

Development of the Pancreas

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The adult pancreas is comprised of at least 10 different cells types including those with endocrine function (α , β , δ , γ , and ϵ), exocrine function (acinar and duct cells), vascular cells, neurons, and mesenchymal cells that are activated in response to injury. The endocrine and exocrine cells are derived from a common endodermal population of cells that also give rise to the liver and parts of the stomach and small intestine. The process by which these cells are specified to take on mature pancreatic phenotypes, and the extrinsic and intrinsic factors that guide these processes will be discussed within this chapter. For a more in depth discussion on the specific aspects of pancreatic development, there are a number of exceptional review articles that focus on transcriptional regulation, epigenetic regulation, cell lineage tracing, distinction from liver tissue, and signaling pathways involved (8, 22, 50, 80, 107, 131, 148).

I. Morphological development – from endoderm to definitive pancreas

Specification of the mouse pancreas is initiated from the distal part of the endodermal foregut and proximal part of the midgut beginning at embryonic day (E) 8.5 based on the initial expression of pancreas-specific genes (52). By E9, the first morphological sign of pancreatic development is the condensation of mesenchyme over the endoderm that will give rise to the dorsal pancreatic bud, distal to where the stomach will

form. In humans, this occurs just prior to 26 days of gestation (81, 116, 126). At E9.5, a clustering or anlage of cells emerges from the dorsal aspect of the gut tube at the point where the notochord comes in contact with the gut (**Figure 1**). This relationship between the notochord and endoderm is of critical importance (described below). Shortly after, the paired dorsal aorta move toward the midline and fuse, thereby displacing the notochord from the developing pancreas (85). Less than one day later in mice, or 6 days later in humans, a second ventrally located anlage appears, just distal to the developing liver, extending from the common bile duct. The two buds continue to develop

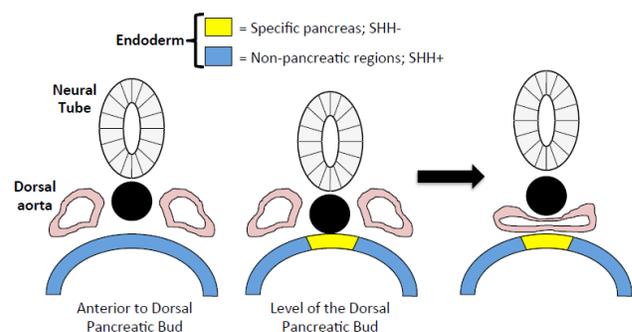


Figure 1. Specification of the dorsal pancreatic bud. Foregut endoderm anterior to the putative pancreatic bud expresses sonic hedgehog (SHH) which does not allow for pancreatic differentiation. Interactions with the notochord (filled black circle) lead to repression of SHH and progression to a pancreatic fate. This fate is maintained even after the paired dorsal aorta fuses at the midline displacing the notochord from direct interaction with the endoderm

independently, affected by different surrounding tissues, until approximately E13 (days 37 to 42 in humans), at which point, the rotational movement of the developing gut tube and elongation of both buds causes alignment and fusion into a single organ. In the majority of cases, one of the pancreatic ducts becomes patent, leaving a single common pancreatic duct, the Duct of Wirsung, for the organ. In about 10% of people, the two buds do not fuse leading to pancreatic divisum and the presence of a second duct, termed the Duct of Santorini or accessory duct (170). Pancreatic divisum is the most common pancreatic developmental anomaly, and in some cases, is an increased risk for recurrent pancreatitis (54, 113). By E15, clear acinar cell clusters and presumptive islets are apparent, and differentiation markers for all pancreatic cell types are expressed.

In general, pancreatic development can be separated into three time periods. The primary transition in mice encompasses E9-12 when specification of different pancreatic cell types takes place (56). During the primary transition, the pancreatic buds initially appear as stratified epithelium with a centrally located lumen (**Figure 2**). Cells within the anlage maintain multipotency, with the ability to give rise to endocrine, acinar and duct cells. The number of multipotent pancreatic progenitor cells (MPCs) is determined during the primary transition and appears to dictate the final organ size (160). Beginning at E10.75, microlumen structures begin to form, with cells establishing an apical polarity eventually leading to duct formation (84). Integrin-based interactions between outer cells of the developing buds and the adjacent basement membrane are required for initiation of branching (154). Minimal expression of pancreatic hormones and digestive enzymes is observed, although endocrine cells expressing multiple hormones exist, present as clusters within the dorsal bud. Whether these initial endocrine cells are maintained in the adult is still debatable.

The secondary transition occurs between E12 and E15 and is characterized by significant expansion and branching of the pancreatic bud, delamination

of individual presumptive islet cells from the pancreatic epithelium, and enhanced expression of both hormones and digestive enzymes. At this point, most of the cells have been specified to become either endocrine, acinar or duct cells, with only a small proportion of cells maintaining multipotency (123, 179). The third stage of pancreatic development occurs after E15 and extends postnatally with continued maturation and expansion of the pancreas. While controversial, it appears that all cells within the pancreas after E15 are unipotent, determined to be either acinar, duct or endocrine in nature. However, multipotency can be stimulated in the adult by injury (28, 70, 123).

High-powered resolution of the developing pancreas reveals a relationship between cell location within the branching epithelium and the different cell types. Progenitor cells giving rise specifically to acinar cells are located predominantly at the tips of the branching duct network. Conversely, mature duct and endocrine cells are derived from the trunks of these branches (**Figure 2**). p120-catenin (p120ctn) mediates surface-tension cell sorting through heterogeneous expression. Low expression of p120ctn allows cells to migrate to tips, where they are influenced by their environment to become acinar cells. While high p120ctn expressing remain in the trunk and become duct or endocrine cells (121). A complete *p120ctn* deletion leads to defects branching and acinar differentiation (66). MPCs exist at the transition position between the tips and the trunks (3, 179). Indeed, the location of these cells provided support for the hypothesis that centroacinar cells, which sit at the junction between acini and ducts, are pancreatic stem cells in the adult. However, studies examining centroacinar cells as stem cells have not supported such a role (87). As mentioned above, by E15, MPCs are rare. Evidence suggests that presumptive endocrine cells undergo a mesenchymal-epithelial transition process and coalesce to form the primitive islets of Langerhans (27, 140). Further recruitment, proliferation and maturation give rise to the mature islets postnatally. In mice, the islets consist of an inner core of β cells, which secrete insulin,

surrounded by a mantle of α (glucagon), δ (somatostatin), ϵ (ghrelin) and PP (pancreatic polypeptide) cells. In humans, these cells are positioned throughout the islets.

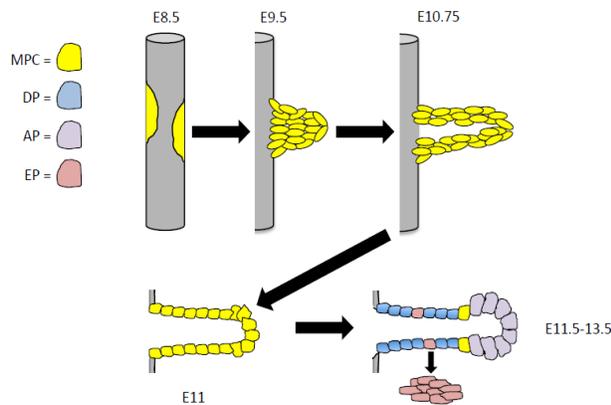


Figure 2. Early cell fate differentiation in pancreatic development. Multipotent pancreatic progenitor cells (MPCs) are first identified at embryonic day (E) 8.5. These cells maintain multipotency through to E10.5, at which point they begin to differentiate into acinar progenitor (AP), endocrine progenitor (EP), and duct progenitor (DP) cells. MPCs are maintained at the neck of pancreatic buds until E14.5.

Differentiation of acinar cells is less overt. Acinar cells maintain attachment to the duct network and develop a classical epithelial phenotype based on their polarity and intercellular junctions. Expression of carboxypeptidase (CPA) is observed as early as E9 (52), but CPA expression can be observed at early time points in MPCs as well as in acinar progenitor cells (179). More extensive expression of pancreatic enzymes begins around E12.5, and zymogen granules, the morphological hallmark of acinar cells, are first observed around E16.5. Acinar cells do exhibit polarity prior to birth based on the localization of tight and adherens junctions. However, the high degree of organization within acinar cells is first observed following birth (76). At this point, mature acinar cell morphology has been obtained, while further proliferation and maturation at the molecular level continues to occur until after weaning, presumably due to alterations in dietary makeup.

II. The three main pancreatic cell types are derived from a common progenitor pool

Elegant genetic lineage tracing experiments in mice have defined the progression of MPCs to individual unipotential populations as well as identified specific markers for this process. Mouse models were developed in which *cre recombinase* expression was driven in specific cell populations during development (67, 68). Initially, these experiments involved spatially expressing *cre recombinase* based solely on the promoter used and mating these “driver” mice to those containing a loxP-stop-loxP (LSL) site upstream of a reporter gene such as green fluorescent protein. Since this LSL site is downstream of a constitutively active and ubiquitous promoter, any cells derived from the initial expressing cells would be positive for the reporter gene. A number of groups used a system in which the *cre*-recombinase could be manipulated temporally through the addition of a tamoxifen-inducible tag linked to *cre* (see **Figure 3** for scheme). From this work, several observations could be made. First, prior to E12, MPCs exist that give rise to all cell types (179). Second, acinar progenitor cells are distinct from endocrine/duct progenitor cells indicating that duct cells have a closer developmental origin to endocrine cells (179). Third, MPCs do not normally exist within the adult, but can be stimulated to re-appear by injury to the pancreas (123). Fourth, acinar cells have the ability of de-differentiation into duct-like cells, and likely contribute to initial PanIN formation (59). These studies were also instrumental in defining that MPCs are located at the junction between tip and trunk cells of the branching pancreatic duct and can be identified by a specific combination of transcription factors (TFs). MPCs identified during the primary transition express Pancreatic Transcription Factor 1A (PTF1A), Pancreatic-Duodenal Homeobox 1 (PDX1), Sry-related HMG box (SOX9) and NK Homeobox 6.1 (NKX6.1). Hepatocyte Nuclear Factor 1 β (HNF1 β) defines epithelial cells in the trunk that give rise to endocrine and duct cells but not acinar cells (156,

179), although there is some controversy as Wright's group has suggested the HNF1 β may actually be expressed in MPCs as well (123). Whether this difference reflects the time points examined or differences in analysis is unclear.

During the secondary transition, PTF1A and NKX6.1 become mutually exclusive with PTF1A cells specifying an acinar cell phenotype and NKX6.1 found in duct/endocrine precursors (145).

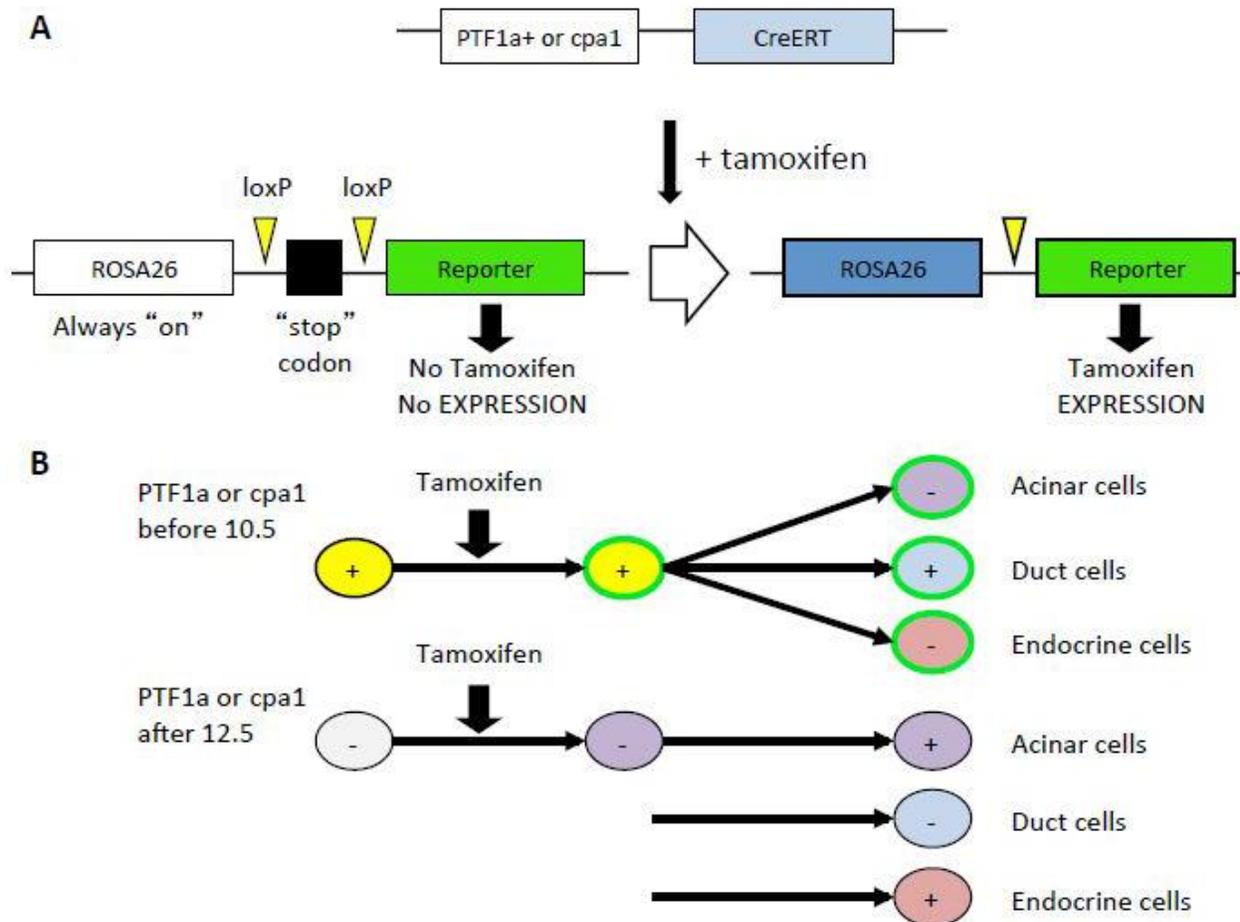


Figure 3. Lineage tracing during pancreatic development. (A) Scheme for permanently marking cells during development. Expression of cre recombinase is limited spatially by the promoter, in this case *Ptf1a* or *cpa1* (*carboxypeptidase 1*), and temporally by the addition of a tamoxifen inducible estrogen receptor (ERT) fused to cre. The constitutively active ROSA26 drives expression of the reporter gene, which is prevented by the presence of stop codons flanked by loxP sites (target for cre recombinase). Upon the introduction of tamoxifen, the stop codons are removed leading to reporter gene expression. (B) Using either the *Ptf1a* or *cpa1* promoter to drive creERT expression, introduction of tamoxifen early in development leads to reporter expression in all pancreatic cell types. Introduction of tamoxifen after E12.5 results in only acinar cells being labeled.

III. Developmental relationships that affect pancreatic development

Specification of the pancreas is dictated by interactions with a number of structures developing in close proximity to the developing endoderm. As mentioned, the ventral pancreatic duct shares a common cellular origin with the liver and, therefore,

signals must be present that dictate one fate from the other. Interestingly, it appears that the dorsal and ventral aspects of the endoderm are governed by either significantly different signaling events, or are able to process specific signaling pathways, such as Fibroblast growth factor (FGF) signaling, in different ways (16, 35, 120, 176). This suggests that the default differentiation pattern differs for

dorsal and ventral endoderm. Indeed, culturing ventral endoderm independent of other structures or signals results in pancreatic differentiation, based on the expression of both endocrine and exocrine cells (99, 175) (**Figure 4**). This suggests that the default pattern of differentiation for the ventral endoderm is pancreas, and that surrounding tissue in the embryo repress pancreatic development to become other organs.

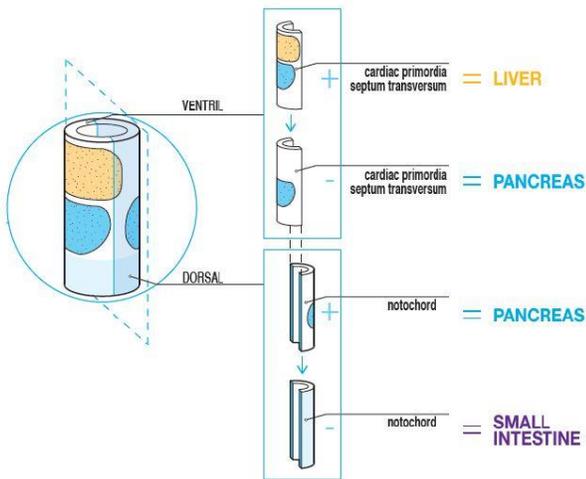


Figure 4. The dorsal and ventral pancreatic buds have different default patterns for development.

The pancreas is derived from a ventral pancreatic bud (VPB) and a dorsal pancreatic bud (DPB) that first appear around E9.5 in mice. The ventral endoderm gives rise to liver tissue due to inhibitory signals from the septum transversum and cardiac primordia. In the absence of these signals, pancreatic development is the default pattern of differentiation. The dorsal endoderm requires inductive signals from the notochord to promote pancreas development. In the absence of these signals, the dorsal endoderm will differentiate into non-pancreatic structures, such as the small intestine. (Figure is modified from (44)).

For example, signals from the cardiac mesoderm and the septum transversum, the structure that eventually gives rise to the diaphragm and parts of the ventral mesentery, promote liver differentiation at the expense of the pancreas (136). Conversely, culturing of the dorsal endoderm does not give rise to pancreas (**Figure 4**) suggesting that signals are required to promote differentiation and the default differentiation program is not pancreas (85).

A. Mesenchyme

Coalescence of the mesenchyme at the level where the dorsal pancreas will form is the first morphological sign of pancreatic development. Removal of the mesoderm, or the fibroblasts within the mesoderm, prior to pancreatic specification results in pancreatic agenesis (53, 110, 169). Mesoderm removal following specification results in a reduction of the total pancreatic size indicating an ongoing requirement for mesoderm signaling to attain complete organ development (96). Interestingly, culturing of pancreatic mesenchyme with other sections of the dorsal endoderm can promote pancreatic differentiation, while mesenchyme from other regions of the anterior-posterior axis does not have this ability (10). This suggests that the mesenchyme provides signals that promote pancreatic specification, yet limits differentiation, thereby allowing expansion of the organ. These signals come in a variety of sources.

Physical interactions between the mesoderm and developing pancreatic bud affect differentiation and maturation in multiple ways. Physical interaction is particularly important in specification of the exocrine pancreas. Glypicans and syndecans promote exocrine cell differentiation (177), and Notch signaling promotes PTF1A's function while repressing Neurogenin (NGN) 3 expression (6). PTF1A and NGN3 are key transcriptional regulators that promote exocrine and endocrine cell specification, respectively (55, 91). Laminin-1, a key extracellular component within the mesenchyme, promotes pancreatic duct formation (29, 101) and substrates that contain laminin-1, such as matrigel, can promote duct formation from early pancreatic buds possibly through $\alpha 6$ -containing integrin complexes (51). Furthermore, direct interaction between the mesenchyme and endoderm represses islet formation. Only after extensive branching excludes the mesenchyme from the developing ductal network can progenitor cells undergo epithelial to mesenchymal transition (EMT) and coalesce to form definitive islets. Finally, direct interactions between the mesenchyme and developing pancreatic bud maintain a progenitor like state. Inhibition of Epi-CAM (epithelial cell adhesion

molecules) in pancreatic bud cultures induces premature endocrine cell maturation, suggesting Epi-CAM helps maintain a ductal endocrine progenitor cell type (24).

In addition to physical interactions, secreted factors from the surrounding mesenchyme have also been identified that either promote or repress pancreatic specification and differentiation. Signaling through the TGF β superfamily affects many steps in pancreatic differentiation. TGF β signaling from the mesenchyme promotes endocrine differentiation from MPCs (144), and TGF β treatment of pancreatic dorsal bud tissue leads to endocrine differentiation at the expense of exocrine tissue. Activin, another member of the TGF β superfamily, also promotes endocrine differentiation while blocking branching and proliferation of the pancreatic bud and repressing exocrine differentiation. Inhibition of activin using follistatin, promotes exocrine cell differentiation at the expense of endocrine tissue (111). Disruption of TGF β signaling affects the secondary transition (166) and once pancreatic fates have been determined, TGF β signaling is required to maintain mature acinar cell fate as over-expression of dominant negative TGF β RII in the pancreas leads to acinar to duct cell metaplasia (ADM) (19). Additionally, a number of Fibroblast Growth factors (FGFs) are secreted by the mesenchyme, which affect pancreatic development. FGF4 represses endocrine differentiation and allows for expansion of the exocrine compartment (36), while FGF7 and FGF10 repress exocrine differentiation, thereby allowing proliferation and expansion of the pancreatic bud (40, 173). *Fgf10*^{-/-} mice exhibit pancreatic agenesis due to the inability to repress sonic hedgehog, a repressor of pancreatic differentiation (see below) (17).

B. Vasculature

At E8.5, de novo blood vessels coalesce from endothelial precursors immediately dorsal to the pre-pancreatic endoderm (reviewed in (135)). Paracrine signaling from these blood vessels is crucial in promoting early pancreatic organ specification, particularly in the dorsal pancreatic

bud. The importance of blood flow was first identified in a genetically modified mouse model containing a targeted deletion of *Cdh2*, the gene encoding N-cadherin. Mice completely null for N-cadherin show dorsal pancreatic agenesis (42), initially suggested to be due to impaired interactions between the mesenchyme and pancreatic endoderm. However, restoring N-cadherin specifically in the heart rescued both heart and pancreatic development indicating that maintaining blood flow to the pancreatic anlage is required for dorsal pancreatic formation (39). Further studies showed that signals from the vasculature could be from both the circulating blood as well as the endothelial cells of the dorsal aorta and surrounding mesenchyme (152). However, within the pancreas E-cadherin does not play a role in maintaining exocrine function postnatally. Four days after birth, pancreas specific *Cadh1*-null mice failed to gain weight and were hypoglycemic. Four days after birth, *Cdh1*-null mice displayed disrupted exocrine tissue architecture and integrity, and activation of the Wnt and Yap signaling pathways (147).

Interactions between the vasculature and endoderm also limit pancreatic differentiation. Over-expression of VEGF-A with the *Pdx1* promoter leads to insulin production within the stomach. Conversely, over-expression of VEGF-A within the pancreatic anlage greatly enhances vasculature development and significantly reduced pancreas formation, specifically affecting exocrine pancreatic mass (95). Ex vivo cultures in which the developing pancreas was treated with VEGF showed increased vasculature and greatly reduced size of the pancreas, stalling epithelial cells in a progenitor like state (103). Conversely, ablation of endothelial cells following pancreatic specification leads to more promiscuous differentiation of acinar cells, ultimately reducing the size of the pancreas as well. Therefore, the endothelium plays a dual role in dorsal pancreatic development. During the primary transition, the vasculature provides signals that specify pancreatic differentiation from the endoderm, yet maintain trunk progenitor populations in an undifferentiated state, preventing

premature development of specification to an endocrine fate. During the secondary transition, the vasculature restricts exocrine differentiation.

Again, the signals derived from the vasculature are diverse. Lammert et al. (95) showed that direct interaction with the aortic endothelial cells induced pancreatic bud-like structures and PDX1 expression in the adjacent endoderm. Endothelial cells are also required for PTF1A expression in the dorsal foregut. Conversely, development of the ventral pancreatic bud does not appear to require direct endothelial interactions (175) but rather relies on paracrine factors for development. For example, Sphingosine-1-phosphate, found in the blood, promotes recruitment to a pancreatic cell fate, and induces proliferation of pancreatic mesenchymal and endothelial cells (39).

C. Notochord and Sonic Hedgehog

A critical negative regulator of pancreatic development is sonic hedgehog (SHH). This is evidenced by experiments in which SHH signaling is elevated either through a transgenic approach where the *Pdx1* promoter drives SHH expression or by ablating the Patched receptor (*Ptc*). *Ptc* represses smoothen, a downstream mediator of SHH signaling. Both *Pdx1-Shh* and *Ptc*^{-/-} mice exhibit pancreatic agenesis (63). These experiments highlight the importance of repressing SHH at the initiation of pancreatic development. Forcing SHH expression, or the closely related Indian Hedgehog (IHH), after pancreatic specification (E12.5) by using the *Pax4* promoter, still leads to a significant loss of exocrine and endocrine tissue that is replaced by mesenchyme and stroma (83). Therefore, hedgehog suppression must be maintained to ensure proper pancreatic development. Indeed, activation of SHH signaling is observed during pancreatic injury correlating to acinar to duct cell metaplasia (180). Surprisingly, in zebrafish endoderm, ectopic SHH signaling expands the *Pdx1*-positive pancreas domain, while inhibiting hedgehog activity results in pancreatic agenesis indicating species differences in signaling pathways (79, 139).

While the mesenchyme expresses factors that promote SHH repression, including activin and FGFs, the notochord appears to be the primary source of these signals at the initiation of dorsal pancreas induction. The foregut expresses SHH along its length except at the point where the notochord comes in close proximity to the endoderm (**Figure 4**). Ectopic notochord engraftment represses SHH expression in the lateral and ventral endoderm, and SHH neutralizing antibodies can induce pancreas gene expression in dorsal endoderm explants (62). However, blocking SHH in non-pancreatic endoderm does not lead to pancreatic development. This suggests that signals from the notochord are not instructive but, rather, permissive. In agreement with this permissive model, *Shh*^{-/-} mice do not show expansion of the pancreas along the foregut, indicating that additional factors are required.

D. Ventral bud differentiation, cardiac mesenchyme and septum transversum

The signals derived from the notochord and mesenchyme that permit pancreatic development are activin (TGFβ family) and FGFs. Surprisingly, these same factors repress ventral pancreatic differentiation, highlighting differences in the developmental processes of the two pancreatic buds. A number of other findings highlight differences between ventral and dorsal pancreatic bud development. *Hhex*^{-/-} embryos fail to specify a ventral pancreas but the dorsal bud develops without issues (18). Alternatively, loss of *Raldh2*, which is required for endogenous retinoic acid signaling, prevents development of the dorsal pancreas while the ventral portion of the organ remains unaffected (105, 115).

Since ventral pancreatic bud formation is the default pattern of ventral foregut differentiation, the factors that govern differentiation of this anlage initially repress pancreatic fate. Similar to the repression of SHH by FGFs and activin in the dorsal pancreatic bud, these factors repress pancreatic specification, thereby allowing

differentiation of the liver. The ventral foregut endoderm lies in close juxtaposition to the cardiac mesoderm and septum transversum mesenchyme, and these tissues induce liver fate at the expense of the pancreas (35). Bone morphogenetic proteins (BMPs) also promote epigenetic reprogramming of ventral endoderm to a liver fate. In the absence of these structures or signaling molecules, the endodermal cells activate pancreatic differentiation pathways (136). Once liver development proceeds, the repressive signals are blocked allowing for pancreatic development from the more distal ventral endoderm to occur. In support of such a model, it has been suggested that *Hhex*^{-/-} fail to develop a ventral pancreas due to lack of proliferation of the endoderm, which would displace the putative pancreatic bud from influences of the cardiac mesoderm. Supporting this hypothesis, *Hhex*^{-/-} endoderm cultured in vitro is fully capable of expressing PDX1 (18).

While these various developmental structures have a significant impact on pancreatic development, their effects are governed by the permissive nature of the developing endoderm. In the next sections, the transcription factors and the signaling pathways that dictate pancreatic development will be discussed.

IV. Transcription Factors Governing Pancreatic Development

In the previous sections, we discussed morphological events and extrinsic factors that regulate pancreatic development. In this section, we will discuss transcription factors (TFs) which govern tissue and cell development. During pancreatic development, coordinated gene expression is critical for cell specification, expansion of the progenitor population, differentiation and then final maturation and function. The TF network has been well characterized in the pancreas, especially regarding β -cell development, with many TFs exhibiting dual roles during development and adult function. In early development, specific TFs govern the establishment and maintenance of the MPCs,

while in mature tissue, TFs affect cell specific function. A complete description of each TF is not possible. Therefore, this section will focus on identifying TFs linked to factors that define MPCs or are involved in exocrine tissue development as more extensive reviews on TFs that affect endocrine and specifically β -cell development can be found elsewhere (30, 118).

A. Transcription factors involved in specifying MPCs from endoderm

In the 1990s, two key TFs - PDX1 and PTF1a - were identified as critical for specification and differentiation of all cell types within the pancreas. Using genetically modified mice, both PDX1 and PTF1a were shown to be absolutely required for differentiation of both endocrine and exocrine pancreatic compartments indicating these factors are required for initial specification of MPCs from the endoderm. Since that time, several other TFs have been linked to specification of MPCs or shown to be required for expansion or maturation of the exocrine pancreas. Many of these proteins exhibit defined roles in development and mature cell function, and have been implicated in various pathologies such as pancreatitis or pancreatic cancer. In this section, we have focused on their role in development.

Pancreatic and Duodenal Homeobox 1 (PDX1).

Pancreatic and duodenal homeobox 1 (PDX1; alternatively known as Insulin Promoting Factor 1 (IPF1), or Somatostatin-Transactivating Factor 1 (STF1)) is a homeobox containing transcription factor. PDX1 is expressed in the developing mouse as early as E8.5 and maintained in all cells of the pancreas until E17.5, when it becomes restricted to islets (58, 122). Initial expression of PDX1 appears to delineate a region of the developing gut that later gives rise to the stomach, small intestine and bile duct, suggesting that it is involved in specifying this region of the gut tube to a subset of tissues (122). Single cell RNA sequencing analysis of the dorsal and ventral pancreatic bud at E10.5 indicate PDX1 high and low expressing cells. PDX1-high cells from both ventral and dorsal

pancreatic regions are pancreatic progenitors. PDX1-low cells from the dorsal pancreatic region are defined as premature endocrine lineages, while those from the ventral pancreatic region are progenitors for hepatic or extrahepatic lineages (100). Germline deletion of *Pdx1* in mice leads to an absence of all pancreatic tissues and neonatal lethality by postnatal day 5 due to hyperglycaemia. Examination of the pancreas during development indicates that initial specification of the gut to become pancreas, as well as initial budding, still occurs in *Pdx1*^{-/-} mice. However, subsequent expansion and branching of the tissue does not occur, indicating that expansion and complete differentiation of the pancreas requires PDX1 activity (4, 77, 122). In the mature pancreas, PDX1 was initially described as limited to β and δ -cells of the islets (58), only being re-expressed in acinar cells upon pancreatic injury. However, recent studies have identified low levels of PDX1 in most mature acinar cells, and targeted deletion of *Pdx1* in post-developmental acinar cells shows that PDX1 is required for maintaining this compartment of the tissue (138).

Heterozygous *Pdx1* (*Pdx1*^{+/-}) mice initially develop normally. However, over time *Pdx1*^{+/-} mice develop insulin insufficiency, indicating a requirement for high levels of PDX1 in insulin production. Transient loss of *PDX1* in adult tissue using a tet-inducible system supports the ongoing requirement for PDX1 in maintaining β cell function, as loss of PDX1 leads to decreased insulin accumulation and apoptosis (102). In humans, homozygous mutation of *PDX1* results in pancreatic agenesis (163), while heterozygous mutations of *PDX1* are found in patients with Maturity Onset Diabetes of the Young (MODY). Genetic analysis identified the *PDX1* gene as MODY4 (142, 162), and PDX1 can directly target and promote the expression of insulin and GLUT2 in β -cells (102).

Pancreatic Transcription Factor 1A (PTF1a).

Pancreatic Transcription Factor 1a (PTF1a; alternatively known as PTF1-p48 or p48) was first identified by its ability to bind combined E-box (CANNTG) and G-box (TGGGA) sequences found

in promoters of digestive enzymes *trypsin*, *cpa1*, *amylase*, and *elastase* (26, 125). Early in pancreatic development, PTF1a is co-expressed with PDX1 in MPCs (2). During the secondary transition, PTF1a becomes restricted to acinar progenitor cells (123). PTF1a is a basic helix-loop-helix (bHLH) transcription factor that forms an unconventional protein trimer with ubiquitously expressed E proteins such as E12 and E47 (90), and Recombinant binding protein J (RBPJ), a downstream mediator of NOTCH signaling. Combined, these factors make up the PTF1 complex, which specifies pancreatic acinar cells. However, while associated with RBPJ, these acinar cell progenitors do not undergo differentiation, thereby allowing for expansion of the progenitor population (41). Upon commitment to acinar cell differentiation, PTF1a preferentially interacts with the RBPJ-like (RBPJL) protein, and nuclear hormone receptor NR5A2 to drive pancreatic differentiation of acinar progenitor cells (15, 106).

Targeted deletion of *Ptf1a* in mice results in postnatal lethality immediately after birth (91), likely due to neuronal functions, as PTF1a is also expressed in the neural tube and cerebellum (146). *Ptf1a*-deficient mice have no pancreatic tissue at birth with PTF1a-deficient cells instead contributing to the common bile duct and duodenum (82). Interestingly, the result of over-expressing PTF1a depends on developmental state. Forced PTF1a expression early in development in cells that would typically give rise to the duodenum and stomach leads to expansion of the pancreas, with increased differentiation of duct, islet and acinar cell compartments (2). In ES cells, forced PTF1a expression requires MIST1 to activate digestive enzyme gene expression (137).

Islet 1 (ISL1).

Islet 1 (*Isl1*) is a member of the LIM/homeodomain family of transcription factors, expressed in a number of tissues during embryogenesis (181). In the developing pancreas, ISL1 expression is initially observed within the mesenchyme and later in pancreatic islets. Targeted deletion of *Isl1* in

mice leads to deficits in pancreatic development and provided initial evidence that the mesenchyme has a role in affecting pancreatic differentiation. Culturing putative mouse *Isl1*^{-/-} pancreatic endoderm with wild type mesenchyme restored pancreatic differentiation confirming that ISL1 acts as non-cell autonomous signal in early pancreas development (5). While ISL1 is restricted to pancreatic islets in the adult, expressing *Isl1* in acinar cells using an adenoviral-mediated approach, induces tubular complex formation through acinar to ductal metaplasia, in which exogenous expression facilitated this process (112).

Hepatocyte Nuclear Factors (HNFs).

The Hepatocyte Nuclear Factors (HNFs) are a homeodomain-containing superfamily of TFs that affect multiple stages of development. *HNF1b* encodes a protein that binds DNA as a homodimer or heterodimer along with HNF1a. During endoderm development, expression of HNF6 activates *HNF1b* expression. HNF1b is critical for endoderm development with HNF1b+ cells giving rise to liver, kidney, pancreas, bile ducts, urogenital tract, lung, thymus and gut (130). Mice with a germline deletion of the *Hnf1b* gene have a very similar phenotype to *Ptf1a*^{-/-} mice (61), with no pancreatic development observed at birth. Temporal and spatial deletion of *HNF1b* throughout pancreatic development has demonstrated important roles in MPC expansion, and acinar, ductal and endocrine cell differentiation (31). In humans, mutations in the *HNF1B* gene result in renal cysts, diabetes syndrome and noninsulin-dependent diabetes mellitus. Some individuals with *HNF1B* mutations display pancreatic exocrine dysfunction, pancreatic hypoplasia, and, in some cases, complete absence of the pancreatic body and tail suggesting specific loss of dorsal pancreatic development (13, 72).

HNF6 (Hepatic Nuclear Factor 6; also known as ONECUT1 or OC-1) binds DNA to elicit transcription of genes that are important throughout endodermal development. In pancreatic development, *HNF6* expression begins

prior to PDX1 in MPCs and is critical to several specific developmental functions depending on developmental time point (73, 167, 178). After the onset of *Pdx1* expression, HNF6 is crucial for endocrine cell development. HNF6 induces HNF1B expression, which promotes a wave of proliferation and initiates *Neurogenin 3 (Ngn3)* expression. Following this increase in *Ngn3* expression, HNF6 expression becomes limited to duct cells and is very marginally expressed in acinar cells (178). *Hnf6*^{-/-} mice exhibit a hypoplastic pancreas with effects mostly limited to non-acinar cell compartments suggesting HNF6 is dispensable for acinar cell differentiation (178). However, in a follow-up study, the pancreatic area of *OC1*^{Δpanc} at postnatal day (P) 2 decreased due to apoptosis. RNA-seq of *OC1*^{Δpanc} exocrine enriched samples showed decreased expression of *Mist1*, *Gata4*, *Nr5a2*, and *Ptfa1*, all TFs promoting the acinar cell phenotype (92), supporting a role for *OC1* in pancreatic development.

Sex-determining region Y-box (SRY-box) containing gene 9 (SOX9).

SOX9 is a member of the SRY-related, high mobility group box transcription factors. Early in development, between E9-E12.5, SOX9 expression overlaps with PDX1 and marks MPCs. SOX9 is required for pancreatic cell fate and repression of intestinal differentiation through binding lineage specific promoters and enhancers (155). A FGF10/SOX9/FGFR2 feed forward loop maintains pancreatic organ identity in MPCs (151). While MPCs express SOX9, as cells begin to differentiate SOX9 expression decreases. By E14, SOX9 accumulation is restricted to a subpopulation of PDX1+ cells located within the epithelial cords (150). Pancreas-specific knockout of *Sox9* using the *Pdx1-Cre* driver leads to stunted growth, elevated blood glucose levels, and death by postnatal day 4. Gross morphological assessment showed hypoplasia of both pancreatic buds beginning at E11.5, due to a reduction of PDX1+ cell proliferation and increase in cell death. Haplo-sufficient *Sox9* mice and individuals with

Campomelic dysplasia (CD), a semi-lethal skeletal malformation syndrome due to a heterozygous loss-of-function mutation in *SOX9*, have reduced islet cell mass, but the exocrine tissue remains unaffected (129, 149). In the adult, *SOX9* accumulates in some duct and centroacinar cells (88, 149), and targeted deletion of *Sox9* in the adult pancreas of mice leads to a cystic phenotype and decreased expression of duct markers (33, 104), indicating *SOX9*'s role in duct cell maintenance.

GATA transcription factors.

GATA transcription factors are characterized by their ability to bind the DNA consensus site (A/T)GATA(A/G). *GATA4* and *GATA6* have ~85% homology, containing a highly conserved DNA binding domain consisting of two zinc finger motifs (114). Initial expression of *GATA4* and *GATA6* occurs early in development and is associated with the development of many organs of endodermal and mesodermal origin (46). *GATA4* and *GATA6* are expressed between E9.5-E15.5 in the developing pancreas. At E9.5, *GATA4* and *GATA6* are co-expressed throughout the pancreatic epithelium (32). As development continues, *GATA4* accumulation becomes restricted first to the tips of branching ducts and then acinar cells by E16.5 where expression is continually reduced until E18.5 when it is undetectable in exocrine cells. However, in the adult, *GATA4* is detectable in subsets of α - and β -cells (32). *GATA6* expression overlaps *GATA4* expression until E14.5-E15.5, when it then becomes restricted to the cells of the endocrine pancreas and duct epithelium (32). Transgenic mouse models in which *GATA6* targets are repressed results in pancreatic agenesis. This is not the case when *GATA4* targets are repressed suggesting *GATA6* is critical for pancreatic development, whereas *GATA4* is dispensable (32).

B. Transcription factors promoting acinar cell differentiation

Nuclear Receptor 5a2 (Nr5a2).

NR5A2, a member of the orphan nuclear receptor family, is critical for embryogenesis as germ line *Nr5a2* deletion results in early embryonic lethality (94). *NR5A2* maintains expression of embryonic stem cell identity genes such as *Oct4* and *Nanog* (57), as well as genes involved in self-renewal and growth (14). Temporal and spatial expression of *Nr5a2* determines its function, suggesting that *NR5A2* function may link early endoderm development and endoderm differentiation (119). *NR5A2* is expressed in the gastrointestinal endoderm and is required for the expansion of pancreatic epithelium. In pancreatic progenitor cells, *NR5A2* promotes expression of genes involved in hepatic and pancreatic maturation (47, 133). In zebrafish, null *Nr5a2* mutations have no exocrine pancreas while development of the endocrine pancreas remains largely unaffected (119). In the mature pancreas, *NR5A2* regulates the expression of other protein complexes driving the assembly of digestive enzymes.

Hairy and Enhancer of Split-1 (Hes1).

Hes1 is one of seven *Hes* gene family members, which encode proteins that heterodimerize with other bHLH proteins, normally leading to target gene repression. *HES1* is the key target of NOTCH signaling in pancreatic development. In the absence of NOTCH, *RBPJ* (also known as *Recombining Binding Protein Suppressor of Hairless*) inhibits *HES1* expression. When NOTCH signaling is activated, *HES1* is expressed and represses expression of NOTCH ligands *Dll1* and *Jagged1* and the endocrine TF, *Ngn3* (155). In pancreatic progenitor cells, *HES1* expression inhibits the expression of *Ptf1a* and *Ngn3*. In *Hes1*^{-/-} mice, ectopic pancreatic tissue is found in the extrahepatic biliary system, posterior stomach, and proximal duodenum. A conversion of the biliary system into pancreatic tissue has also been noted in *Hes1*^{-/-} deficient mice, suggesting *HES1* restricts pancreatic differentiation from the endoderm (164). Subsequent studies showed that *HES1* and *SOX17* are part of a complex regulatory network that controls organ cell fate commitment of pancreatobiliary progenitors in the ventral foregut,

by restricting ectopic pancreatic development (157).

MIST1.

MIST1 is a member of the bHLH family of transcription factors expressed at high amounts in mature acinar cells. Activated shortly after PTF1a in a subset of pancreatic cells at E10.5, it is unclear whether MIST1 marks only potential acinar cells or MPCs. By E14.5, MIST1 clearly marks committed acinar cells and is excluded from duct cells through the rest of development and in the adult pancreas (128). Deletion of *Mist1* leads to loss of acinar cell organization and incomplete maturation of acinar cells (128). While still functional, *Mist1*^{-/-} cells are more likely to undergo acinar-to-duct cell metaplasia, and these animals are more sensitive to pancreatic injury (89).

Several targets of MIST1 transcriptional activity, including *Cx32*, *Rab3d* and *Atp2c2*, have been identified (43, 76, 132, 141, 165). However, it is believed that MIST1 does not initiate the transcription of these genes, but rather functions to enhance expression of genes required for regulated exocytosis (109). Therefore, MIST1 has been described as a scaling factor. Importantly, reactivation of MIST1 in adult *Mist1*^{-/-} tissue restores expression and acinar cell organization, suggesting this is a primary role for MIST1 function (37). The regulation of MIST1 is less understood. While it is clearly downstream of PTF1a and PDX1 in the pancreas, MIST1 is expressed in other serous exocrine tissues, including salivary glands and chief cells (127), and no studies have shown direct targeting of MIST1 by PTF1a or PDX1. However, both NR5A2 and X-box binding protein 1 (XBP1) appear to directly regulate MIST1 (1, 37).

X-Box Binding Protein 1 (XBP1).

X-box Binding Protein 1 (XBP1) is a bHLH transcription factor and a key mediator of the unfolded protein response (UPR) pathway, activated under conditions in which protein folding capacity of the cells is adversely affected. In non-stressed cells, XBP1 shows limited transcriptional

ability. Upon activation of the UPR, Inositol-requiring enzyme 1 (IRE1) becomes active and deletes a 26 bp sequence from the *Xbp1* mRNA, producing spliced *Xbp1* transcript which encodes a transcription factor (21, 174). sXbp1 targets genes involved in ER-associated degradation and increased protein folding as well as promoting apoptosis depending on the magnitude and length of the cell stress.

Likely due to the heavy protein folding capacity required in the pancreas, sXBP1 is present and functional even under physiological conditions (93). Targeted deletion of *Xbp1* during development results in embryonic lethality (71). Liver specific rescue allows mice to survive for a short time postnatally to observe the phenotypic abnormalities that exist in other secretory organs. In the pancreas *Xbp1* deletion leads to incomplete development of acinar cells and as a result undergo apoptosis during development (98). Interestingly, XBP1 function is also required for maintenance of the acinar cell phenotype as induced deletion in adult cells leads to widespread apoptosis and regeneration specifically from acinar cells that escaped cre-mediated recombination (69). It appears that XBP1 targets several important factors required for acinar cell differentiation including *Nr5a2* and *Mist1*.

V. Signaling Pathways Involved in Pancreatic Development

While many signaling pathways have been identified to regulate pancreatic development, we have focused on a few key pathways that have been identified in many studies.

A. β -catenin/Wnt

Wingless-related integration site (Wnt) signaling controls many embryonic developmental processes including body axis patterning, cell fate specification, and cell proliferation (108, 124, 161). Wnt signaling encompasses three different signaling pathways including the canonical or β -catenin-mediated pathway, and two non-canonical pathways that involve planar cell polarity and

calcium. Signaling through the canonical Wnt pathway regulates expression of key mediators in pancreatic development (117, 168), while the non-canonical Wnt pathways regulate cell shape and intracellular calcium (34). In pancreatic development, several WNT ligands are expressed including WNT2b, WNT4, WNT5a and WNT7b (65). Binding of WNT ligands to Frizzled (Fzd) receptors leads to Fzd interaction with Dishevelled (Dvl; (171)), at which point the WNT signaling pathway diverges into one of the three pathways mentioned above (78, 172). Activation of the canonical pathway leads to the dissociation of β -catenin from the APC/Axin/GSK3 β complex, leading to β -catenin's translocation to the nucleus where it interacts with lymphoid enhancer factor (Lef-1)/T-cell factor (TCF) transcription factors to affect gene expression (12, 20, 134).

The timing of β -catenin expression and activation of Wnt signaling is critical in pancreatic development. Typically, WNT signaling maintains a progenitor like state, thereby allowing expansion of the tissue prior to differentiation (34, 38, 117). Forced expression of WNT signaling prior to pancreatic specification prevents liver and pancreas development (64, 65).

Detectable amounts of nuclear β -catenin are observed as early as E12.5-E14.5 in the pancreas, prior to the secondary transition (65). Activated β -catenin is critical during this time period as mice lacking β -catenin have smaller pancreata by E16.5 (168). Targeted deletion of β -catenin results in the loss of exocrine pancreatic tissue along with increased tubular structures, increased parenchymal fibrosis and inflammatory infiltrate. The smaller pancreatic size in β -catenin null animals is due to a decrease in proliferation of PTF1A expressing progenitor cells and most likely not due to a loss of adherence junctions. These studies indicate that β -catenin is initially required for expansion of the pancreatic epithelium prior to differentiation, as well as for terminal differentiation of acinar cells. Although the exocrine pancreas was abolished, a loss of Wnt signaling did not

disrupt the development of fully functional islets (168).

B. Retinoic Acid

Retinoic Acid (RA) is generated through the metabolism of Vitamin A by aldehyde dehydrogenases enzymes (ALDHs; (9, 143)). RA is a ligand for the nuclear hormone receptor - retinoic acid receptor (RAR) - which exists as a DNA-bound repressor complex in the absence of RA. Heterodimers of RAR and Retinoid X Receptors (RXR) change conformation upon binding of RA to RAR, allowing recruitment of additional transcriptional regulators, thereby altering the expression of RAR-associated genes (49).

In zebrafish, blocking RA signaling results in undetectable expression levels of endocrine (*insulin*) or exocrine (*trypsin*) markers and specifies initiation of pancreatic progenitors upstream of *Pdx1* (159). In *Xenopus*, pharmacological and genetic approaches to block RA signaling diminished *Pdx1* expression only in the dorsal pancreas, suggesting that RA signaling might be required only for endocrine pancreatic development in *Xenopus*. However, RA inhibition at later developmental stages blocked expression of differentiated exocrine markers but retained *Pdx1*. Therefore, in *Xenopus*, RA signaling is not required for specification of ventral pancreas but is necessary for later exocrine cell differentiation (158).

In mice, Retinaldehyde dehydrogenase 2 (*Raldh2*) is expressed between E8.75 and E12.5 in the dorsolateral mesenchyme that is in contact with the dorsal pancreatic bud. RA is synthesized in dorsolateral mesodermal cells, and the developing tissues responsiveness to RA follows a general dorsal to ventral gradient. Targeted deletion of *Raldh2* in mice diminishes *Pdx1* and *Ptf1a* expression in the presumptive dorsal pancreatic bud, while ventral pancreatic development is largely unaffected. Absence of *Raldh2* during pancreatic development also decreases HB9 and ISL expression in the dorsal mesenchyme,

supporting a mechanism by which dorsal bud agenesis may be due to deficient mesodermal signaling (105).

C. Hippo Signaling

Hippo (or Salvador/Warts/Hippo (SWH)) signaling regulates organ size through controlling cell proliferation and apoptosis. Hippo signaling involves activation of Mammalian Ste20-like kinases 1/2 (Mst1/2) also known as Hippo in *drosophila* and Save family WW domain-containing protein 1 (SAV1), also known as Salvador in *drosophila*, complex. This leads to phosphorylation of Large tumor suppressor 1/2 (LATS1/2). LATS1/2 maintains Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) in a cytoplasmic localization and inactive conformation. Therefore, upon LATS1/2 phosphorylation, dephosphorylated YAP and TAZ translocate to the nucleus where they interact with TAE domain family member (TEAD) 1-4 and alter gene expression that promotes proliferation and inhibits apoptosis (23). Pancreata of *Mst1/2* double knockout mice have a decreased pancreatic mass due to a failure in exocrine cell maturation (48). Additionally, overexpressing YAP in later pancreatic development expands the duct network while decreasing the number of acinar and endocrine cells (48).

D. NOTCH Signaling

The NOTCH pathway plays a role in dictating different developmental fates for closely associated cells. Since duct, exocrine and endocrine cells arise from common epithelial compartments, NOTCH signaling has been suggested as a mechanism to ensure limited differentiation of endocrine cells. In neuronal development, NOTCH signaling triggers *lateral inhibition*, which prevents adjacent cells from having the same phenotype (11). In pancreatic development, cells expressing NGN3 are destined to become endocrine cells, and NGN3-expressing cells have enhanced expression of NOTCH ligands Delta (DII), Jagged and Serrated. NOTCH

signaling is triggered by interaction of these ligands with NOTCH receptors on adjacent cells (74) resulting in receptor cleavage and release of the NOTCH intracellular domain (NICD). Translocation of NICD to the nucleus leads to modulation of transcriptional regulators *mindbomb* and RBPJ (97), which enhances expression of HES1, a repressor of *Ngn3*. Therefore, lateral inhibition through increased HES1 has been suggested as a way of preventing widespread endocrine differentiation. In support of this theory, deletion of *Dll* or *Hes1* in the pancreas during development increased endocrine differentiation at the expense of acinar cells (7, 75). However, lateral inhibition cannot explain many of the effects of NOTCH signaling in pancreatic development, nor the final arrangement of exocrine vs. duct vs. endocrine cells. NOTCH signaling is time dependent, and forced early expression of NOTCH signaling also reduces the acinar cell population, implying a role for NOTCH in the expansion of this population of cells before exocrine differentiation (60).

RBPJ activity can be modulated by NICD when it is present in the nucleus. RBPJ is a key component of the PTF1 complex, which includes PTF1a and the ubiquitous bHLH, Transcription factor 3 (TCF3). During early pancreatic development, the PTF1 complex includes RBPJ, which allows for acinar cell expansion but limits differentiation (25). When RBPJ-like (RBPJL) replaces RBPJ in the PTF1 complex the role of this complex switches from one that maintains a specified acinar cell fate to a complex that drives and maintains differentiated acinar cells (106). This RBPJ to RBPJL switch is consistent with targeted pancreatic RBPJL deletion, which decreases expression of genes involved in differentiated acinar cell processes such as digestive enzyme production, regulated exocytosis or mitochondrial metabolism (45).

NOTCH signaling has also been implicated in trunk cell (endocrine/duct progenitor cells) specification (3), duct cell differentiation, and endocrine lineage commitment (6, 153, 158). Centroacinar cells and a small percentage of duct cells seem to maintain

HES1 expression (86) suggesting that these cells might make up a pancreatic progenitor/stem cell population.

VI. Conclusion

The plethora of genetically modified mouse models that allow for targeted and inducible deletion or activation of genes has greatly improved our understanding of exocrine pancreas development, and provided insight into disease processes in which the developmental processes are not activated properly (e.g. pancreatic agenesis or insufficiency), or re-activated (e.g. pancreatic

cancer). Understanding how these various signaling pathways and transcriptional factors work in concert to cause acinar cell differentiation is still an active area of discussion and many of the findings still need to be translated to human development. In particular, research will be needed to understand the impact of environmental factors (such as diet) on exocrine pancreatic disorders, both during development and diseases such as pancreatitis. Likely, these studies will identify the importance of epigenetic regulators or events that mediate the environmental impact on pancreatic development.

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