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The role of non-coding RNAs in pancreatic birth defects

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Abstract

Congenital defects in the pancreas can cause severe health issues such as pancreatic cancer and diabetes which require lifelong treatment. Regenerating healthy pancreatic cells to replace malfunctioning cells has been considered a promising cure for pancreatic diseases including birth defects. However, such therapies are currently unavailable in the clinic. The developmental gene regulatory network underlying pancreatic development must be reactivated for *in vivo* regeneration and recapitulated *in vitro* for cell replacement therapy. Thus, understanding the mechanisms driving pancreatic development will pave the way for regenerative therapies. Pancreatic progenitor cells are the precursors of all pancreatic cells which use epigenetic changes to control gene expression during differentiation to generate all of the distinct pancreatic cell types. Epigenetic changes involving DNA methylation and histone modifications can be controlled by non-coding RNAs (ncRNAs). Indeed, increasing evidence suggests that ncRNAs are indispensable for proper organogenesis. Here, we summarize recent insight into the role of ncRNAs in the epigenetic regulation of pancreatic development. We further discuss how disruptions in ncRNA biogenesis and expression lead to developmental defects and diseases. This review summarizes in vivo data from animal models and in vitro studies using stem cell differentiation as a model for pancreatic development.

Keywords

pancreatic development; pancreatic birth defects; ncRNA; miRNA; lncRNA; epigenetic regulation

Introduction

The pancreas has diverse and essential roles in nutrition and metabolism. The pancreas is composed of endocrine and exocrine cells. The endocrine pancreas consists of five types of cells that form distinct clusters called islets of Langerhans and secrete hormones required to regulate blood glucose and energy homeostasis. The exocrine pancreas contains acinar and ductal cells. Acinar cells synthesize and secret digestive zymogens, and the ductal cells constitute the duct system that funnels zymogens into the duodenum where

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they are activated to digest food (Longnecker et al., 2018; Mahadevan, 2019). The endocrine and exocrine cells are generated from the same pancreatic progenitor cells (PPCs) during development. Disruptions in PPC proliferation and differentiation lead to pancreatic birth defects including pancreatic agenesis, pancreas divisum, annular pancreas, and some types of diabetes mellitus (Lorberbaum et al., 2020). Diabetes is a chronic disease that requires life-long treatment. Over time, abnormal blood glucose leads to complications such as heart disease, stroke, kidney disease, loss of visual function, and peripheral nerve damage (Nathan, 1993). More than 11% of the population in the United States have diabetes mellitus (*National Diabetes Statistics Report | Diabetes | CDC*, n.d.), costing an estimated $327 billion annually (American Diabetes Association, 2018). In newborns, β-cell differentiation defects lead to insufficient insulin production and elevated blood glucose, which can ultimately develop into diabetes mellitus. Increasing functional β-cell mass is the optimal cure for diabetes patients and two goals have been set forward, (1) activating endogenous β-cell proliferation or transdifferentiation from other pancreatic cell types such as acinar cells and (2) transplanting exogenous β-cells such as β-cells differentiated from stem cells *in vitro*. However, the field is still trying to figure out how to achieve the first goal in animal models and we are still far from translating these findings to the clinic. There are ongoing clinical trials that transplant stem cell-derived islets into patients (Ramzy et al., 2021; Shapiro et al., 2021), however, these trials are still in their infancy so the outcomes still need to be determined and they use costly devices which makes them unaffordable to some patients. Birth defects in the pancreas also lead to inefficient transportation of zymogens which can be activated prematurely inside the pancreas instead of the duodenum, causing acinar cell damage and inflammation in the pancreas termed pancreatitis. Acinar cells have plasticity to de-differentiate into ductal-like cells after injury through a process called acinar-to-ductal metaplasia (ADM). However, for pancreatic regeneration to occur, the ADM must be resolved by the re-differentiation of metaplastic cells back into acinar cells. Otherwise, persistent ADM and pancreatic inflammation can result in neoplastic precancerous lesions which may develop into pancreatic cancer (Stanger & Hebrok, 2013). The five-year survival rate for pancreatic cancer is less than 11% which is the lowest among all types of cancer (Siegel et al., 2022). Indeed, increasing acinar cell re-differentiation after ADM can significantly decrease the risk of pancreatic cancer (Storz, 2017). Even though regenerative medicine is a promising, potentially permanent therapy for patients with pancreatic birth defects, there are no effective therapies currently available. Most patients adapt their lifestyles to delay disease progression and manage symptoms. Understanding how the pancreas develops is critical for identifying the cause of pancreatic birth defects. Since the underlying mechanisms controlling pancreatic development are reactivated during pancreatic regeneration to replace damaged cells, it is also critical to understand the gene regulatory network driving development to determine targetable pathways for future regenerative therapies.

As mentioned, the pancreatic endocrine and exocrine cells are derived from the same progenitor population with the same genetic material. Epigenetic modifications change chromatin accessibility and structure to alter gene expression and cellular identity without changing the DNA sequence, and their effects on gene expression are inherited during cell division, thereby pushing PPCs to adopt different cell fates (Goldberg et al. 2007; Bernstein

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and Allis 2005). Chromatin is composed of DNA and histones (Akhtar et al., 2000). DNA methylation and histone modifications modulate the opening and closing of chromatin and thereby control the accessibility of chromatin to transcriptional machinery (Bannister et al. 2001; Cosgrove et al. 2004; Hebbes et al. 1988; Hall et al. 2002; Keshet et al. 1985). Non-coding RNA (ncRNA) is also considered to be an epigenetic modifier (Penny et al. 1996; Bernstein and Allis 2005; Mohammad et al. 2012). Non-coding RNAs are functional RNA molecules that do not translate into proteins and it has been estimated that ncRNAs take up more than 90% of the transcriptome in eukaryotic cells (Palazzo & Lee, 2015). NcRNAs can be classified based on their lengths into long ncRNAs (longer than 200bp) and small ncRNAs (shorter than 200bp) such as PIWI-interacting RNAs (piRNAs) and microRNAs (miRNAs) (Bhat et al., 2020). Both long and short ncRNAs have been shown to control epigenetic status via multiple mechanisms including directing DNA methylation, recruiting chromatin remodelers and histone modifiers, and acting as a scaffold for transcriptional regulators. Not only do ncRNAs epigenetically regulate normal biological processes such as differentiation and development (Bhat et al. 2020), but also are involved in the pathology of human diseases such as cancer and diabetes (Hajjari & Salavaty, 2015; Kondo et al., 2017; Kumar et al., 2020; Lardenoije et al., 2015; Zarzour et al., 2019). Thus, targeting ncRNAs may be a novel strategy for manipulating epigenetic status and gene expression for regenerative medicine.

Animal models are the most widely used tools to study pancreatic development and disease (Lorberbaum et al., 2020). Additionally, the differentiation potential of stem cells has emerged as a powerful *in vitro* tool for modeling pancreatic development (Rezania et al. 2013; Huang et al. 2021; Trott et al. 2017; Lee and Chung 2011; Rezania et al. 2014; Rezania et al. 2012; Kroon et al. 2008). Here we summarize results from *in vivo* and *in vitro models* on the epigenetic regulation of pancreatic development by ncRNAs and how disruptions in ncRNA biogenesis and function contribute to pancreatic birth defects.

Overview of pancreas development

The development of the pancreas is similar between humans and rodents. In this section, pancreatic development in mice is used as an example (Figure 1). After gastrulation, the primary germ layers (endoderm, mesoderm, and ectoderm) are established. The endoderm is a flat layer of epithelial cells adjacent to the mesoderm (Wells & Melton, 1999). A crescent-shaped fold forms at both the anterior (anterior intestinal portal, AIP) and posterior end (caudal intestinal portal, CIP) of the endoderm. From embryonic (E) day E8.0 to E9.0 in mouse embryos (E17 to E21 in humans), the AIP and CIP elongate and migrate towards each other until they meet at the yolk stalk where they connect to the yolk sac and form the primitive gut tube (Spence et al., 2011). Concurrently, the gut tube is patterned along the anterior-posterior axis with different transcription factors expressed in each region, namely the foregut, midgut, and hindgut. The dorsal endoderm is in contact with the notochord between E8.5 and E8.75 in mice, and by E9.0, the two paired dorsal aortae fuse between the notochord and gut epithelium. The aorta and notochord are both associated with the formation of the pancreatic primordia (Lammert et al. 2001; Kim et al. 1997). Sonic hedgehog (Shh) is expressed along the gut tube except in the pancreatic domain. The notochord secrets factors including activin-βB and FGF2 to repress Shh and induce

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the expression of Pdx1 which is the earliest transcription factor expressed in the developing pancreas (Hebrok et al., 1998). On the ventral side of the gut tube, a bipotential precursor population is capable of activating both pancreatic and hepatic programs. The default fate of these bipotential progenitors is to express pancreatic genes. However, FGF signals from the cardiogenic mesoderm (Deutsch et al., 2001) and BMP signals from the septum transversum mesenchyme (Rossi et al., 2001) divert those cells to the hepatic track.

Once the pancreatic domain is specified along the gut tube, additional transcription factors required for pancreatic development are induced including Ptf1a, Sox9, Nkx6–1, and Hnf6 (Jørgensen et al., 2007). The mesenchyme expands to envelop the pancreatic epithelium and separate it from the dorsal aorta. Signals from the pancreatic mesenchyme are essential for expanding the pancreatic progenitor pool (Golosow & Grobstein, 1962; Landsman et al., 2011). The mesenchymal FGF10 promotes the expression of Sox9 in the pancreatic progenitors, and Sox9 maintains the expression of FGF receptor 2b (Fgfr2) which transduces the mesenchymal FGF signal into PPCs. Sox9, Fgfr2, and Fgf10 form a feed-forward loop to maintain the pancreatic identity and promote the proliferation of PPCs (Bhushan et al., 2001; Norgaard et al., 2003; Seymour et al., 2012). From E8.5 to E10.5 in mice (E20 to E30 in humans), PPCs are induced on the dorsal and ventral side of the gut tube, proliferate and form two pancreatic buds, and convert from a “predifferentiatied” to “protodifferentiated” state where low levels of pancreas-specific proteins are expressed. This process is referred to as the primary regulatory transition (Pictet et al., 1972; Rutter et al., 1968).

Shortly after the primary transition, the PPCs remain as undifferentiated multipotent stem cells that are tightly packed within pancreatic buds. After E10.5, the pancreatic epithelium expands rapidly and branches into two domains, the tip and trunk. This expansion is initiated by transcriptional cross-repression between Ptf1a and Nkx6–1 (Schaffer et al., 2010). The tip cells expressing Ptf1a will develop into acinar cells while the trunk cells marked by Nkx6–1 will form the bipotent progenitors which give rise to ductal and endocrine cells. Notch inhibits Ptf1a activity and acinar differentiation while promoting the expansion of trunk cells (Afelik et al., 2012; Esni et al., 2004). As the PPCs adopt a tip or trunk fate, the secondary regulatory transition begins when the “protodifferentiated” cells undergo cytodifferentiation and upregulate the synthesis of pancreatic proteins (Pictet et al., 1972). By E12.5 in mice (E42 in humans), the gut tube rotates, and the dorsal and ventral pancreatic buds fuse into an interconnected organ. In tip cells, Ptf1a forms a transcriptional activating complex with Rbp-jl to activate the expression of key acinar genes like Nr5a2 and Mist1. Together, these genes maintain the acinar identity and drive the expansion of acinar cells (Masui et al. 2008; Thompson et al. 2012; Masui et al. 2010; Masui et al. 2007). Within the trunk domain, some bipotent progenitor cells activate the expression of Ngn3, which initiates endocrine differentiation (Gu et al., 2002). Ngn3 induces epithelial-to-mesenchymal transition (EMT) in endocrine cells and promotes delamination out of the epithelium (Gouzi et al., 2011). The Ngn3 positive cells differentiate into all five types of endocrine cells within the islet of Langerhans: α-cells (produce glucagon), β-cells (produce insulin), δ-cells (produce somatostatin), PP-cells (produce pancreatic polypeptide), and ε-cells (produce ghrelin). The Notch signaling pathway controls the activation of Ngn3 in the bipotent progenitors. Intermediate Notch activity promotes Sox9 expression, which induces Ngn3 cell-autonomously. However, high Notch activity also activates the expression of Hes1, an

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Ngn3 repressor (Lee et al. 2001). Bipotent progenitors that do not express Ngn3 will adopt a ductal fate and eventually develop into the branching ductal system (Delous et al. 2012; Shih et al. 2012).

Outside of mice, other systems such as flies, fish, frogs and birds have been used to study pancreatic development. Invertebrate species such as *D. melanogaster* do not have pancreatic islets, however, they do have cells producing insulin- and glucagon-like peptides. In flies, such cells are present in midgut muscle and *pars intercerebralis* of the brain (Ikeya et al., 2002; Veenstra et al., 2008). Basal chordates such as Hagfish represent the most primitive vertebrates with a pancreas-like structure containing insulin and somatostatin-producing cells (Heller, 2010). Over the course of vertebrate evolution, insulin-producing cells along and with more pancreatic hormone-producing cells became more organized into distinct structures resembling islets (Madsen, 2007). The structure of the pancreas in fish, frogs, and birds are similar to mammals with distinct localization of endocrine cells in islets, but they differ in the composition and position of different hormone-producing cells (Heller, 2010). The gene regulatory network governing pancreatic development in vertebrates is also conserved. Pdx1 expression can drive pancreas formation from nonpancreatic regions across multiple species (Afelik et al., 2006; Grapin−Botton et al., 2001; Yee et al., 2001). Inhibiting Ptf1a in zebrafish converts acinar cells to insulin-producing cells, suggesting Ptf1a is also required for maintaining acinar identity in zebrafish (Hesselson et al., 2011). Ectopic expression of Ngn3 in chicken embryos is sufficient to differentiate endodermal cells into endocrine cells expressing glucagon and somatostatin (Grapin−Botton et al., 2001). The conserved gene regulatory network across species allows us to take advantage of different model organisms to study pancreatic organogenesis.

Compared to animal models, the availability of human embryonic and fetal tissue to study pancreas development is limited. Current knowledge from animal models has guided the development of protocols for differentiating human pluripotent stem cells (hPSCs) into pancreatic cells. There are multiple protocols, but in general, they involve using Activin and Wnt agonists to induce definitive endoderm formation from hPSCs, retinoic acid and FGF to pattern the posterior foregut cells, and Shh and BMP inhibitors to promote pancreatic progenitor cells induction (Pagliuca et al. 2014; Rezania et al. 2013; Rezania et al. 2014; Rezania et al. 2012). Despite the success in differentiating hPSCs into pancreatic cells, there are drawbacks limiting the capacity of those differentiated cells. The cells generated from hPSCs are still immature compared to somatic cells. The differentiation is conducted and cultured in 2D and thus, cannot model the interaction with surrounding tissues. In addition, the efficiency of generating exocrine cells remains low compared to endocrine cells (Gaertner et al., 2019). Further optimizations are needed to better model human development *in vitro* and serve as a source of cells for regenerative therapies.

Models for pancreatic birth defects

Human and rodent pancreas development is similar in that they both undergo primary and secondary transition and share many conserved transcription factors that govern these processes. In addition, the mature pancreas structure in rodents (Figure 2A) also resembles the mature human pancreas. Thus, rodent models have been a very powerful tool to

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understand pancreas development. In this section, we summarize different types of human pancreatic birth defects and how they can be recapitulated in animal models.

Pancreatic agenesis

Pancreatic agenesis is a rare congenital disease in which all or part of the pancreas fails to form (Figure 2B). Patients can be asymptomatic or develop pancreatic diseases like hyperglycemia and pancreatitis. Ptf1a or Pdx1 knockout in mice leads to pancreatic agenesis, hyperglycemia, and perinatal death (Krapp et al., 1998; Offield et al., 1996; Sellick et al., 2004). Persistent expression of Hlxb9 also results in agenesis of the pancreas (H. Li & Edlund, 2001). One genomic study in 27 patients *identified GATA6* haploinsufficiency as a cause of pancreatic agenesis (Allen et al., 2011). The role of *GATA6* in human pancreatic development was later confirmed using *in vitro* stem cell differentiation which found that loss of *GATA6* prevented endoderm differentiation and β-cell formation (Shi et al., 2017; Tiyaboonchai et al., 2017). In mice, pancreas-specific deletion of Gata6 did not significantly impact pancreatic formation. Only when another GATA family member, Gata4, was deleted together with Gata6, did the mice develop pancreatic agenesis and hyperglycemia and die shortly after birth (Carrasco et al., 2012; Xuan et al., 2012). Xuan et al. deleted Gata6 and Gata4 together in the gut endoderm using Foxa3-Cre at E8.5 and found that the PPCs were still induced in the KO embryos, but PPC proliferation and branching morphogenesis were arrested by E11.5, thereby contributing to agenesis in the pancreas.

Pancreas divisum

During pancreatic development, the ventral pancreas rotates with the gut tube and fuses with the dorsal pancreas, and the ducts in the ventral and dorsal pancreas also fuse together and form the main pancreatic duct. Pancreas divisum (Figure 2C) occurs when the ventral and dorsal ducts fail to fuse together. It is the most common congenital anomaly in the pancreas and is found in 4–14% of the population (Nijs et al., 2005). The pancreatic duct system drains and funnels the pancreatic enzymes into the duodenum through the papilla which is the opening of the duct into the duodenum. In embryos, the majority of the gland drains from the dorsal duct into the minor papilla (opening of the accessory pancreatic duct) and the ventral duct drains the minority of the pancreas into the major papilla (opening of the main pancreatic duct). In adults, the situation is reversed. If the fusion of dorsal and ventral fails, the dorsal duct will still drain the majority of the pancreas. This can lead to functional stenosis in the ducts causing some patients to develop recurrent pancreatitis which increases the risk for pancreatic cancer (Chalazonitis et al., 2008; Kuzel et al., 2017).

Annular pancreas

The annular pancreas (Figure 2D) is a rare birth defect that occurs when rotation of the ventral pancreas has failed or is incomplete, causing pancreatic tissue to encircle the duodenum (Borghei et al., 2013; Etienne et al., 2012). Newborns with annular pancreas may not feed well, spit up more often, and develop pancreatitis and duodenal obstruction. Pancreatitis usually occurs in the annulus of the pancreas since the pancreatic secretions cannot pass through the annular duct, resulting in the accumulation of secretions behind the obstruction and increasing the susceptibility of the annular pancreas to damage (Aleem

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& Shah, 2022; Itoh et al., 1989). Only one example of annular pancreas is found in mice, which is caused by the inactivation of Indian hedgehog (Ihh) (Hebrok et al., 2000).

Diabetes mellitus

Multiple forms of congenital diabetes (Figure 2E) can occur in newborns and children due to defects in β-cell differentiation and function, and they are often caused by genetic mutations and environmental insults during *in utero* stages of development. Neonatal diabetes mellitus (NDM) patients present with severe hyperglycemia at birth. Flanagan et al. analyzed mutations in key transcription factors involved in pancreatic development using samples from 37 NDM patients and identified mutations in *NKX2–2* as an etiological gene for NDM (Flanagan et al., 2014). Consistent with that, mice lacking Nkx2–2 develop severe hyperglycemia and die shortly after birth (Sussel et al., 1998). Maturity onset diabetes of the young (MODY) is a familial monogenic disease where patients harbor a single mutation that disrupts insulin production (Fajans et al., 2001). MODY is classified based on its genetic causes, including mutations in Hnf1α, Hnf4α, Hnf1β, Gck, Pdx1, and Neurod1 (Dickens et al., 2019; Fajans et al., 2001; Horikawa et al., 1997; Pihoker et al., 2013). Patients inheriting these mutations usually develop MODY and are diagnosed with diabetes under the age of 25 (McDonald & Ellard, 2013). Disruptions in these genes during animal development and hPSC differentiation also recapitulate the MODY phenotypes (De Vas et al. 2015; Niborski et al. 2021; Servitja et al. 2009; Low et al. 2021; Cardenas-Diaz et al. 2019; Shih et al. 2002; Ng et al. 2019; Song et al. 2020; Bali et al. 1995; van Bürck et al. 2010; Sachdeva et al. 2009; Bohuslavova et al. 2021; Hermann et al. 2022).

Disruption of epigenetic regulation can cause developmental defects in the pancreas

Epigenetic regulation of pancreatic development and diseases, especially DNA methylation and histone modification, has been reviewed in detail elsewhere (Arnes & Sussel, 2015; Golson & Kaestner, 2017; Kaimala et al., 2022; Quilichini & Haumaitre, 2015). Here we briefly summarize how these two epigenetic mechanisms contribute to pancreatic birth defects (Figure 1).

Histone modifications

Histones are basic proteins that provide structural support for chromosomes. DNA wraps around the histone octamers which consist of H2A, H2B, H3, and H4 dimers. The histone H1 is a linker that connects DNA to the octamers. The N-terminal tails of histones can undergo post-translational modifications which affect their interaction with DNA, chromatin structure and the accessibility of DNA to transcriptional machinery. The most well-known types of histone modifications include acetylation, methylation, phosphorylation, and ubiquitylation. Other types of modifications such as deamination, GlcNAcylation, ADP ribosylation, sumoylation, and isomerization have also been discovered (Andrew J Bannister & Kouzarides, 2011). Histone modifications are added (writers) and removed (erasers) by histone-modifying enzymes. Histone modification readers contains effector domains that recognize and bind to specific modifications and mediate downstream functional outcomes such as transcriptional activation and inactivation. For example, histone acetylation, which usually activates gene expression, is added by histone acetyltransferases (HATs) and removed by histone deacetylases (HDACs), and is recognized by bromodomain.

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In embryonic stem cells (ESCs), the promoters of developmental genes are enriched with bivalent chromatin domains which contain both repressive (H3K27me3) and active (H3K4me3) marks. These bivalent chromatin domains keep developmental genes poised for expression (Bernstein et al. 2006). In response to developmental cues, the repressive H3K27me3 marks are removed by demethylases Kdm6a and Kdm6b which allows rapid activation of lineage-specific genes. The demethylases drive definitive endoderm differentiation by activating Eomes and regulating the Wnt signaling pathway components, Wnt3 and Dkk1 (Jiang et al., 2013; Kartikasari et al., 2013). The undifferentiated endoderm is pre-patterned to express pancreatic genes by default. However, in a subset of cells, the H3K27 methyltransferase Ezh2 and histone acetyltransferase p300 promote hepatic instead of pancreatic fate by suppressing Pdx1 and activating liver genes (Figure 1) (Xu et al., 2011). Decreases in heterochromatin marked by H3K9me3 are also required for liver gene expression (Nicetto et al., 2019). The pioneer factor Foxa2 binds to compact nucleosomal DNA and establishes a primed enhancer state by interacting with H2A.Z, a histone variant that is involved in nucleosome depletion, deposit H3K4me1, and recruit Gata6 during endodermal and pancreatic differentiation (Lee et al. 2019; Li et al. 2012). In Xenopus embryos, knocking out the methyltransferase that catalyzes H3K4me1, Setd7, eliminates the specification of PPCs (Kofent et al., 2016). Once PPCs are induced, Pdx1 engages with the Swi/Snf chromatin remodeling complex to promote proliferation (Spaeth et al., 2019). The Swi/Snf complex is an ATP-dependent chromatin remodeling complex with multiple subunits that can hydrolyze ATP to relocate the nucleosomes to adjacent DNA (sliding) or even evict nucleosomes from the chromatin. Brg1 and Brm are two ATPase subunits in the complex. Losing Brg1 and Brm during development leads to pancreatic agenesis due to reduced proliferation of PPCs while deleting both units in the adult results in fasting hyperglycemia, glucose intolerance, and reduced serum insulin levels (Spaeth et al., 2019). Histone modifications also regulate the differentiation of PPCs. Acinar cell differentiation is abolished when HDACs are inhibited or deleted, while endocrine differentiation is enhanced (Haumaitre et al., 2008; Lenoir et al., 2011; Noël et al., 2008; Zhou et al., 2011). During endocrine differentiation, the repressive mark H3K27me3 on endocrine-specific genes is lost both *in vitro* and *in vivo* (Xie et al., 2013; Xu et al., 2014). Consistent with that finding, deleting Ezh2 during development increased Ngn3 expression and β-cell number. Indeed, Ezh2 heterozygous animals showed enhanced glucose tolerance. However, Ezh2 knockout animals developed diabetes due to aberrant Ink4a/Arf induction which impaired β-cell function (H. Chen et al., 2009; Xu et al., 2014). H3K27me3 demethylase is also required for endocrine differentiation as deleting Jmjd3 leads to impaired endocrine progenitor formation (Yu et al., 2018). Inhibiting the Bromodomain extra-terminal (BET) proteins, the reader of acetylated histones, increases the number of $Ngn3^+$ endocrine progenitors and $Ghrl^+$ ε-cells, but it leads to incomplete development of both β-cells and acinar cells as shown by decreased expression of mature cell markers (Huijbregts et al., 2019).

DNA methylation

In addition to histones, DNA molecules themselves are often methylated. The methyl group is added to the C5 position of the cytosine by DNA methyltransferases to form 5-methylcytosine (5-mC). Interestingly, no enzymes have been found that cleave the methyl

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group directly off the 5-mC. Instead, DNA methylation can be diluted during cell division (passive demethylation), or the methyl group on the 5-mC can be oxidized by ten-eleven translocation (TET) enzymes to form 5-hydroxymethylcytosine (5hmC). The TET enzymes further oxidize 5hmC into 5-carboxylcytosine (5caC) and 5-formylcytosine (5fC), both of which can be recognized by base excision repair system and revert back to unmethylated state (active demethylation) (Liyanage et al., 2014; Moore et al., 2013). DNA methylation represses gene expression by inhibiting the binding of transcription factors to DNA and recruiting HDAC and chromatin remodelers.

Dynamic DNA methylation is required during development. Georgia et al. found that one of the DNA methyltransferases, Dnmt1, methylates the p53 locus in PPCs to inhibit apoptosis. Knocking out Dnmt1 decreases the PPC number and leads to pancreatic agenesis, and the decrease in PPC number in Dnmt1 KO embryos can be rescued by p53 haploinsufficiency (Georgia et al., 2013). In addition, two studies showed that Dnmt1 was indispensable for acinar cell differentiation as the knockdown of Dnmt1 in embryos inhibited acinar cell formation. They also showed that the regulation of acinar differentiation by Dnmt1 is dependent on the carboxyterminal domain which catalyzes cytosine methylation (Anderson et al., 2009; Rai et al., 2006). In the endocrine lineage, Dnmt1 controls the differentiation from endocrine progenitor cells to α- or β-cells. In β-cells, the promoter of Arx (α-cell specific gene) is methylated by Dnmt1. Inhibiting Dnmt1 during pancreatic development leads to hypomethylation of Arx and promotes α-cell formation at the expense of β-cells (Dhawan et al. 2011; Liu et al. 2019). The repression of Arx in β-cells is also mediated by Dnmt3a which forms a repressive complex with Nkx2–2, a gene critical for β-cell differentiation (Doyle & Sussel, 2007). DNA demethylation is also required for proper differentiation. Li et al. deleted TET enzymes in hPSCs and found that pancreatic progenitor and β-cell formation were significantly inhibited. TET depletion disrupted the demethylation of *FOXA2* binding sites which leads to decreased binding of other pancreatic transcription factors such as *GATA6* and *PDX1* (Li et al. 2022). However, there are still many open questions about how TET enzymes regulate demethylation during pancreatic development, particularly the role of TET enzymes *in vivo* is currently limited. For example, what is the role of TET enzymes in activating the expression of endoderm genes in ESCs and what genes are TET enzymes targeting during pancreas organogenesis? Since DNA methylation is also enriched in heterochromatin which is removed during liver specification of bipotential endoderm progenitors, do TET enzymes control the pancreatic versus liver fate decisions?

Non-coding RNAs

NcRNAs are RNA molecules that are not translated into proteins. The coding exons of protein-coding genes only account for less than 2% of the genome (Venter et al., 2001), and more than 90% of the RNA in the transcriptome of mammalian cells are ncRNAs (Palazzo & Lee, 2015). An increasing amount of data has highlighted that ncRNAs, like protein-coding genes, play an important role in regulating normal biological processes, and misregulation of ncRNA expression and function lead to birth defects (Esteller, 2011). Based on their function, ncRNAs can be categorized into housekeeping ncRNAs and regulatory ncRNAs. Housekeeping ncRNAs include transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) and are the key components of cellular structure and metabolism. Regulatory RNAs

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can be classified by their lengths into small ncRNAs (shorter than 200bp) and long ncRNAs (lncRNA, longer than 200bp). The small RNAs include micro RNAs (miRNAs), piwi RNAs (piRNAs), small interfering RNAs (siRNAs), small nucleolar RNAs (snoRNAs), and small nuclear RNAs (snRNAs). LncRNAs can also be further categorized based on their genomic location and orientation, such as intronic, enhancer, intergenic, promoter, antisense, sense, and bidirectional lncRNAs (Dahariya et al., 2019).

NcRNAs regulate every step of gene expression. The piRNAs and lncRNAs are most well-known to regulate transcription in the nucleus whereas miRNAs canonically silence transcripts in the cytoplasm. The role of ncRNAs in β-cell function has been reviewed elsewhere (Dumortier & Van Obberghen, 2012; Font−Cunill et al., 2018; Guay et al., 2012; Ozcan, 2014; Singer et al., 2015). In the following sections, we focus on how different classes of ncRNAs modulate the epigenetic status of the genome during pancreatic development, and discuss how disruptions in ncRNA expression and function can lead to pancreatic birth defects (Table 1).

Long non-coding RNA

LncRNAs have diverse biological functions, including epigenetic modifications (Rinn et al. 2007; Dinger et al. 2008; Pandey et al. 2008; Pontier and Gribnau 2011), transcription (Wang et al. 2008; Feng et al. 2006; Akerman et al. 2017), post-transcriptional modifications (Beltran et al., 2008), and nuclear trafficking (Willingham et al., 2005). LncRNAs play an essential role in pancreatic differentiation and development, and lncRNA expression is also misregulated in pancreatic diseases such as T2D (Mirzadeh Azad et al. 2021; Morán et al. 2012; Font-Cunill et al. 2018). Though it has been established that lncRNAs regulate β-cell function, the role of lncRNAs in pancreatic development is just starting to be appreciated.

Using hPSC differentiation, Jiang et al. characterized the expression of lncRNA during *in vitro* differentiation via transcriptome analysis (Jiang et al., 2015). They identified *LINC00261* as a definitive endoderm-associated lncRNA that promotes *FOXA2* expression by recruiting SMAD2/3 to the *FOXA2* promoter. Deleting *LINC00261* via short hairpin RNA (shRNA) decreased *FOXA2* expression and endoderm differentiation efficiency (Jiang et al., 2015). The positive regulation of *FOXA2* via *LINC00261* also exists during lung epithelial homeostasis and regeneration (Swarr et al., 2019). However, Gaertner et al. recently found that knocking out *LINC00261* via CRISPR/Cas9 impaired the differentiation of β-cells but did not decrease *FOXA2* expression. They also suggested that *LINC00261* regulated pancreatic differentiation via trans-regulatory mechanisms since the nearby *FOXA2* and other proximal genes were not affected by Linc00261 deletion, and affected genes were distributed throughout the genome (Gaertner et al., 2020). The authors in the latter study suggested that the discrepancy between the two studies might be due to different methods of differentiation and gene manipulation. Another lncRNA that regulates definitive endoderm during hPSC differentiation is *DIGIT*. *DIGIT* expression is induced by Activin signaling during definitive endoderm differentiation, and *DIGIT* upregulates the expression of a gene involved in gastrulation and establishing body axis, Goosecoid (*GSC*), *in trans* to promote differentiation (Daneshvar et al., 2016). LncRNAs also regulate chromatin architecture to modulate the expression of key pancreatic transcription factors.

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The promoter of lncRNA *PLUTO* is located ~3kb upstream of *PDX1*. Akerman et al. used chromosome conformation capture sequencing to evaluate the interactions among different DNA sequences and showed that *PLUTO* promoted the contact between the *PDX1* promoter and distal enhancers to regulate *PDX1* expression (Akerman et al., 2017). Using human β-cells, Moran et al. showed that knocking down a β-cell-enriched lncRNA *HI-LNC25* led to the downregulation of *GLIS3* which is mutated in NDM (Morán et al., 2012; Senée et al., 2006). *H19* is a lncRNA that forms a complex with methyl-CpG-binding domain protein 1 (MBD1). The *H19* lncRNA-MBD1 complex interacts with histone lysine methyltransferases and deposits repressive histone marks on the targeted genes (Monnier et al., 2013). *H19* is downregulated in the pancreas during postnatal development. Silencing of *H19* in newborn rats decreased β-cell expansion. MiRNA let-7 and AKT phosphorylation are involved in promoting β-cell proliferation by *H19* (Sanchez−Parra et al., 2018). The lncRNA βlinc1 is an endocrine-specific lncRNA. Knocking out βlinc1 in mice leads to decreased endocrine differentiation in embryos and impaired glucose tolerance in adults. The genes regulated by βlinc1 are related to endocrine differentiation and β-cell function such as Pax6, Mafb, and Nkx2.2. Interestingly, those genes are significantly enriched around βlinc1 on the same chromosome, suggesting that βlinc has a cis-regulatory role during endocrine differentiation such as organizing the chromosome structure near these endocrine genes (Arnes et al., 2016). Of note, it is not known how lncRNAs regulate exocrine cell differentiation. LncRNA expression during pancreatic development has not been fully profiled either. More studies are needed to understand how lncRNAs contribute to the epigenetic regulation of pancreatic development.

MicroRNA

Biogenesis and function of microRNA—MiRNAs are the most studied class of ncRNAs. They are small ncRNAs between 20–22 nucleotides, and canonically silence gene expression by binding to the three prime untranslated region (3’ UTR) of the targeted mRNA, although targeting the 5’ UTR or coding sequence is possible. More than 60% of human protein-coding genes are regulated by miRNAs (Friedman et al., 2009). Each protein-coding gene, including the epigenetic regulators discussed above, can be targeted by multiple miRNAs, and each miRNA can target multiple genes (Peter, 2010), thus miRNAs and mRNAs form a complex gene regulatory network.

Canonically, miRNA biogenesis starts with transcription by RNA polymerase II (Lee et al. 2004) or III (Borchert et al., 2006). The transcription product, primary miRNA (pri-miRNA), folds back on itself and forms a hairpin structure. The microprocessor is a complex composed of one molecule of DROSHA and two molecules of DGCR8 (Nguyen et al., 2015). The microprocessor then cuts the hairpins at the stem and releases a ~70 nucleotides stem-loop structure termed the pre-miRNA (Lee et al. 2002; Lee et al. 2003). Then, the pre-miRNAs are transported from the nucleus to the cytoplasm by Exportin 5 and RAN-GTP (Lund et al., 2004; Yi et al., 2003). In the cytoplasm, Dicer cuts the terminal loop off the pre-miRNA to generate the miRNA duplex (Zhang et al. 2004). Once the miRNA duplex is released, it is loaded into the functional module in the gene silencing pathway termed RNA-induced silencing complex (RISC), in which the Argonaute family (e.g. Ago2) protein expels one strand of the miRNA duplex, while the remaining strand

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remains in RISC to form the mature RISC complex (Schwarz et al. 2003; Liu et al. 2004; Rivas et al. 2005; Suzuki et al. 2015). The mature miRNA then directs RISC to mRNA by pairing its seed sequence to the 3' UTR of the mRNA, and gene silencing occurs through translational repression or mRNA degradation (Huntzinger & Izaurralde, 2011; Jonas & Izaurralde, 2015). Most miRNAs are generated and regulate gene expression via a canonical pathway (Figure 3); however, other non-canonical pathways have also been discovered and summarized by other reviews (Bartel, 2018; O'Brien et al., 2018; Stavast & Erkeland, 2019).

Alternations in microRNA biogenesis can cause birth defects in the pancreas—MiRNAs play an indispensable role during pancreatic development, and disruptions in miRNA biogenesis lead to severe developmental defects in the embryos. The loss of Dicer in mice results in early lethality during development (Bernstein et al. 2003), and loss of Dicer in zebrafish leads to developmental arrest around day 10 (Wienholds et al., 2003). Using a Dicer1-hypomorphic mouse model (Fukasawa et al., 2006), Kalis et al. found that histology of the pancreas showed abnormal structures in adults. Starting at four weeks of age, the Dicer1-hypomorphic pancreas showed decreased islet size, multi-nucleated cells in the duct expressing insulin and glucagon, and obscure boundaries between islets and ducts. However, glucose metabolism was not affected in the Dicer-hypomorphic animals (Morita et al., 2009).

Using another Dicer1 conditional knockout (KO) model in which the second RNase III domain in Dicer1 is knocked out in the developing gut tube by Foxa3-Cre, Prévot et al showed that Dicer1 KO repressed acinar differentiation and induced hepatic gene expression starting from E15.5, suggesting that miRNAs are required for repressing hepatic genes and promoting pancreatic differentiation in endoderm. They also knocked out Dicer1 specifically in the acinar cells and found that KO mice failed to thrive by post-natal day 15 due to intestinal malabsorption (Prévot et al., 2013). The biogenesis of let-7b and miR-495 was inhibited upon Dicer1 deletion, which led to upregulation of Hnf6 and hepatic genes. Lynn et al used Pdx1-Cre to delete Dicer1 in all pancreatic cells and showed that Dicer1 KO pancreata displayed agenesis and differentiation defects in all pancreatic lineages. KO embryos could survive until birth but died by post-natal day 3. They also found that the defects in the endocrine lineage were due to increased Notch activity and Hes1 expression which suppressed the expression of Ngn3 (Lynn et al., 2007).

When Dicer1 was depleted in endocrine progenitors using Ngn3-Cre, the mice developed hyperglycemia during neonatal development, and KO islet cells showed a significant increase in apoptosis (Kanji et al., 2013). Interestingly, Dicer1 KO islets upregulated neuronal genes after birth, suggesting that miRNAs are critical in suppressing neuronal gene expression during the maturation of endocrine lineages (Kanji et al., 2013).

Two studies deleted Dicer1 in β-cells conditionally using the rat insulin promoter (RIP)-Cre. They found that Dicer1 KO mice developed glucose intolerance at a young age (less than two months), progressive hyperglycemia, and diabetes starting from 5 weeks of age. KO pancreata had fewer β-cells and smaller islets. Ultrastructural analysis revealed that KO β-cells contained less insulin granules (Kalis et al., 2011). In the study by Mandelbaum et

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al, the authors labeled KO β-cells using lineage tracing and found that KO β-cells were progressively depleted during post-natal development (Mandelbaum et al., 2012).

Another key enzyme in the miRNA biogenesis pathway, Ago2, has also been investigated in the context of diabetes. Ago2 is required for insulin release from β-cells and β-cell proliferation during insulin resistance by promoting the biogenesis of miR-375, which is a β-cell enriched miRNA known to control β-cell differentiation, proliferation, and secretion (Tattikota et al. 2014; Tattikota et al. 2013; Poy et al. 2009; El Ouaamari et al. 2008; Zhang et al. 2013; Eliasson 2017; Kloosterman et al. 2007). However, unlike Dicer1, the role of Ago2 during pancreatic development is unknown.

Individual miRNAs involved in pancreatic birth defects

MiRNAs targeting epigenetic modifiers

miR-26a: MiR-26a targets ten-eleven translocation (TET) enzymes and thymine DNA glycosylase (TDG) which catalyze the oxidation of methylated DNA (Fu et al., 2013). MiR-26a overexpression in mice leads to the downregulation of TETs and increases the number of endocrine cells (Fu et al., 2013). The authors also used an *in vitro* assay and showed that miR-26a overexpression enhanced endocrine differentiation of pancreatic progenitor cells. Interestingly, knocking down TETs in stem cells downregulates pluripotency factors including Oct4, Sox2, and Nanog, while increasing primitive endoderm genes like Gata6 and Gata4 (Ito et al., 2010). These data suggest that miR-26a could modulate DNA methylation during multiple time points of pancreatic development.

miR-29: MiR-29 regulates lipid metabolism and glucose metabolism during insulin resistance (He et al., 2007; Kurtz et al., 2014). Overexpression of miR-29 decreases glucose-stimulated insulin secretion (GSIS) (Bagge et al., 2012) and one target of miR-29 during GSIS is Mct1 which is a plasma membrane monocarboxylate transporter. (Pullen et al., 2011). During myogenesis, miR-29 has been shown to suppress YY1 which is a member of the polycomb group which represses transcription via chromatin modifications (Wang et al. 2008). In leukemia and lung cancer, miR-29 has been shown to regulate DNA methylation via targeting DNA methyltransferases, Dnmt3a and Dnmt3b (Fabbri et al., 2007; Garzon et al., 2009). The mechanisms regulating miR-29 expression during pancreatic development require further investigation.

miR-9: Joglekar et al. profiled the miRNA expression in developing human pancreatic islets between 8 to 37 weeks of pregnancy and found that miR-9 was expressed during endocrine development (Joglekar et al. 2009). During hPSC differentiation, miR-9 expression is the highest during the formation of primitive gut tube and posterior foregut and is decreased when cells acquire pancreatic identity (Fogel et al., 2015). MiR-9 suppresses insulin release by decreasing the expression of Onecut2 which activates Granuphilin/Slp4 to promote insulin release (Plaisance et al., 2006). Sirt1, a deacetylase of histones and transcription factors, is also a target of miR-9. During spontaneous differentiation of mouse ESCs, miR-9 is upregulated and suppresses Sirt1 expression (Saunders et al., 2010). During glucose-stimulated insulin secretion, miR-9 expression is also increased and the Sirt1 protein level

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is downregulated (Ramachandran et al., 2011). These data indicate that miR-9 can regulate histone acetylation via targeting Sirt1 in both embryos and adults.

miR-124: The expression of miR-124a is increased in the pancreas from E14.5 to E18.5 (Baroukh et al., 2007). MiR-124a expression is also upregulated by glucose in a pancreatic β-cell line (MIN6 cells) and during differentiation from pancreatic islet-derived mesenchymal stem cells to β-cells (Coskun et al., 2018; Tang et al., 2009). MiR-124a targets two K_{ATP} channel components (Kir6.2 and Sur1) that are involved in sensitizing β-cells to Ca^{2+} (Baroukh et al., 2007). In a study by Lovis et al., the authors found that overexpression of miR-124a altered insulin secretion by regulating the expression of Snap25, Rab3a, synapsin1a, Rab27a, and Noc2 (Lovis et al., 2008). MiR-124a has also been found to target a plasma membrane monocarboxylate transporter, Mct1, to modulate glucose concentration and insulin secretion in β-cells (Pullen et al., 2011). Hes1, a negative regulator of Ngn3, was also reported to be targeted by miR-124a during neuronal differentiation (Wang et al. 2010). During development, miR-124a targets Foxa2 which is the pioneer factor for pancreatic differentiation as mentioned above. MiR-124 and miR-9 have been shown to target chromatin remodeling complex subunit Baf53a and facilitate the exchange of Baf53a for Baf53b during neuronal development (Yoo et al. 2011; Yoo et al. 2009). In fact, miR-124 and miR-9 induce chromatin remodeling which enables neuronal reprogramming in human fibroblasts (Abernathy et al., 2017). The epigenetic functions of miR-124 and miR-9 during neuronal development suggest that they could modulate epigenetic regulations during pancreatic development as well.

MiRNAs well studied in pancreatic diseases

miR-375: MiR-375 is one of the most highly expressed miRNAs in both the developing and mature pancreas (Lynn et al., 2007). During differentiation of hPSCs, the expression pattern of miR-375 is similar to human fetal pancreas development (Correa−Medina et al., 2009; Wei et al., 2013). In adults, miR-375 is expressed in β-cells and acinar cells (Avnit−Sagi et al., 2009; Bravo-Egana et al., 2008; Dixit et al., 2016; van de Bunt et al., 2013).

MiR-375 plays an important role in regulating β-cell proliferation and function. Knocking down miR-375 in zebrafish embryos leads to morphological changes in islets such as endocrine cells not being clustered, but found in a scattered distribution (Kloosterman et al., 2007). Mice lacking miR-375 are viable; however, they have decreased β-cell mass and increased α-cell mass as early as 3 weeks of age, leading to hyperglycemia at 4 weeks and ultimately diabetes (Poy et al., 2009). Consistent with the role of miR-375 *in vivo,* overexpression of miR-375 in human pluripotent stem cells during spontaneous differentiation promotes the formation of glucose-responsive insulin-producing cells (Lahmy et al., 2014). Upon insulin resistance, β-cells proliferate to compensate for the increased demand for insulin. MiR-375 promotes compensatory expansion along with Ago2 by targeting Cadm1, a growth suppressor (Poy et al., 2009; Tattikota et al., 2014). One study by Zhang et al. showed that miR-375 also inhibits pancreatic progenitor proliferation by targeting YAP1 which promotes transcription of genes involved in cellular proliferation. (Zhang et al. 2013). Several studies found that miR-375 reduces insulin production and secretion by targeting Pdk1 (Pdk1 is a kinase that is involved in phosphoinositide

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3-kinase pathway and mediates cellular response to insulin), Mtpn (myotrophin is a cytoplasmic protein that promotes exocytosis of insulin granules), Gephyrin and Ywhaz (both are regulators of insulin release) (El Ouaamari et al., 2008; Poy et al., 2004; Tattikota et al., 2013).

MiR-375 is upregulated in animal models for T1D as well as in human patients (Assmann et al., 2017; Erener et al., 2013), thus it has been considered as a marker for β-cell death (Erener et al., 2013). Apart from its role in endocrine regulation, it is also downregulated in pancreatitis (Wang et al. 2016) and pancreatic cancer (Bloomston et al., 2007; Szafranska et al., 2007), suggesting that miR-375 can contribute to exocrine diseases as well.

miR-7: Similar to miR-375, miR-7 is highly expressed during pancreatic development and in adult β-cells (Wei et al., 2013). In mice, miR-7 expression is upregulated from E13.5 to E14.5, and then decreases at E18.5 (Nieto et al., 2012). In humans, miR-7 is induced at 9 weeks of gestational age (wGA) and reaches the highest levels between 14 to 18 wGA (Correa-Medina et al. 2009; Joglekar et al. 2009). However, unlike miR-375 which is expressed in both endocrine and exocrine cells, miR-7 appears to be predominantly enriched in the islet (Bravo-Egana et al. 2008; Joglekar et al. 2009).

Knocking down miR-7a and miR-7b simultaneously by morpholinos in mice at E10.5 leads to increased β-cell death and decreased insulin production, and newborn mice develop glucose intolerance (Nieto et al., 2012). Interestingly, another study by Latreille et al deleted miR-7a2 using RIP-Cre and glucose tolerance in adult mice increased, whereas mice overexpressing miR-7a in β-cells developed diabetes. This study also revealed that miR-7a2 targeted the SNARE complex which regulates insulin granule fusion with the plasma membrane, thereby limiting insulin secretion (Latreille et al., 2014). The discrepancy between these two studies could be due to the time points when miR-7 was being silenced or deleted, potential compensatory function of other miR-7 members, and the method of gene silencing or deletion used.

MiR-7 has also been reported to target a key regulator of endocrine differentiation, Pax6 (Dames et al., 2010; Heller et al., 2005; Sander et al., 1997; St−Onge et al., 1997). Knocking down miR-7 in E12.5 pancreatic explants leads to upregulation of Pax6 expression and α- and β-cell formation (Kredo−Russo et al., 2012). In adults, miR-7 limits β-cell proliferation by targeting multiple components of mTOR signaling pathway such as Mapkap1, p70S6K, Mknk1/2, and eIF4E (Wang et al. 2013). These data suggest that miR-7 family members have diverse roles in β-cell differentiation and function.

miR-30: MiR-30 family members target mesenchymal genes such as Vimentin and Snail1 to maintain an epithelial identity during endocrine cell development (Joglekar, Patil, et al., 2009). However, miR-30 family members have distinct roles in pancreatic diseases. MiR-30a targets Beta2/NeuroD (NeuroD1) to inhibit insulin secretion (Kim et al. 2013). Indeed, suppressing miR-30a increases insulin secretion and prevents β-cell dysfunction in diabetic mice (Kim et al. 2013). In contrast, miR-30d promotes insulin secretion via targeting Map4k4 (Tang et al., 2009; Zhao et al., 2012). MiR-30d also targets Rfx6, a gene that when mutated can cause neonatal diabetes (Liao et al., 2013; Smith et al., 2010).

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miR-21: Using T1D murine models, Ruan et al. found that miR-21 expression was activated by NF-κB, and increased miR-21 downregulated tumor suppressor Pdcd4, which prevented β-cell death and disease progression (Ruan et al., 2011). In addition to being upregulated in T1D patients, miR-21 has also been shown to be misregulated in pancreatitis and pancreatic cancer (Assmann et al., 2017; Dixit et al., 2016; Khan et al., 2015; Rachagani et al., 2015), suggesting that miR-21 has multiple roles in pancreatic diseases.

miR-24: MiR-24 has been shown to regulate the expression of a tumor suppressor, Men1. Decreased Men1 expression promotes β-cell proliferation (Vijayaraghavan et al., 2014). Melkman-Zehavi et al. reported that miR-24 targeted Sox6 to increase the level of insulin mRNA (Melkman−Zehavi et al., 2011). In a study by Zhu et al., two MODY genes, Hnf1α and Neurod1, were found to be direct targets of miR-24 (Zhu et al., 2013). However, the role of miR-24 in the pathogenesis of MODY requires further investigation.

Other types of ncRNAs

PiRNAs are short single-stranded RNAs. PiRNAs form a complex with PIWI proteins to induce a repressive chromatin state of transposable elements by driving DNA methylation (Watanabe et al., 2018). Silencing transposable elements is crucial in maintaining genome stability and integrity. In germline stem cells, piRNAs ensure the fidelity of genetic material for the next generation (Teixeira et al., 2017). One study by Henaoui et al. revealed that piRNAs were differentially expressed during postnatal development and were misregulated in T2D. They also found that overexpressing T2D-related piRNAs in normal islets impaired GSIS (Henaoui et al., 2017). These data suggest that piRNAs might regulate the maturation and function of β-cells. The role of other types of ncRNAs such as snoRNA and snRNA in pancreatic development is unknown.

Conclusion

Newborns with pancreatic birth defects experience problems such as obstruction of the duodenum, nutritional malabsorption, hyperglycemia, and pancreatitis. These problems impede postnatal growth and development and predispose the patient to severe pancreatic diseases like diabetes mellitus and pancreatic cancer later in life. Activating the developmental gene regulatory network is necessary to regenerate pancreatic tissue and represents a major area of focus for treating impairments during pancreatic development. Thus, improving our understanding of developmental regulation will advance our ability to treat and cure patients with birth defects. All pancreatic cells are derived from the same progenitor population. The PPCs acquire different epigenetic modifications on chromatin, thus allowing the expression of different genes and adopting different cell fates. While histone modifications and DNA methylation are mediated by specific enzymes encoded by protein-coding sequences, the non-coding RNAs, which are transcribed from non-coding sequences, make up 98% of the genome and have diverse functions in addition to the epigenetic regulation of gene expression. Understanding ncRNA biology will significantly expand our knowledge of gene regulatory mechanisms. MiRNAs can control the expression of epigenetic modifiers post-transcriptionally via a canonical pathway. Intriguingly, some data showed that miRNAs can also direct the RNA-induced transcriptional silencing

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complex (RITS), which includes histone deacetylases, DNA methyltransferases, and histone methyltransferases, to target DNA sequences in the nucleus to trigger chromatin structure alterations and gene transcriptional silencing. Additionally, evidence suggests that miRNAs can mediate transcriptional gene activation. For example, miR-373 has been shown to bind to the promoter of Cdh1 and Csdc2 to induce gene expression (Place et al., 2008). LncRNAs can modulate gene expression by recruiting chromatin modifiers, acting as a scaffold, and altering chromatin structure. The exact epigenetic regulatory mechanisms used by ncRNAs are gene and cell-type dependent. In this review, we summarized how epigenetic misregulation by ncRNAs can cause pancreatic birth defects, but we are just beginning to appreciate the complex interplay of ncRNAs and epigenetic regulation. In summary, expanding our knowledge of how ncRNAs regulate pancreatic development will help uncover disease mechanisms and develop therapeutics for treating birth defects.

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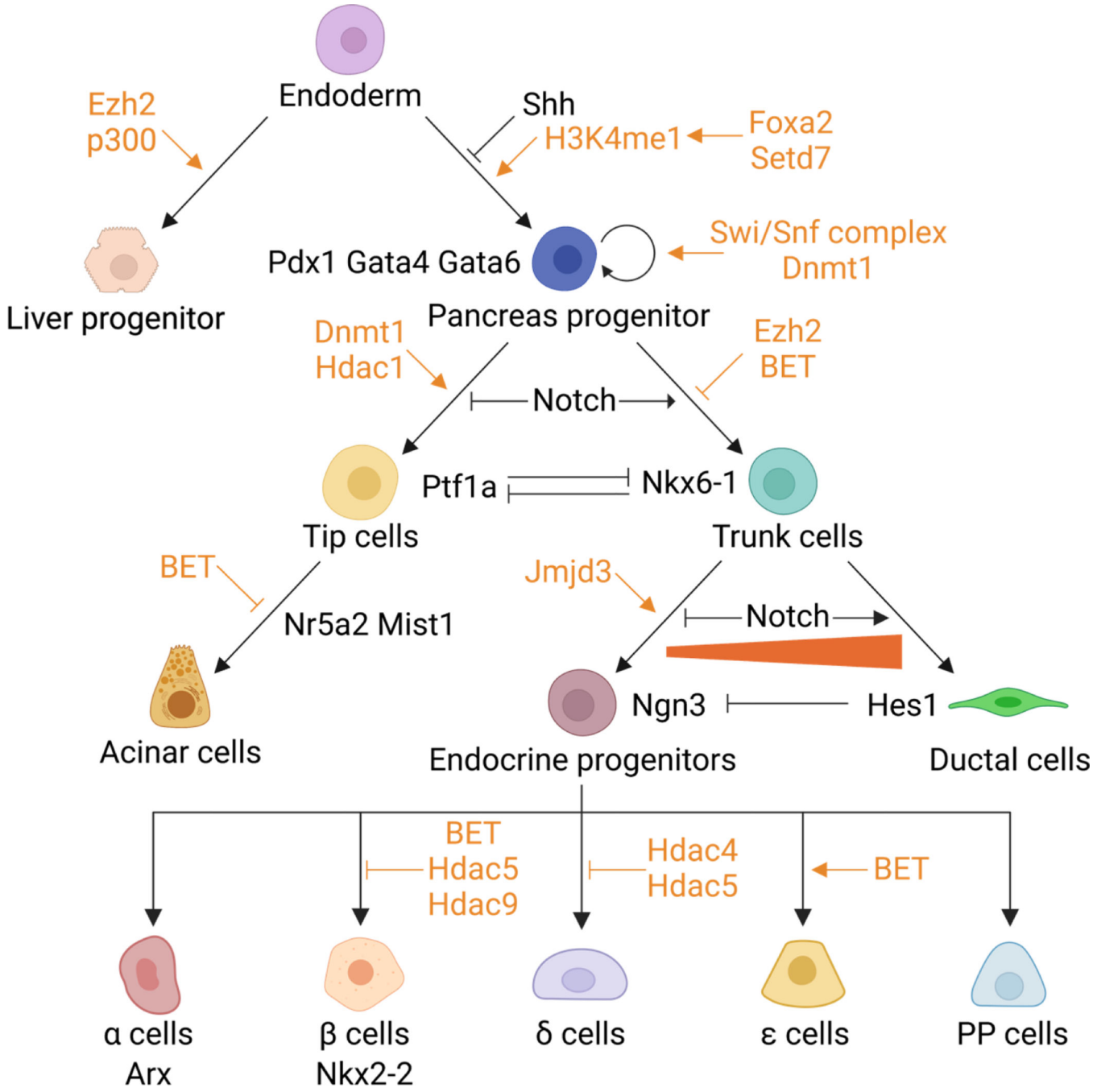

Figure 1.

Illustration of pancreatic development. Transcription factors and signaling pathways regulating pancreatic development are labeled in black. DNA methylation and histone modifications are labeled in orange.

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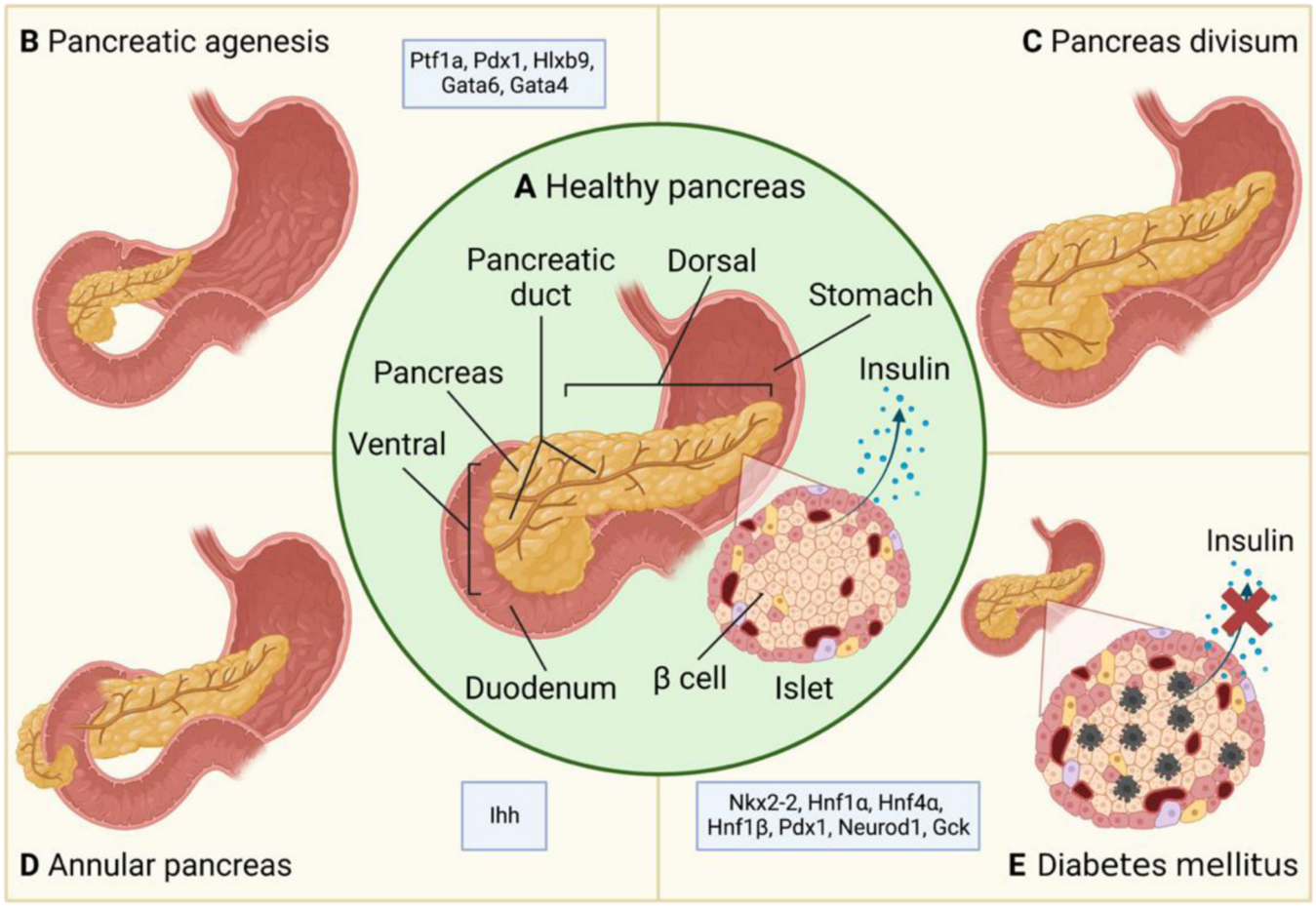

Figure 2.

Illustration of birth defects in the pancreas. (A) In a healthy pancreas, the ducts in the dorsal and ventral pancreas fuse to form a single duct, and the β-cells in the islet of Langerhans synthesize and secret insulin. (B) Agenesis of the pancreas with partially developed pancreas. (C) Failure in the fusion between dorsal and ventral ducts leads to pancreas divisum. (D) Formation of the annular pancreas. Instead of rotating with the gut tube and fusing with the dorsal pancreas, the ventral pancreas encircles the duodenum. (E) Insulin secretion is decreased due to β-cell loss in diabetes. Factors known to contribute to each birth defect are labeled in each panel.

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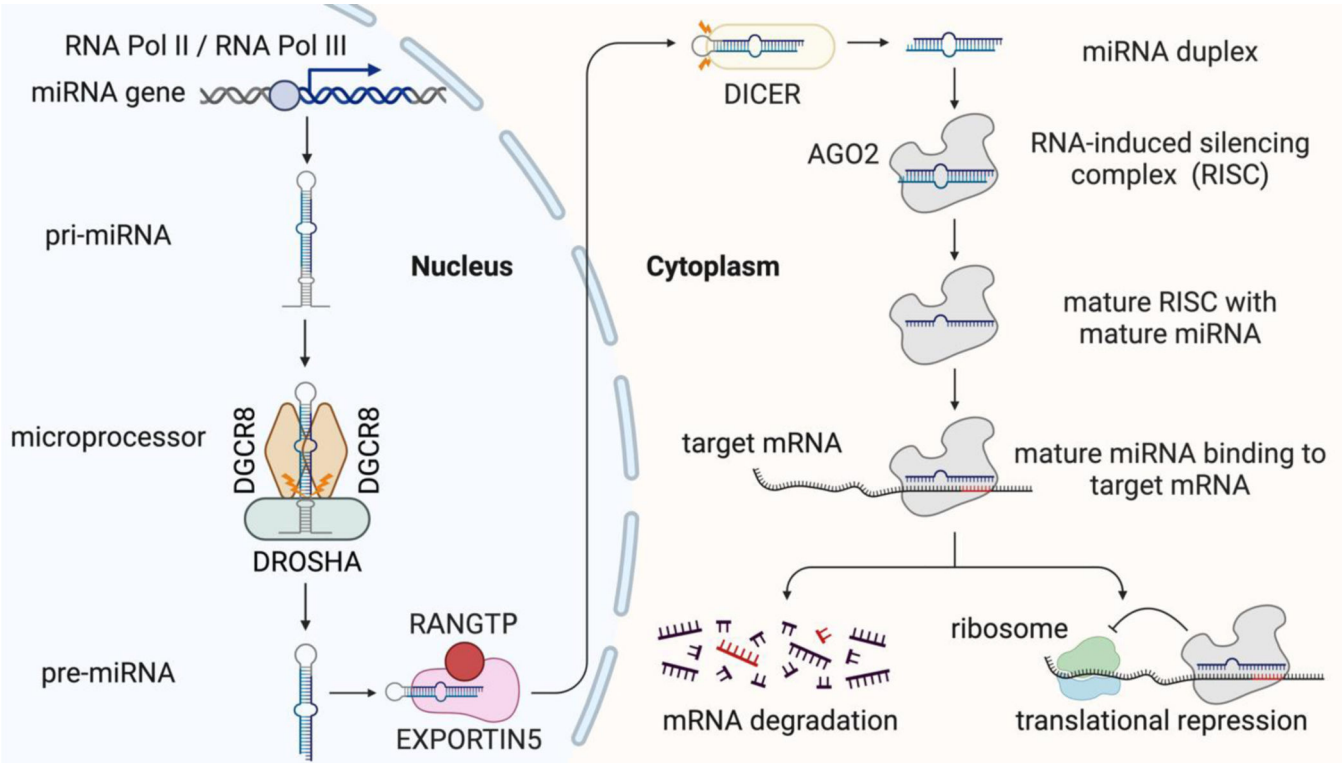

Figure 3.

The biogenesis and function of canonical miRNAs. The RNA Pol II or Pol III transcribes the miRNA gene to pri-miRNA, which then is processed by the microprocessor to form pre-miRNA. The pre-miRNA is exported to the cytoplasm by EXPORTIN5. In the cytoplasm, the pre-miRNA is cleaved by DICER to produce the miRNA duplex. The duplex is loaded onto AGO2. Only one strand will form the mature RISC with AGO2, and the other strand is ejected. The mature RISC will bind to target mRNA and silence gene expression by mRNA degradation or translational repression.

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Table 1.

ncRNAs involved in pancreatic diseases

ncRNA	Targets/Mechanism	Related phenotypes/diseases	Reference
LINC00261	Recruit SMAD2/3 to Foxa2 promoter and promote Foxa2 expression	Knockdown of *LINC00261* decreases endoderm differentiation	(Gaertner et al., 2020; Jiang et al., 2015; Swarr et al., 2019)
DIGIT	Upregulate GSC in trans	Depletion of *DIGIT* inhibits endoderm differentiation	(Daneshvar et al., 2016)
PLUTO	Regulate the interaction of Pdx1 enhancer clusters and promoter	*PLUTO* is downregulated in patients with impaired glucose tolerance and T2D	(Akerman et al., 2017)
HI-LNC25	Regulate GLIS3	Knocking down *HI-LNC25* decreased *GLIS3*, which contributes to diabetes	(Morán et al., 2012)
H19	Form a complex with MBD1 and deposit repressive histone modifications on target genes	*H19* regulates β-cell proliferation during postnatal development and insulin resistance	(Monnier et al., 2013; Sanchez−Parra et al., 2018)
βlinc1	Regulate the expression of endocrine genes *in cis*	Mice lacking βlinc1 show reduced β-cell number during embryo stages and develop glucose intolerance	(Arnes et al., 2016)
miR-26a	TET enzymes	MiR-26a overexpression promotes β-cell number	(Fu et al., 2013)
miR-29	YY1, Dnmt3a, Dnmt3b	MiR-29 suppresses insulin secretion	(Wang et al. 2008; Fabbri et al. 2007; Garzon et al. 2009)
miR-9	Sirt1, Baf53a	MiR-9 decreases insulin exocytosis	(Ramachandran et al. 2011; Yoo et al. 2011; Yoo et al. 2009; Abernathy et al. 2017; Saunders et al. 2010)
miR-124	Baf53a	MiR-124 increases Ca2+ concentration in β-cells	(Yoo et al. 2011; Yoo et al. 2009; Abernathy et al. 2017)
miR-375	Cadm1, Pdk1, Mtpn, Gephyrin, Ywhaz	Diabetes	(Poy et al. 2009; Kloosterman et al. 2007; Lahmy et al. 2014; Tattikota et al. 2014; Tattikota et al. 2013; Poy et al. 2004; El Ouaamari et al. 2008)
miR-7	Snca, Cspa, Pfn2, Basp1, Pax6, Mapkap1, p70S6K, Mknk1/2, eIF4E	Diabetes	(Nieto et al. 2012; Latreille et al. 2014; Wang et al. 2013; Kredo-Russo et al. 2012)
miR-30	Vimentin, Snail1, NeuroD1, Map4k4, Rfx6	Diabetes	(Tang et al. 2009; Joglekar et al. 2009; Zhao et al. 2012; Kim et al. 2013; Liao et al. 2013)
miR-21	Pdcd4	Diabetes, pancreatitis, pancreatic cancer	(Dixit et al. 2016; Ruan et al. 2011; Assmann et al. 2017; Khan et al. 2015; Rachagani et al. 2015)
miR-24	Men1, Sox6, Hnf1α, Neurod1,	Diabetes	(Vijayaraghavan et al. 2014; Zhu et al. 2013; Melkman-Zehavi et al. 2011)