients, who manifest fasting plasma hyperglycemia [113]. In addition, postnatal inactivation of *Hnf1b* in mouse pancreatic ducts leads to chronic pancreatitis characterized by duct dilation, acinar cell loss, acinar-to-ductal metaplasia, and fat infiltration [114]. *Hnf1b* deficiency also promotes the formation and progression of pancreatic intraepithelial neoplasia and impairs pancreatic regeneration after injury, resulting in persistent metaplasia and initiation of neoplasia [114] (Table 1).

Stem cell models have been used to understand the function of *HNF1b*. A study showed that overexpression of *HNF1 α* in *HNF1B*-null ESCs can restore a normal endodermal-like differentiation program, suggesting that *HNF1 α* can functionally replace *HNF1B* and that the different developmental functions of these TFs are mainly due to

different expression patterns [115]. In another study, it was shown that the Neurog3-positive cells that are thought to be precursors of pancreatic endocrine cells arise from *HNF1B*-positive ductal cells during embryogenesis [116]. These investigators found that the majority of *HNF1B* immunostaining in endocrine cells and DNA binding activity in Pancreas occurred before embryonic day 14.5 [116]. Moreover, the expression of *HNF6* and subsequently *PDX1*, which is the earliest marker of pancreatic precursor cells, also relies on *HNF1B* [108]. Consequently, the sequential cascade activation of *HNF1B*, *HNF6*, and *PDX1* in the endoderm seems to regulate the development of pancreatic precursor cells.

MODY5-iPSCs derived from patients with heterozygous *HNF1B*^{S148L/+} mutations exhibited increased expression of several pancreatic progenitor TFs such as *PDX1*, *FOXA2*, *TCF2*, *ISL1*, *MNX1*, *REF6*, *GATA4*, and *GATA6*, when compared with those generated from control iPSCs [117]. To further elucidate the impact of the *HNF1B*^{S148L/+} mutation on the upregulation of these TFs, Teo et al. further discovered that the overexpression of mutant *HNF1B*^{S148L/+} in control iPSCs resulted in a compensatory upregulation of *PDX1* expression without affecting the expression of other upregulated TFs. Conversely, overexpression of wild-type *HNF1B* did not alter the expression of *PDX1* or other TFs [117]. This finding is in line with the conditional deletion in β -cells mouse model by Wang et al. [113]. The expression of *PAX6* TF has also been observed to be upregulated in *HNF1B*^{S148L/+} iPSC-derived progenitors by Teo et al. [117].

Another study revealed that homozygous KO of *HNF1B* results in failure of foregut and pancreatic progenitor development. Heterozygous KO of *HNF1B*, on the other hand, results in impairment of pancreatic progenitor and endocrine cell production. This could be attributed to impaired induction of key pancreatic developmental genes, including *SOX11* and *ROBO2* [118].

HNF1B is essential for the ventral endoderm to gain the competence necessary to transition into the hepatic lineage. The liver induction defect observed in *Hnf1b*^{-/-} embryos parallels that seen in *Foxa1/Foxa2* mutants, suggesting a common pathway in hepatic specification. Although it has been demonstrated that *Hnf1b* is not a direct target of FGF signaling, it may regulate downstream targets of the FGF signaling pathway. *Foxa1* and *Foxa2* were not strongly downregulated in the *Hnf1b* KO, showing that *Hnf1b* is not required for their initial induction, yet for their sustained expression and for the subsequent induction of other hepatic transcription factors [119]. In line with observations made during murine development, *Hnf1b* mutants in zebrafish exhibit an absence of both liver and pancreatic bud formation, coupled with abnormalities in gut endoderm [120]. These findings demonstrate that *Hnf1b* plays an evolutionarily conserved role in hepatic specification, underscoring its significance across vertebrate species.

HHEX

HHEX, also known as hemat homeobox or *PRH* (proline-rich homeobox), is a TF critically involved in the development of various tissues, including the liver and pancreas [121, 122]. In mice, *Hhex* is expressed in the ventral foregut endoderm by E8.5 [123]. It plays a critical role in the spatial positioning and fate determination of ventral endoderm cells during early organogenesis, influencing both liver and ventral pancreas development [124]. It is expressed in the ventral-lateral endoderm, where these organs emerge,

and regulates the proliferation and movement of endodermal cells beyond the cardiogenic mesoderm, a region that promotes liver development but inhibits pancreatic specification [123, 124].

In *Hhex*-null embryos, the hepatic diverticulum forms but shows reduced cell proliferation and fails to migrate properly, preventing liver bud formation and resulting in embryonic lethality [121, 124, 125]. Although liver specification is still induced, ventral pancreas specification fails entirely in *Hhex*-deficient embryos. Interestingly, when *Hhex*-null ventral endoderm is isolated before interacting with cardiogenic mesoderm and cultured in vitro, it can activate early pancreatic genes (Table 1). This suggests that *HHEX* does not directly control pancreas-specific gene expression but instead influences organ fate through morphogenetic regulation—by controlling endodermal proliferation and positioning relative to inductive mesodermal signals [124].

To investigate its role in later liver development, Hunter et al. created conditional *Hhex* KO mice and observed that the deletion of *Hhex* in the hepatic diverticulum caused embryonic lethality, a small cystic liver, loss of *Hnf4α* and *Hnf6* expression in hepatoblasts, and absence of the gallbladder and extrahepatic bile ducts. Further, deletion in the embryonic liver disrupted intrahepatic bile duct formation, leads to loss of *Hnf1b* in many biliary cells, and results in progressive polycystic liver disease in adults [126]. These findings demonstrate that *Hhex* is crucial at multiple stages of hepatobiliary development and plays a key role in regulating genes involved in hepatoblast differentiation and bile duct morphogenesis.

Hhex expression is negatively regulated by Sonic Hedgehog (Shh) signaling in a hESC model of pancreatic development, where it is downregulated alongside other epithelial markers such as *HNF4α*, *PAX6*, and *PTF1α* [127]. Recent findings in an iPSCs model identified *HHEX* as a “gatekeeper” of pancreatic fate, with its deletion redirecting differentiation toward liver and duodenum lineages. This pancreatic commitment driven by *HHEX* occurs in coordination with key transcription factors including *FOXA1*, *FOXA2*, and *GATA4* [128]. Furthermore, inhibition of all-trans retinoic acid signaling in a pancreatic endoderm model using hESCs also resulted in downregulation of *HHEX* [129].

Hhex plays a critical role in the embryonic development of vertebrate foregut-derived organs, including the pancreas, and continues to have functional importance in the adult pancreas. In adults, *Hhex* is specifically expressed in somatostatin-producing delta cells [130]. Loss of *Hhex* led to reduced somatostatin levels, impairing the paracrine inhibition of insulin secretion from β -cells [130]. Additionally, in β -cells, *Hhex* expression is repressed by *Lsd1* through H3K4me1/2-mediated chromatin modification, which helps maintain β -cell identity by preventing conversion to delta cells [131]. This dysregulation of paracrine signaling is thought to contribute to T2D by accelerating β -cell exhaustion [130]. In humans, *Hhex* RNA and protein are highly expressed in the pancreatic islets, exocrine acini, and ductal epithelium, but not significantly in liver parenchyma or colonic epithelium [132].

Further, *HHEX* is a key factor in various endocrine and metabolic disorders involving pancreas. Specific SNPs within *HHEX*, such as rs1111875, rs5015480, and rs7923837, are linked to a higher risk of T2D and gestational diabetes mellitus from GWAS [133]. A study by Dayeh et al. found that *HHEX* may exert its role in the pancreas by directly repressing *CDKN2A* [134]. Notably, the *CDKN2A* SNP rs10811661 frequently co-occurs

with *HHEX* SNPs, and both are well-established genetic risk factors for T2D. Additionally, *CDKN2A* and other genes showed altered DNA methylation not only at the CpG-SNP site but also at surrounding CpG regions [134]. These findings suggest that *HHEX*-associated SNPs may contribute to T2D pathogenesis by modulating local epigenetic regulation in pancreatic islets.

Forkhead box factors

Forkhead box A1, A2, and O1 (FOXA1, FOXA2, and FOXO1) play key roles in the development of the pancreas and liver (Table 1).

FOXA1

Forkhead Box A1 (FOXA1), also referred to as HNF3 α , is a pioneering member of the FOXA subfamily of TFs [135]. It has an important impact on organ development, mainly in endoderm-derived tissues such as the liver and pancreas [136]. As a pioneer factor, FOXA1 is unique in its capacity to bind to compacted chromatin and start transcriptional cascades through remodeling chromatin structure, enabling other TFs to access DNA [137, 138]. FOXA1 plays a critical and dynamic role in pancreas development by regulating the expression of Pdx1, a master gene required for pancreatic organogenesis [27, 139]. FOXA1 is coexpressed with FOXA2 and interacts dynamically with the distal and proximal enhancers of Pdx1, which regulates early pancreatic progenitor development and differentiation [27]. The pancreas of *Foxa1*^{-/-} mice is morphologically normal, but they have lower levels of GCG transcripts and die postnatally after birth [140, 141]. FOXA1 is essential for maintaining mature β -cell function and identity [142]. In *Foxa1*^{-/-} mice, defects in β -cell function are observed [143]. Moreover, mice deficient in both *Foxa1* and *Foxa2* exhibit severe metabolic disturbances, including hypoglycemia, hyperinsulinemia, impaired insulin production, and defective calcium signaling within β -cells [142]. These findings highlight the essential and partially overlapping roles of FOXA1 and FOXA2 in pancreatic development. Studies using hPSCs have shown that the deletion of FOXA1 and FOXA2 leads to a near-complete absence of significant pancreatic markers such as PDX1 and NKX6.1, emphasizing their essential role in pancreatic lineage commitment [136].

In liver, FOXA1 plays an essential role in the development and metabolic homeostasis [144]. FOXA1 is expressed in the foregut endoderm during embryogenesis and promotes liver specification by activating hepatic markers such as alpha-fetoprotein (AFP), albumin (ALB), and transthyretin, along with FOXA2 and other factors such as GATA4 [14, 26, 145]. While deletion of FOXA1 does not affect liver development because of functional redundancy with FOXA2, simultaneous ablation of FOXA1 and FOXA2 completely prevents liver bud formation and the expression of early hepatic genes [26, 145, 146]. FOXA1 in adult liver promotes chromatin accessibility, enabling the binding of hepatocyte-enriched TFs such as HNF4 α , which preserves hepatic identity and prevents liver failure [147]. Overexpression of FOXA1 suppresses triglyceride synthesis, increases fatty acid β -oxidation, and promotes ketogenesis, reducing hepatic lipid buildup, highlighting FOXA1's crucial roles in liver organogenesis, chromatin remodeling, and protection against metabolic liver disorders such as nonalcoholic fatty liver disease (NAFLD) [26, 148, 149]. FOXA1/2 depletion in HepG2 cells and hPSC-derived hepatic progenitors

impairs hepatic gene expression, including ALB, HNF4A, and T-box transcription factor 3 (TBX3), thereby reactivating stemness pathways and affecting liver development [150]. These findings emphasize the crucial role of FOXA1 in directing endodermal cells toward a hepatic fate while preserving their differentiated state by inhibiting nonhepatic transcriptional pathways [150].

FOXA2

Forkhead Box A2 (FOXA2) has a wide expression in many tissues with distinct functions [144]. It is among the earliest TFs expressed during the formation of the pancreas and continues to be present in all pancreatic cell types [151]. In human pancreatic development, FOXA2 expression begins around the fourth week of gestation and persists thereafter [20–22]. As FOXA2 is expressed early from the endoderm stage and increases during the formation of endocrine cells, it remains low in exocrine and ductal lineages [151, 152]. Previous studies have shown that FOXA2 regulates the expression of several TFs and genes critical for the development of pancreatic endocrine cells and the proper functioning of β -cells [153, 154]. Studies in mice have shown that FOXA2 is essential for early embryonic development, with its knockout leading to early lethality and malformations in the foregut and neural tube [155–157]. Other mouse studies also indicate that *Foxa2* plays a critical role in islet formation and β -cell function [27, 142]. Additionally, mice lacking *Foxa2* specifically in β -cells develop hyperinsulinemic hypoglycemia [158, 159]. In humans, heterozygous mutations of FOXA2 have been linked to a range of issues including hyperinsulinemia, hypoglycemia, hypopituitarism, and developmental defects of endoderm-derived organs [160, 161]. Moreover, a case identified a patient with a form of monogenic diabetes due to a heterozygous missense mutation in FOXA2 [162]. In hPSC studies, one research report used FOXA2 knockout hESCs (*FOXA2*^{-/-} hESCs) to investigate the role of FOXA2 during pancreatic progenitor differentiation [163]. To further explore FOXA2's involvement in β -cell development and diabetes progression, another recent study generated iPSCs from a patient carrying a heterozygous FOXA2 deletion (*FOXA2*^{+/-} iPSCs) as well as *FOXA2*^{-/-} iPSC lines [164]. Their findings revealed that several critical genes necessary for pancreatic development are dysregulated in pancreatic cells derived from these *FOXA2*^{+/-} iPSCs and *FOXA2*^{-/-} iPSCs [164]. Moreover, the number of INS⁺ and GCG⁺ cells generated from *FOXA2*^{+/-} iPSCs is significantly reduced, and these cell types are nearly absent in the complete absence of FOXA2 [164]. Moreover, findings in other studies revealed that absence of FOXA2 during differentiation of iPSCs into pancreatic islets results in the upregulation of several miRNAs that target crucial genes essential for both exocrine and endocrine pancreatic development [165, 166]. Moreover, loss of FOXA2 in iPSCs disrupts lncRNA expression during pancreatic differentiation, with many downregulated lncRNAs strongly correlating with key pancreatic genes affected by FOXA2 deficiency [167]. These findings indicate that FOXA2 plays a pivotal role in human pancreatic development and function by regulating key transcriptional and post-transcriptional networks essential for endocrine cell differentiation and β -cell identity, with its deficiency leading to impaired islet formation and diabetes-related phenotypes.

In the liver, FOXA2 is also involved in the development and function. It was initially discovered for its ability to bind gene promoters and regulates the expression of

α 1-antitrypsin and transthyretin [168, 169]. Foxa2 is essential for enabling chromatin access by the glucocorticoid receptor (GR), allowing for maximal activation of target genes during fasting [170]. Since mice models lacking *Foxa2* die shortly after birth owing to defects in the notochord, a Cre-LoxP system was developed that preserves Foxa2 expression in the axial mesoderm while deleting it from the foregut endoderm after day 8.5 [169]. This model exhibited normal initiation and progression of liver development, attributed to the compensatory function of the related gene, Foxa1 [169]. However, embryos with a double KO of Foxa1 and Foxa2 failed to survive beyond day 10 of development, highlighting the critical roles of both genes in hepatic specification [26]. Additionally, FOXA2 has been shown to regulate liver function by controlling lipid metabolism and ketogenesis during fasting [171]. Through genomic mapping and tissue-specific gene knockout studies, it has been recently demonstrated that Foxa2 regulates numerous genes involved in bile acid metabolism, including those responsible for conjugation, detoxification, and transport across the sinusoidal and canalicular membranes of hepatocytes [172]. As a result, hepatocyte-specific deletion of Foxa2 in mice causes mild hepatic cholestasis [172]. Most of these findings are based on animal models, but a study on hepatocytes derived from human iPSC lacking FOXA2 showed defects in the development and function of iPSC-derived hepatocytes, highlighting the essential role of FOXA2 in liver development and function [173]. Together, these studies underscore the significant role of FOXA2 in pancreatic endocrine differentiation and hepatic development and its potential involvement in diabetes pathogenesis.

FOXO1

The role of FOXO1 has been reported in pancreatic β -cells, particularly in maintaining beta cell identity [174, 175]. A previous study demonstrated that, during mild hyperglycemia, Foxo1 translocates from the cytoplasm to the nucleus of β -cells, suggesting a role in preserving β -cell function [176]. Loss of Foxo1 in β -cells renders them more susceptible to metabolic stress and reduces the expression of key genes such as Pdx1, Mafa, and insulin [176, 177]. Furthermore, Foxo1 has been shown to suppress β -cell proliferation and differentiation by inhibiting Pdx1 transcription [178]. In addition, Foxo1 protects β -cells from oxidative stress by directly regulating Mafa and NeuroD [179], and Foxo1-KO db/db mice showed decreased Neurog3 expression [177]. These findings highlight the critical role of Foxo1 in pancreatic β -cell development, though further research is needed to clarify its function in the human pancreas.

In the liver, FOXO1 directly regulates gluconeogenesis and plays a significant role in hepatic lipid metabolism and autophagy. It has been shown that FOXO1 plays a key role in regulating hepatic insulin responses, particularly during fasting. In animal models, constitutive expression of Foxo1 in the liver results in elevated fasting blood glucose [180], while liver-specific deletion of Foxo1 causes fasting hypoglycemia [181]. During fasting, Foxo1 is dephosphorylated at Akt sites, translocates to the nucleus, and activates the transcription of gluconeogenic enzymes, G6Pc and PEPCK [182], thereby increasing hepatic glucose production. In contrast, insulin signaling in the fed state activates PI3K and Akt, which phosphorylates Foxo1 at specific sites (Thr24, Ser253, and Ser316), leading to its nuclear exclusion and inactivation. This suppresses gluconeogenesis and helps maintain glucose homeostasis [183]. Liver-specific deletion of Akt causes chronic

hyperglycemia, but this is completely normalized when Foxo1 is also deleted in the liver [183]. Mice lacking both Akt and Foxo1 can regulate blood glucose levels normally during both fasting and feeding, indicating that Foxo1 is a key driver of glucose production. These findings suggest that Akt's primary role in insulin signaling is to suppress Foxo1 activity and limit gluconeogenesis in the fed state. Additionally, liver-specific FOXO1 knockout mice develop fasting hypoglycemia [181]. Importantly, Foxo1 does not interfere with insulin-stimulated anabolic pathways such as glycogen and lipid synthesis [183].

FOXO1 activity in regulating blood glucose is influenced by mechanisms beyond Akt phosphorylation. Acetylation status plays a key role, with deacetylation by Sirt1 and class IIa HDACs (activated by AMPK during fasting) enhancing FOXO1's transcriptional activity and promoting gluconeogenesis [184]. Additional regulatory mechanisms include XBP-1, which increases insulin sensitivity by binding FOXO1 and targeting it for degradation [185], and O-GlcNAc modification [186, 187], which boosts FOXO1 activity independently of nuclear translocation and paradoxically upregulates gluconeogenic genes in response to hyperglycemia [188].

FOXO1 also plays a critical role in hepatic lipid metabolism, particularly in regulating very-low-density lipoprotein (VLDL) production and clearance during fasting. It promotes the expression of microsomal triglyceride transfer protein (MTP) and apolipoprotein C-III (ApoC-III), which enhance VLDL secretion and inhibit its clearance, respectively [189]. Normally, insulin inactivates FOXO1 after feeding to prevent excess lipid and glucose in the blood, but in insulin resistance, this regulation is impaired, contributing to both hyperglycemia and hypertriglyceridemia [190].

In addition, hepatic FOXO1 promotes autophagy through both transcription-dependent and transcription-independent mechanisms. Under nutrient stress, acetylated cytosolic FOXO1 interacts directly with Atg7 to stimulate autophagosome formation [191]. This activity supports adaptation to fasting and contributes to lipid degradation, preventing hepatic steatosis [192].

Moreover, several key FOXO1-related studies using human iPSC models have highlighted its role in controlling endocrine cell fate and hepatic function. Using pancreatic endoderm derived from human iPSCs, temporary inhibition of FOXO1 enhanced the production of NGN3⁺ endocrine progenitor cells and hormone-secreting cells, leading to an increased yield of insulin-producing cells [193]. Additionally, in human iPSC-derived gut organoids, inhibiting FOXO1—either through a dominant-negative mutant or shRNA—reprogrammed gut endocrine progenitors into insulin-positive cells. These β -like cells were capable of secreting C-peptide in response to glucose stimulation and demonstrated functional activity both in vitro and after transplantation [194]. In a study using human iPSC-derived hepatocytes to model hepatic insulin resistance, FOXO1 emerged as a critical regulator of gluconeogenic genes in these liver cells [195].

GATA4 and GATA6 factors

Among the several TFs that play a crucial role in the intricate regulatory mechanisms governing pancreas and liver development, GATA regulatory proteins are a highly conserved family of six zinc finger TFs that are essential in embryonic development for several endoderm- and mesoderm-derived organs [196–199]. They are involved in diverse

processes such as germ layer specification, organ formation, and cell lineage determination. While GATA1, GATA2, and GATA3 are essential for hematopoiesis [196, 200, 201], GATA4, GATA5, and GATA6 contribute to the development of mesoderm and endoderm derived organs, including the heart, liver, and pancreas [197, 198, 202] (Table 1).

In the pancreas, GATA4 and GATA6 are initially co-expressed in the pancreatic progenitors but gradually localize to distinct regions [202]. GATA4 becomes confined to the exocrine compartment, while GATA6 is primarily expressed in the endocrine compartment [203, 204]. During the early stages of human pancreatic development GATA4 is expressed, specifically between 4 and 5 weeks of gestation, coinciding with the expression of PDX1 [21]. This timing suggests that GATA4 may play a role in the formation of the human pancreas [21]. As development progresses, GATA4 expression significantly decreases in pancreatic progenitor cells and becomes restricted to mature acinar cells, a pattern that is similarly observed in mice [21]. Studies in mice have indicated that *Gata4* plays a role in pancreatic development. Mice lacking *Gata4* (*Gata4*^{-/-}) die before the pancreas begins to form owing to abnormalities in extraembryonic tissue development [205, 206]; however, when embryonic lethality was rescued in this mouse model, *Gata4*^{-/-} mice exhibited absence of the ventral pancreas [207]. On the contrary, heterozygous mice (*Gata4*^{+/-}) appear normal and do not display any obvious developmental defects [205, 206]. Moreover, in studies on rodents, simultaneous deletion of *Gata4* and *Gata6* in pancreatic progenitor cells results in pancreatic agenesis in newborn mice [208, 209]. Diabetes caused by intragenic GATA4 mutations or deletions causing GATA4 haploinsufficiency have been described in many patients [199, 210]. GATA6 also shows an important role in mouse pancreas development with an expression in pancreatic progenitors [207]. Heterozygous-null mice of GATA6 have no phenotype; on the other hand, GATA6 homozygous null mice show embryonic lethality during the gastrulation stage, emphasizing its role in mouse pancreatic organogenesis [211]. Furthermore, loss of GATA6 in hPSCs disrupts their in vitro differentiation into β -like cells and impairs the functionality of those cells [212–214]. The critical role of GATA4 and GATA6 in human pancreas development has also been emphasized in genetic studies of pancreatic agenesis [215]. GATA6 haploinsufficiency is the leading cause of pancreatic agenesis [215], while GATA4 haploinsufficiency has been identified in a smaller subset of affected individuals [199]. The first clinical study to link GATA6 to Pancreatic development was conducted in 2011, when multiple GATA6 mutations were found in patients with pancreatic underdevelopment [215].

Molecular and genetic studies have indicated that GATA TFs also play a regulatory role in liver development [216, 217]. GATA4 and GATA6 are both essential for liver bud expansion during embryonic development, although they play overlapping roles in hepatic specification [207, 218]. GATA4 expression begins at the 4-somite stage (embryonic day E8.0), appearing in the ventral foregut endoderm and cardiac mesoderm [207]. By the 16-somite stage, GATA4 remains expressed in the foregut endoderm, including the Liver bud and surrounding septum transversum mesenchyme. However, by the 25-somite stage (E10.0), its expression becomes selectively downregulated in hepatoblasts [207, 218, 219], indicating that GATA4 functions primarily during the earliest phases of hepatocyte specification. During this critical window, GATA4 is necessary for the full activation of certain hepatic genes, such as ALB and HNF4 [207]. GATA6, on the

other Hand, is first expressed slightly later, between the 6- and 8-somite stages, in the ventral foregut endoderm [218]. By the 12-somite stage, it appears in both the liver bud and septum transversum mesenchyme, and unlike GATA4, GATA6 expression continues in hepatocytes through the 25-somite stage. Investigating the liver-specific roles of GATA4 and/or GATA6 in knockout mice has been challenging owing to early embryonic death, probably a consequence of extraembryonic endoderm dysfunction [205, 211].

Additionally, a study developed human iPSC lines from individuals with GATA6 haploinsufficiency, a condition linked to pancreatic agenesis. During differentiation, these GATA6-deficient iPSCs showed impaired activation of key pancreatic transcription factors, including PDX1, SOX9, and HNF1B. This offers clear evidence that GATA6 is critical for directing human cells toward the pancreatic lineage [212].

Overall, GATA4 and GATA6 are key regulators of endodermal organogenesis, coordinating gene expression critical for the proper formation and function of the liver and pancreas.

PROX1

PROX1 TF is highly conserved among vertebrates and is crucial for development, influencing cell fate decisions and promoting progenitor cell formation in various organs [220]. The activity of this 737-amino-acid-long protein is critical during embryogenesis and is essential for the development of the lymphatic vasculature [221, 222], differentiation of lens fiber cells [221], specification of retinal cell types [223], pancreatic development [224–227], and liver morphogenesis [228].

The homeodomain TF family includes key regulators essential for β -cell development and maintenance [229, 230]. Prox1 is one of these homeodomain TFs that contains two highly conserved regions: a homeobox domain and a prospero domain. Prox1 expression is present in the mouse pancreatic region even before the pancreatic bud emerges [224]. Specifically, Prox1 expression has been reported to be highly expressed in all endocrine progenitors (Neurog3+ cells) within the developing pancreas [225], islet cells, and ductal cells within the pancreas of mouse embryos, as well as in most epithelial cells of the adult mouse pancreas, except for acinar cells [226, 227]. In the adult pancreas, strong Prox1 expression is retained only in islet cells including α -cells, δ -cells, PP cells, and ϵ -cells [226]. To explore whether prolonged Prox1 expression affects β -cell development or maintenance, a transgenic model indicated that elevated Prox1 levels significantly hinder β -cell maturation and expansion and causes severe hyperglycemia in mice [225]. Moreover, pancreas-specific deletion of Prox1 leads to premature differentiation of acinar cells [226], defective ductal morphogenesis during embryonic stages, and increased acinar cell apoptosis along with mild chronic inflammation in postnatal stages [227].

During mouse liver organogenesis, Prox1 is initially expressed during early embryonic development at embryonic day 8.5 (E8.5) in the endodermal cells and continues to be present in adult hepatocytes [224, 231]. Its expression pattern is highly conserved across mouse and human embryos [231]. Alongside albumin and α -fetoprotein (AFP), Prox1 is one of the earliest markers of liver development [224]. In the adult liver, Prox1 is found in hepatocytes but is absent in bile duct epithelial cells and non-parenchymal cells, including Kupffer cells, hepatic stellate cells, sinusoidal endothelial cells, and myofibroblasts [231]. Prox1 is essential for hepatocyte migration, and its absence results in the

development of a smaller liver with fewer clustered hepatocytes [228]. Lim et al reported that Prox1 is a key factor in maintaining hepatocyte identity by suppressing master regulators of alternative cell fates during reprogramming [232]. Liver-specific Prox1 knockout mice displayed glucose intolerance independent of obesity and exhibited hepatic damage linked to excessive reactive oxygen species (ROS) production [233].

According to meta-analysis of a genome-wide association study (GWAS), the rs340874 SNP has been identified in the PROX1 gene as being linked to T2D [234]. Another study reported that individuals carrying this variant exhibit greater glucose intolerance and increased visceral fat compared with noncarriers [235]. Prox1 heterozygous adult mice develop obesity, elevated serum insulin levels, and hepatic lipid accumulation [236], on the other hand, pancreas-specific Prox1 inactivation do not induce a diabetic phenotype in mice [227]. In this case, it appears that obesity is the primary driver of insulin resistance in both Prox1 heterozygous mice and individuals carrying the rs340874 SNP in PROX1 [227].

Taken together, these findings indicate that PROX1 is essential for the proper development and function of both the pancreas and liver, influencing cell fate decisions and organ morphogenesis. Dysregulation of PROX1 expression in these organs can lead to metabolic dysfunction, such as impaired β -cell maturation in the pancreas and hepatic damage, highlighting its potential role in diseases such as T2D and obesity.

Glucose sensing genes

Glucose transporters 1, 2, and 3 (GLUT1, 2, and 3)

Knowing that glucose is the primary fuel for cells in the body, glucose regulation and metabolism are essential for proper body functionality. A set of glucose sensing systems allow the appropriate response to the fluctuation of body glucose levels and its passive transport [237], known as the glucose transporters family (GLUTs). Their malfunction or dysregulation of blood glucose levels has a great impact in causing serious diseases such as diabetes and metabolic syndrome, highlighting their crucial role in glucose transport and metabolism. In this review, the focus will be on GLUT2 that is encoded by the *SLC2A2* gene, located at q26.2 of chromosome 3 [238]. GLUT2 is mainly expressed in the liver, pancreatic β -cells, and other tissues as kidney and intestine. RNA-seq analysis of 27 different tissues from 95 participants showed that the *SLC2A2* encoding gene has the highest expression in the liver with the duodenum and small intestine following [239]. It is also known that GLUT2 is a low-affinity glucose transporter (K_m 15–20 mmol/l) [240, 241].

Previous studies suggest notable differences between rodent and human pancreatic islets, concerning the expression and function of *SLC2A2*. In rodent β -cells, *Slc2a2* has been established as the primary glucose transporter, supported by evidence from impaired glucose tolerance observed in *Slc2a2* knockout mice [242–244]. However, its role in human islets has been a subject of debate [245]. In human pancreatic islets, *SLC2A1* and *SLC2A3* have been suggested as the primary glucose transporters with high affinity to glucose, with *SLC2A1* being more dominant. When *SLC2A1* reaches saturation, *SLC2A2* facilitates glucose responsiveness under conditions of relatively high glucose levels [245–249]. *SLC2A2* protein is expressed during human pancreatic development in adult pancreatic islets but at lower levels compared with *SLC2A1* and

SLC2A3 [245, 247, 250–252]. However, there is debate about the role of SLC2A2 in glucose uptake in human β -cells. Examination of 207 human islets revealed that SLC2A2 is expressed at lower levels than SLC2A1 [253]. Another study proposed that SLC2A2 plays a significant role in glucose uptake in human β -cells [254]. Simultaneous knockdown of SLC2A1 and SLC2A2 significantly decreases glucose transport and eliminates glucose-stimulated insulin secretion (GSIS) [254]; however, individual KD of either SLC2A1 or SLC2A2 showed no significant effects [254]. These findings suggest that the presence of either SLC2A1 or SLC2A2 is sufficient to maintain GSIS in human β -cells, which aligns with previous studies demonstrating the ability of human SLC2A1 or SLC2A2 genes to restore GSIS in mouse β -cells lacking *Slc2a2* [255].

Although several studies have suggested that SLC2A2 is not required for the functionality of human β -cells [245, 247], the importance of SLC2A2 in human β -cells is clearly demonstrated by the fact that mutations in *SLC2A2* are associated with neonatal diabetes [256–263]. Recent data further support the potential significance of SLC2A2 in adult human β -cells, as knockdown (KD) experiments in human islets have demonstrated impaired insulin secretion [264]. Moreover, SNPs in *SLC2A2* have been associated with the progression from impaired glucose tolerance to T2D [265]. Furthermore, *SLC2A2* variants have been linked to impaired fasting glucose and diabetes [234, 264, 266–269]. These data suggest that the reduced expression of SLC2A2 in islets may play a role in the impaired insulin secretion observed in individuals with diabetes.

Although the role of SLC2A2 in human pancreatic β -cells is still controversial, in human liver, SLC2A2 is the main and most abundant glucose transporter, representing >97% of all glucose transporters [238] and regulates glucose-sensitive genes. GLUT2 in the hepatocytes has bidirectional function, allowing the uptake of glucose for processes such as glycolysis and glycogenesis [270]. Additionally, GLUT2 governs the release of glucose out from the hepatocytes during gluconeogenesis, highlighting the importance of this glucose sensing transporter in glucose metabolism and regulation. Inactivation of *Glut2* specifically in mouse liver leads to inhibition of glucose uptake but does not suppress glucose output, indicating the presence of an alternative pathway for glucose release. This alternative pathway has been found to be associated with a membrane traffic-based mechanism starting in the endoplasmic reticulum [271–273]. Furthermore, *Glut2* inhibition in hepatocytes results in an impairment in the GSIS, suggesting the presence of an axis between the liver and β -cells [240, 274]. SLC2A2 mutation is associated with glycogen accumulation in hepatocytes; therefore, patients with Fanconi–Bickel Syndrome (FBS) develop hepatomegaly. On the contrary, GLUT3 is not detectable in human liver [275], while GLUT1 has a low expression in hepatocytes but serves as the primary glucose transporter in nonparenchymal liver cells [276]. However, GLUT1 levels are significantly elevated in pathological conditions such as non-alcoholic steatohepatitis (NASH), alcoholic liver disease (ALD) [277], and hepatocellular carcinoma (HCC) [278]. Moreover, GLUT1 has been shown to play a role during postnatal liver development and organogenesis of the liver [279]. Mouse embryos with a homozygous antisense-Glut1 (GT1AS) genotype did not survive gestation, and decreased Glut1 expression during development was linked to increased apoptosis. These findings suggest that Glut1 deficiency may contribute to embryonic abnormalities associated with maternal diabetes-induced hyperglycemia [279].

Glucokinase (GCK)

One member of the hexokinase family is glucokinase (GCK) also known as hexokinase IV [280]. The gene encoding human GCK is located on chromosome 7 that covers ten exons [281]. Being an active enzyme, GCK has a 52 kDa molecular weight, being composed of 465 amino acids that configure two globular domains, one small and one large domain [282]. This unique conformation of GCK forms a cleft between the two domains, allowing glucose to settle and thus highlighting that this enzyme exhibits glucose sensing characteristics [283]. GCK was first identified in rat liver and pancreatic islet tissues [284, 285]. Later studies expanded these findings by showing GCK expression in a variety of other tissues, including pancreatic acinar cells, brain, lungs, kidney, and spleen [286, 287]. In one study, GCK expression in human fetal Pancreatic tissue has been shown to be at week 17–19 of gestation [287], but in a different report its expression has been documented after gestational week 15 [251]. Supporting these observations, recent data using pancreatic cells derived from hPSCs indicate that GCK is mainly expressed during the mature stages of pancreatic cell development [288, 289]. At the mRNA level, studies have shown that GCK expression reaches its highest levels during Pancreatic differentiation, remaining elevated from day 18 until differentiation is completed on day 29 [288]. As a key TF for pancreatic development and the differentiation of progenitor cells into pancreatic β -cells [290], Pdx1 plays a role in regulating the activity of the GCK promoter in pancreatic β -cells [291]. GCK differs from other hexokinases because it exhibits an exceptionally low affinity for glucose and is not inhibited by its metabolic end product, glucose-6-phosphate (G6P). These distinctive features make GCK the primary glucose sensor in many vertebrate species, including humans [292].

GCK is vital for glucose metabolism, helping to maintain blood sugar levels within a normal range. The critical role of GCK in glucose metabolism was firmly established in 1992 when a heterozygous GCK-inactivating mutation was found to cause a mild form of monogenic diabetes known as MODY2 [293]. As a key metabolic enzyme in the pancreas, GCK catalyzes the phosphorylation of glucose to G6P in an adenosine triphosphate (ATP)-dependent manner. G6P then enters glycolysis and the Krebs cycle, leading to an increase in cellular ATP production and thus raising the ATP/adenosine diphosphate (ADP) ratio [294]. The elevated ATP/ADP ratio inhibits ATP-sensitive K^+ (K_{ATP}) channels, reducing K^+ efflux and causing membrane depolarization [295]. This depolarization triggers the opening of voltage-dependent Ca^{2+} channels, allowing an influx of Ca^{2+} into the cytosol [294]. The resulting increase in intracellular Ca^{2+} concentration, along with other essential coupling factors, stimulates the exocytosis of insulin-containing granules [296]. This process involves coordination between the endoplasmic reticulum, Golgi apparatus, and secretory machinery to release insulin from the β -cells into the bloodstream.

On the other hand, the liver regulates blood glucose levels through more complex mechanisms than the pancreatic islets. GCK facilitates this by converting glucose into G6P, thereby supporting glycogen storage and reducing glucose concentration in the portal circulation [297]. During fasting, the liver is also a key source of endogenous glucose production, helping to maintain normal glucose levels [298]. Consequently, GCK must be active after meals to aid in glucose clearance but remain inactive during fasting to avoid unnecessary glucose conversion to G6P [298, 299]. The expression of GCK in

the liver is strongly dependent on insulin and is completely suppressed in insulin-deficient rats [300, 301].

Other than MODY2, homozygous GCK-inactivating mutations result in the severe condition of permanent neonatal diabetes mellitus (PNDM) [302, 303]. Conversely, mutations that enhance GCK activity lead to hyperinsulinism (GCK-HI), a disorder characterized by excessive insulin secretion [304]. There are more than 700 identified mutations in the GCK gene, with about 80 of them studied in vitro [281, 305, 306], with the majority of GCK mutations having unknown function. β -cell-specific KO mice show severe hyperglycemia leading to death early after birth [307]. On the other hand, mice lacking liver-specific GCK exhibited dysfunction in glycogen synthesis and insulin secretion [307]. Advancements in hPSC technology facilitated the generation of hiPSC from patients with MODY2 and PNDM caused by heterozygous and homozygous mutations in the GCK gene, respectively [308] making it a great tool for disease modeling [280]. These findings indicate the essential role of GCK in glucose metabolism by regulating insulin secretion in pancreatic β -cells and promoting glycogen synthesis in the liver, with mutations in the *GCK* gene leading to different forms of diabetes, highlighting its essential function in both organs.

Crosstalk and interorgan signaling between the pancreas and the liver

Communication between tissues plays a crucial role in regulating organ function, thus establishing interorgan signaling assists in coordinating their metabolic responses. Interorgan signaling through hormonal and metabolic factors between pancreatic β -cells and multiple distal metabolic organs, such as liver, adipose, intestine, and skeletal muscle, balance islet function. This interaction is particularly significant for the pancreas and the liver, as both organs contribute to glucose regulation and lipid metabolism. Dysfunction and eventual failure of β -cells are key contributors to the development of diabetes. This process is marked by impaired insulin secretion, endoplasmic reticulum (ER) stress, and progressive loss of β -cells [309–311]. In addition to the well-defined intra-islet signaling and self-regulation, interorgan communication also regulates islet functionality. The interaction between insulin-producing β -cells and liver cells highlights how the liver senses the decline in β -cell function and mass, releasing signaling molecules to communicate with the pancreas and modulate islet homeostasis and dysfunction (Fig. 2). This exchange can either enhance or disrupt islet function. Here, we discuss the hepatokines and circulating factors from the liver, their role in communication with beta cells, and the implications for the pathogenesis of diabetes. In response to variations in the metabolic state, these hepatokines and metabolic mediators are secreted, highlighting their roles in metabolic dysfunction [312].

Communication from liver cells to pancreatic cells

Kisspeptin, encoded by the *KISS1* gene, is expressed in various tissues and was originally identified as a tumor suppressor [313, 314]. Additional roles for kisspeptin and its receptor, KISS1R, have been reported in hormonal regulation and pancreatic islet activity [313]. Notably, kisspeptin production in the liver can inhibit GSIS from β -cells [315]. This liver–pancreas communication is disrupted in T2D models, where elevated

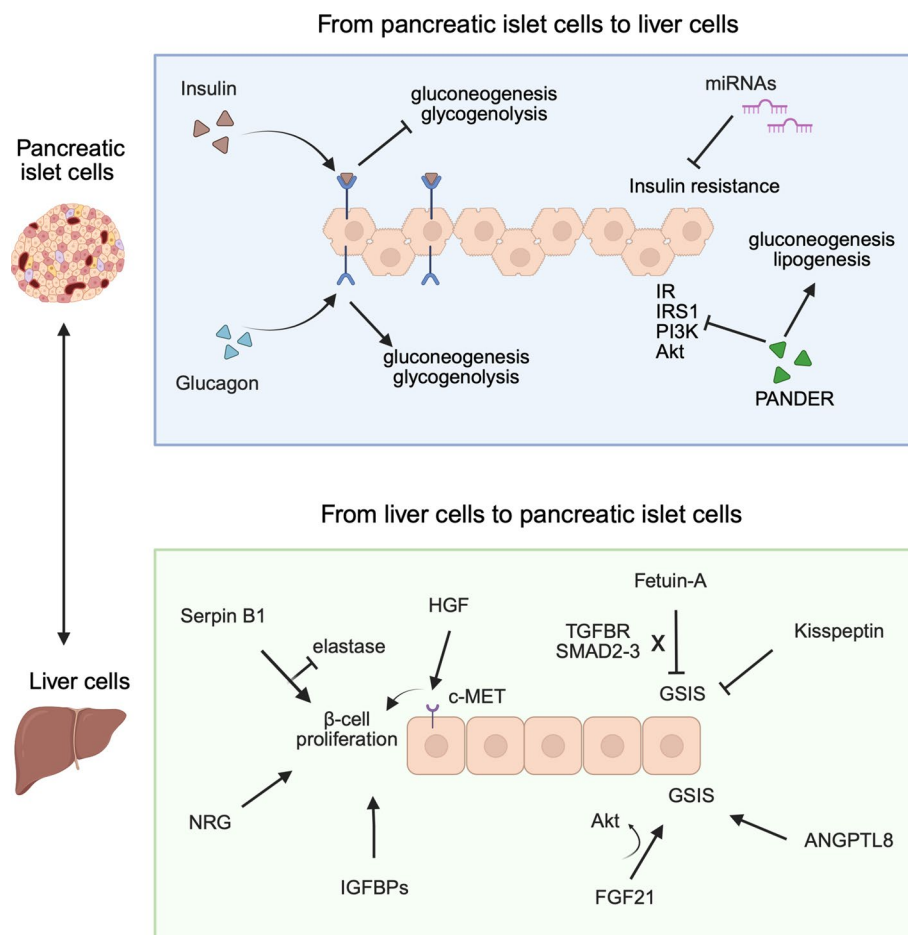


Fig. 2 Interorgan signaling between pancreas and liver. The pancreas communicates with the liver through multiple signals that regulate hepatic function, and metabolic adaptation. Pancreatic endocrine hormones such as insulin and glucagon, secreted by β - and α -cells, respectively, play critical roles in controlling hepatic glucose metabolism by modulating gluconeogenesis, glycogen synthesis, and lipid metabolism. In the context of insulin signaling pathways, the pancreas also secretes factors, such as exosomes carrying microRNAs (miRNA-26a and miRNA-29) and peptides (PANDER) that can enhance insulin sensitivity and inhibit insulin stimulated proteins respectively. The liver also secretes a variety of factors, known as hepatokines, that influence pancreatic β cell proliferation, function, and survival. During development and in response to certain metabolic factors, hepatokines such as HGF, IGFBPs, NRG, and serpin B1 modulate β -cell mass and proliferation. Other liver-derived signals affect the pathways regulating glucose stimulated insulin secretion in β cells such as Fetuin-A, Kisspeptin, FGF21, and ANGPTL8. The figure was created using BioRender

glucagon levels lead to increased kisspeptin production, which in turn contributes to reduced insulin secretion [315].

Fetuin-A, a member of the fetuin family, is a protein secreted from the liver that inhibits its glucose-stimulated insulin secretion in adult human islets [316]. In a subsequent study, they elucidated the underlying mechanism of this inhibition [317]. Fetuin-A was found to impede the functional maturation of pancreatic islets by disrupting the TGFBR-SMAD2/3 signaling pathway. Additionally, it downregulates the transcription factor FOXM1 and its downstream target genes, thereby limiting β -cell adaptive proliferation [317].

Angiopoietin-like protein 8 (ANGPTL8), also referred to as lipasin or betatrophin, is a hormone that has a role in regulating serum triglyceride levels and is likely involved

in the metabolic shift between fasting and refeeding [318]. Additionally, in terms of β -cell function, ANGPTL8 has been observed to promote the proliferation of pancreatic β -cells and enhance insulin secretion in insulin-deficient mouse models of insulin resistance [319].

Fibroblast growth factor 21 (FGF21) is a key hormone belonging to the FGF family that is considered to be a major regulator of metabolism, primarily produced by the liver in response to fasting or a ketogenic diet [320]. One of the key targets of FGF21 are pancreatic islets. In diabetic animal models, FGF21 has been shown to enhance β -cell function and promote cell survival [321]. Mice lacking FGF21 (FGF21-KO) exhibit abnormal islet architecture and impaired GSIS, suggesting that FGF21 plays a critical role in islet physiology, possibly through modulation of growth hormone (GH) signaling [322]. Additionally, reduced FGF21 expression has been observed in db/db mice, a model of obesity-induced diabetes [323]. This downregulation implies that FGF21 is involved in preserving insulin homeostasis and β -cell integrity. In these mice, deletion of FGF21 exacerbates lipid-induced β -cell dysfunction and suppresses GSIS, whereas overexpression of pancreatic FGF21 enhances insulin gene expression, improves GSIS, preserves islet structure, and reduces β -cell apoptosis. Early research has shown that FGF21 can enhance pancreatic β -cell function and survival by stimulating the Akt signaling pathway [321]. Mechanistically, FGF21 appears to act by upregulating TFs involved in insulin gene expression and SNARE proteins, while activating the PI3K/Akt pathway within islets [323]. Additional mechanisms include: (i) increased expression of carnitine palmitoyltransferase 1 (CPT1) and decreased levels of SREBF1 and fatty acid synthase (FASN), thereby reducing lipid accumulation in β -cells and (ii) restoration of genes essential for β -cell identity and function—PDX1, INS, and MafA [324].

Insulin-like growth factor binding proteins (IGFBPs) are produced in various tissues, with the liver being the main source of circulating IGFBPs, primarily in response to GH [325]. Recent studies have highlighted the role of several IGFBPs in regulating glucose metabolism and the progression of nonalcoholic fatty liver disease (NAFLD). IGFBPs are also essential modulators of insulin signaling. Low serum levels of IGFBPs have been linked to the development of T2D, whereas increasing IGFBP levels in mice have been shown to enhance insulin sensitivity [326]. Furthermore, IGFBP1 plays a significant role in β -cell regeneration across multiple species. In zebrafish, mice, and human pancreatic islets, IGFBP1 has been found to stimulate α -to- β -cell transdifferentiation. In vitro experiments demonstrated that culturing mouse and human islets with recombinant IGFBP1 increased the number of cells co-expressing insulin and glucagon, indicating the activation of β -cell regeneration pathways [327].

Hepatic growth factor (HGF) was originally identified as a mesenchyme-derived regenerative factor and has been shown to play a role in liver regeneration, especially after liver damage, in addition to enhancing cell survival and other tissue regeneration by acting through its receptor c-MET [328, 329].

Beyond regeneration triggered by injury, it is well established that obesity and/or insulin resistance (IR) also stimulate β -cell proliferation [330, 331]. In order to maintain glucose homeostasis, insulin resistance in the liver stimulates changes in its secretome, which enhances β -cell proliferation [332]. Serpin B1 has been classified as a hepatocyte-derived secretory protease inhibitor protein that stimulates β -cell regeneration through

inhibiting elastase [333]. The synthetic specific inhibitor of serpin B, sivelestat, also exhibited this regenerative function in cultured and transplanted pancreatic islets [333, 334].

Neuregulin (NRG) growth factors are part of a complex protein family structurally related to the epidermal growth factor (EGF) [335, 336]. NRG1 is a growth factor characterized by the presence of an EGF-like domain, and it exists in six major isoforms, each distinguished by unique N-terminal regions [337]. According to the analysis of a recent study, neuregulin-1 α acts as a liver-derived hormone (hepatokine) that stimulates β -cell proliferation [338]. Collectively, these findings provide strong evidence that hepatic neuregulin-1 α plays a key role in driving compensatory β -cell expansion in obese diabetic mice [338].

Communication from pancreatic islet cells to liver cells

In addition to the extensive dialog from the liver to the pancreas, we report additional key factors through which the pancreas communicates with the liver (Fig. 2).

Glucose production by the liver is the most prominent glucose source in the body and is regulated by the release of insulin by pancreatic β -cells. Insulin exerts direct effects on the liver by binding to hepatic insulin receptors and consequently activates downstream signaling pathways. This mechanism has been confirmed across various experimental models. For instance, in isolated rat liver cells, insulin suppresses glucose production by inhibiting both gluconeogenesis [339] and glycogenolysis [340]. Furthermore, liver-specific insulin receptor knockout (LIRKO) mice, exhibit pronounced hepatic insulin resistance [341]. This was further confirmed in a study showing that, when restoring hepatic insulin receptors to LIRKO mice, hepatic glucose production was not inhibited by insulin [342]. Collectively, these findings clearly show that insulin directly regulates hepatic glucose production through its action on the liver.

While β -cell-derived signals have been extensively studied in the context of pancreas–liver communication, recent research has underscored the importance of α -cell–liver crosstalk in maintaining metabolic homeostasis. Under normal physiological conditions, insulin and glucagon work in opposition to maintain stable blood glucose levels (euglycemia) [343]. With low glucose levels, glucagon levels increase while insulin levels decrease simultaneously [344]. Glucagon is a peptide hormone produced by the pancreatic alpha cells that exerts its effects on multiple organs, including the liver, kidneys, heart, and brain [345, 346]. Hypoglycemia triggers glucagon release from pancreatic alpha cells to stimulate gluconeogenesis and glycogenolysis in the liver, ultimately stimulating the increase of glucose export from the liver [347–350]. Beyond glucose metabolism, glucagon signaling in the liver influences lipid turnover and amino acid catabolism, thereby contributing to systemic energy balance. Notably, Richter et al. [351] demonstrated that the α -cell–liver axis operates as a feedback loop, where hepatic amino acid metabolism modulates α -cell function and glucagon secretion, linking nutrient sensing to endocrine regulation. These findings highlight that disruptions in α -cell–liver communication may contribute to hyperglucagonemia, dyslipidemia, and metabolic dysregulation in diabetes, emphasizing the need to consider α -cell signaling alongside β -cell pathways for a more complete understanding of pancreas–liver interactions [351].

A pancreatic derived factor known as PANDER is considered a hormone that has a role in glucose and lipid metabolism [352]. Being a 235-amino-acid protein [353], PANDER is secreted together with insulin and shares the same glucose-induced secretion pathway via a Ca^{2+} influx-dependent manner in β -cells and primary mouse islets [354–356]. Research is still lacking on the PANDER receptor in the liver, despite it having been reported that it binds with certain proteins on the liver membrane of mouse liver cells and human HepG2 causing insulin resistance, highlighting the liver as a new target for PANDER [357]. Moreover, pretreatment of PANDER to HepG2 cells showed significant inhibition of insulin-stimulated proteins such as IR, IRS-1, PI3K, and Akt [358].

In pancreatic islets, exosomes support β -cell development, functionality, and survival. Moreover, alterations in miRNA expression have been observed both in diabetic mouse models and in patients with diabetes, indicating their potential involvement in disease progression [359]. In addition to the intra-effect of miRNAs within the same tissue, certain exosomal miRNAs originating from β -cells also influence liver cells. A previous study reported that miRNA-26a not only regulates insulin secretion and β -cell proliferation but also helps to protect the liver from obesity-related metabolic disturbances and insulin resistance [360]. Additionally, miRNA-29 family members have been found to modulate insulin sensitivity in the liver and play a role in maintaining glucose balance [361].

Conclusions and future directions

The pancreas and liver originate from the endoderm, and while they have distinct functions, they share some developmental pathways and interact closely to regulate metabolism. This review has outlined their shared embryonic origins and highlighted the pivotal roles of common TFs and regulatory genes that govern both pancreatic and hepatic development. These overlapping genetic programs not only orchestrate early organogenesis but also play crucial roles in adult tissue function and in the pathogenesis of various forms of diabetes.

A key novel contribution of this review is its integrative focus on the shared genes and pathways that simultaneously influence pancreas and liver development, adult function, and diabetes pathogenesis. By bridging developmental biology with metabolic disease mechanisms, we provide a comprehensive framework that emphasizes the importance of interorgan signaling and genetic crosstalk, areas that remain relatively underexplored in prior literature.

By exploring the bidirectional crosstalk between the pancreas and liver, we underscore the significance of hepatokines and pancreatic-derived factors in coordinating glucose metabolism and maintaining metabolic homeostasis. Disruptions in this interorgan communication, as seen in T2D and other metabolic disorders, further emphasize the need to understand how these signaling pathways contribute to disease pathogenesis. The involvement of factors secreted by both the pancreas and liver that act on the other organ illustrates the complexity and therapeutic potential of these interorgan interactions.

From a clinical perspective, many of the genes discussed herein are also mutated in monogenic forms of diabetes, reinforcing their functional relevance across developmental and disease contexts. Importantly, these findings suggest that insights from developmental

biology can enhance our understanding of metabolic diseases and lead to more refined diagnostic and therapeutic approaches.

Looking ahead, the integration of emerging technologies such as hPSC-derived models, gene editing, single-cell genomics, and spatial transcriptomics offers unprecedented opportunities to dissect the molecular mechanisms linking pancreatic and hepatic function. These tools can facilitate the identification of novel disease genes, model patient-specific mutations, and guide the development of personalized interventions for diabetes.

In conclusion, bridging the developmental and functional relationships between the pancreas and liver not only deepens our understanding of diabetes pathogenesis but also opens new avenues for therapeutic innovation. Future research focusing on the temporal and spatial dynamics of shared gene networks, interorgan communication, and cellular plasticity will be key to developing precision medicine strategies aimed at restoring metabolic balance.

Abbreviations

GCG	Glucagon
GSIS	Glucose-stimulated insulin secretion
HI	Hyperinsulinism
hPSCs	Human pluripotent stem cells
INS	Insulin
KO	Knockout
MD	Monogenic diabetes
MODY	Maturity-onset diabetes of the young
MODY2	Maturity-onset diabetes of the young 2
PNDM	Permanent neonatal diabetes mellitus
SOX	Sex-determining region Y-box
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TF	Transcription factor

Acknowledgements

Not applicable.

Author contributions

S.S.G. contributed to the design, data collection, figure preparation, and writing the original draft of the manuscript. T.A. and R.B. contributed to the data collection and writing the original draft of the manuscript. E.M.A. contributed to the conception and design of the manuscript, and the review and editing of the manuscript. All authors read and approved the final version of the manuscript.

Funding

This work was supported by a budget from Sidra Medicine (project no. SDR400215; SDR400217).

Data availability

No datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 13 June 2025 Accepted: 3 September 2025

Published online: 03 October 2025

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