



Pancreatic ductal cells in development, regeneration, and neoplasia

Maximilian Reichert and Anil K. Rustgi

Division of Gastroenterology, Department of Medicine, Abramson Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA.



The pancreas is a complex organ comprised of three critical cell lineages: islet (endocrine), acinar, and ductal. This review will focus upon recent insights and advances in the biology of pancreatic ductal cells. In particular, emphasis will be placed upon the regulation of ductal cells by specific transcriptional factors during development as well as the underpinnings of acinar-ductal metaplasia as an important adaptive response during injury and regeneration. We also address the potential contributions of ductal cells to neoplastic transformation, specifically in pancreatic ductal adenocarcinoma.

Introduction

The pancreas is an organ that has endocrine and exocrine compartments (1). The endocrine compartment consists of α , β , δ , ϵ , and pancreatic polypeptide cells organized into islets, whereas the exocrine compartment consists of acinar, ductal, and centroacinar cells (Figure 1). Acinar cells synthesize and secrete digestive enzymes, which are concentrated into a bicarbonate rich fluid that traverses through a complex network of ducts (Figure 1). The terminal, or intercalated, ducts are lined by flat, almost squamous-like epithelia. Terminal end duct cells that interface with acini are called centroacinar cells (2). Intercalated ducts merge to form intralobular ducts (lined by cuboidal epithelia), and these in turn merge to form interlobular ducts, which finally merge to form into the main duct (lined by simple columnar epithelia) that traverses the pancreas to the duodenum, delivering fluid laden with digestive enzymes.

This review will focus initially on what is known about the role of specific transcriptional factors that govern ductal cell morphogenesis and biology during development and in adult tissues. Second, we will address acinar-ductal metaplasia (ADM), which is an important component of pancreatitis and neoplastic transformation. Understanding the governance of ADM provides potential insights into ductal cell morphogenesis. Finally, how ductal cells might contribute to neoplastic transformation will be discussed. The field of ductal cell biology is still evolving, and here we place what is known into the context of what still needs to be discovered. For some recent comprehensive reviews on the endocrine and exocrine lineages during development as well as their physiological functions in the adult pancreas, see refs. 3–7.

Regulation of pancreatic development

The pancreas, along with the liver and biliary tract, arises from a shared multipotent population of cells in the foregut endoderm (8, 9). In the human, the pancreas is first discernible as the dorsal bud that emerges from the proximal duodenum at four weeks of gestation. A collection of primitive epithelial tubules within the pancreas is evident at week seven. The epithelial tubules comprise central ducts that have an admixture of loose mesenchyme and peripheral ducts encompassed by a peripancreatic mesenchyme. These tubules undergo branching, and mature acini develop from

cell buds that surround their ends. Development of endocrine cells begins in the central duct area and, with increasing developmental age, moves toward the periphery. Endocrine cells are apparent in the developing islets after 10 weeks of gestation. During the third month of gestation, both mature secretory acini and islets of Langerhans can be recognized.

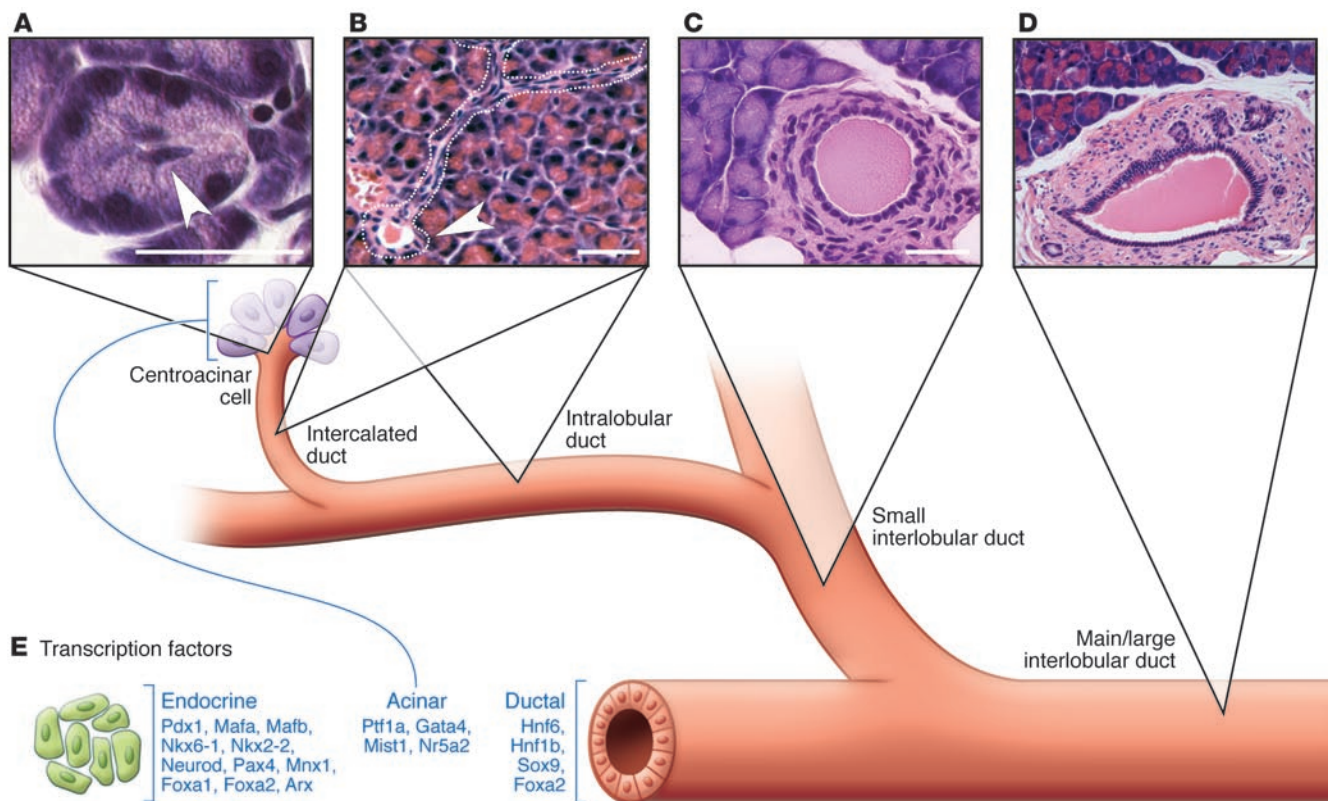
In the mouse, the earliest morphological evidence of the pancreas arises around E8.5 to E9.5. The ventral and dorsal pancreatic buds fuse as a result of gut tube rotation around E13. Up to this point, the pancreas consists of protodifferentiated epithelium (termed pancreatic cords or pancreatic trunk epithelium). During a time termed “secondary transition” (starting around E13.5 to E14.5), a burst of proliferation accompanied by differentiation occurs (4). Histologically distinct acinar and ductal cells do not appear until approximately E15 (10).

Pancreatic development is a tightly regulated process, with the endocrine and exocrine compartments emerging from a common progenitor population. This process involves the interplay of Hedgehog signaling during early pancreatic development (11–13), Notch signaling, and other cues from the mesenchyme (14–17). In addition, genetic studies have identified a number of transcription factors critical for pancreatic development; notably, *Pdx1* is required for the specification of all pancreatic lineages (18–20), and *Pdx1*, *ngn3*, *NeuroD* (also known as *BETA2*), *Hnf6*, and *Pax4* all contribute to proliferation, differentiation, and endocrine lineage commitment (20–26). Exocrine lineage specification or differentiation is influenced both by the lack of proendocrine transcription factors and by the presence of permissive signals furnished by contiguous pancreatic mesenchyme (12, 15, 27), including Wnt signaling (28), laminin-1, and soluble follistatin (29, 30). Furthermore, the levels of FGF-1, FGF-7, and TGF- β_1 , activin and EGFR are important in determining the balance between endocrine and exocrine differentiation (31–34). Notably, these findings are based upon *ex vivo* organ cultures.

Acinar cell differentiation during development appears to be regulated by the bHLH transcription factor, *Ptf1a* (also known as *p48*) (35–37). Although detected early in pancreatic development in multipotent progenitor cells, *Ptf1a* expression becomes restricted to differentiating and mature acinar cells (18). Knockout of *Ptf1a* in mice leads to an absence of the exocrine pancreas and displacement of islet cells to the spleen, in which the endocrine compartment resides in some lower vertebrates (38). However,

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**Figure 1**

Anatomical organization of the pancreatic ductal tree. (A) Centroacinar cells are terminal end duct cells that interface with acini (white arrowhead; scale bar: 10 μ m). (B) Terminal ducts or intercalated ducts (dotted line), respectively, are composed of flat epithelia and merge into intralobular ducts (white arrowhead) that are lined by cuboidal epithelia (scale bar: 10 μ m). (C) Intralobular ducts merge to form small interlobular ducts surrounded by mesenchyme (scale bar: 10 μ m). (D) Larger interlobular ducts are lined by columnar epithelia (scale bar: 10 μ m). (E) Some key acinar, ductal, and endocrine cell transcription factors are depicted (see refs. 4, 6).

studies in similar mouse models reveal the persistence of early endocrine cells closely associated with the pancreatic ductal remnant (18, 35, 39). Mist1 is another bHLH transcription factor that becomes important at the approximate time of secondary transition, and, as elaborated upon below, mice lacking Mist1 exhibit defective acinar cellular organization (40).

Regulation of the ductal cell lineage during development

Ductal cells express markers such as cytokeratin 19 (K19), cystic fibrosis transmembrane receptor, carbonic anhydrase II (CAII), and DBA lectin and transcriptional factors such as HNF1 β , HNF6, and SOX9. Recent work has helped to elucidate the hierarchy of transcriptional factors required to foster the formation and maturation of ductal cells during development.

Gu et al. showed that pancreatic ducts emerge from Pdx1-expressing cells that separate from the endocrine and exocrine lineages between E9.5 and E11.5 (41). It has been demonstrated that non-islet Pdx1-positive cells display physical traits of ductal branching starting at E14.5, and there is even some evidence of these cells – which are insulin negative and K19 positive – as early as E12.5 (42). In addition, a 3D cell culture model of branching morphogenesis, using primary pancreatic duct cells, identified a transient surge of Pdx1 expression exclusive to branching cells (42). This suggests that Pdx1 might be involved temporally in a

program of gene expression sufficient to facilitate the biochemical and morphological changes necessary for branching ductal morphogenesis, both during development and in the adult pancreas.

The Hnf6 transcription factor appears to be important in pancreatic ductal development. Mice lacking the gene (*Hnf6*^{-/-} mice) develop cysts in interlobular and intralobular pancreatic ducts but not in intercalated pancreatic ducts (43). Intriguingly, this could imply that Hnf6 function might be restricted to distinct ductal segments. Furthermore, there is an absence of primary cilia in the pancreatic tubular structures of *Hnf6*^{-/-} mice (43). Conditional *Hnf6* knockout in the murine pancreas recapitulates most of the features of the global knockout (44). Additionally, the pancreata from these mice display increased ductal cell proliferation and metaplasia as well as other features of pancreatitis (44).

At the time of secondary transition, the pancreatic trunk epithelium includes a progenitor population that can give rise to ductal and endocrine lineages (45). It has been demonstrated that Hnf6 is a positive regulator of the proendocrine factor *ngn3* (46). Malformed ducts in global as well as conditional *Hnf6* knockout mice have reduced numbers of *ngn3*⁺ cells, along with persistent expression of endocrine markers, including glucagon, insulin, and Pdx1, in these ducts (44, 46). It is tempting to speculate that the developmental abnormalities in *Hnf6*^{-/-} mice stem, in part, from the failure of *ngn3*-positive progenitor cells to function properly.

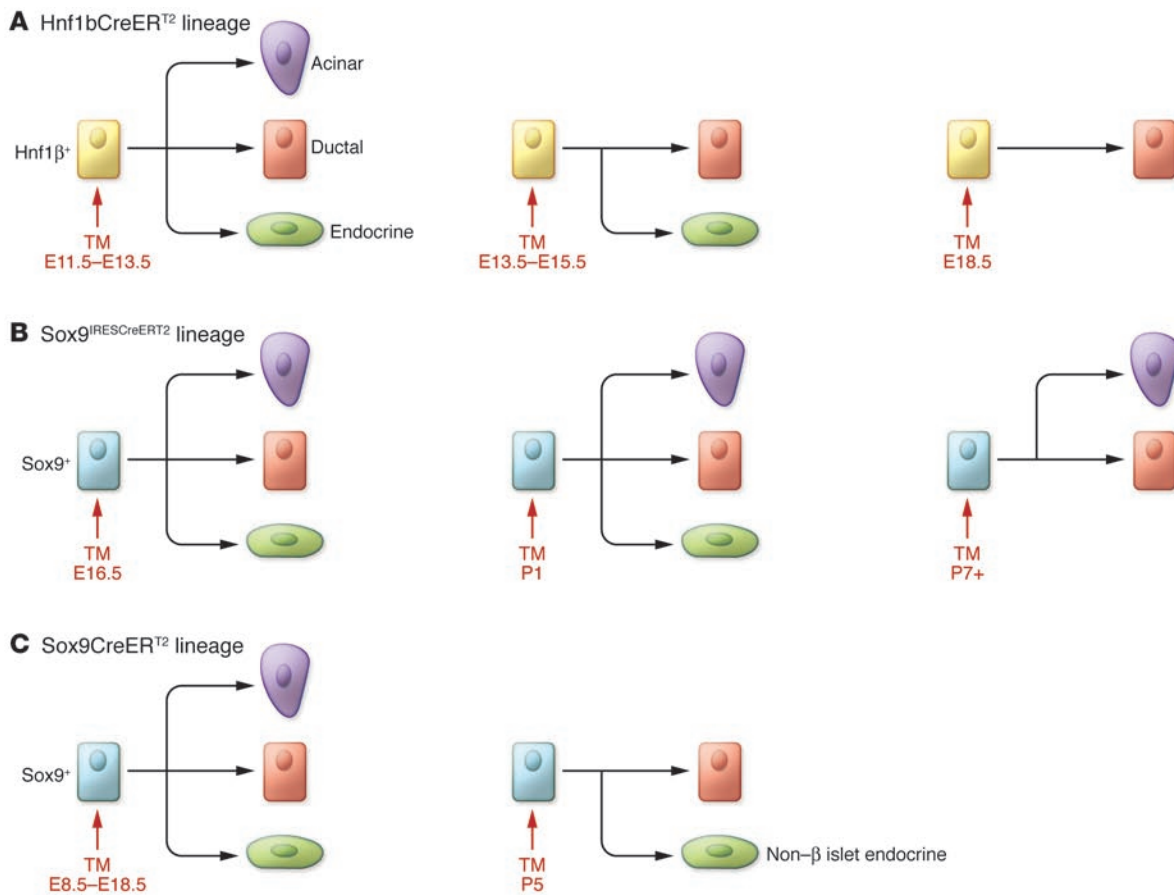


Figure 2

Role of Hnf1β and Sox9 in pancreatic ductal lineage specification. **(A)** Solar et al. (51) performed pulse-chase experiments using the *Hnf1bCreER^{T2};R26R* mouse model. Hnf1β-positive cells give rise to all pancreatic lineages when recombination was induced prior to secondary transition. When pulse labeled between E13.5 and E15.5, progeny cells were found only within the endocrine and ductal compartments. Induced at E18.5, Hnf1β-positive cells are located exclusively within ducts. **(B)** Furuyama et al. (52) demonstrated with their *Sox9^{IRESCreERT2};R26R* model that Sox9-positive cells give rise to acinar, ductal, and endocrine cells when induced at E16.5 and P1, respectively. Any time after P7, Sox9-positive cells repopulate the acinar and ductal compartment. **(C)** Kopp et al. (53) labeled Sox9-positive cells with a transgenic approach, using *Sox9CreER^{T2};R26R* mice, and confirmed that Sox9-expressing cells give rise to all pancreatic lineages when induced between E8.5 and E18.5. When analyzing pancreata that were labeling at P5, recombination was observed in ducts and endocrine cells. TM, tamoxifen.

Another transcription factor critical for pancreatic ductal development and whole-organ formation is Hnf1β (also known as Tcf2). Hnf1β, encoded by the maturity-onset diabetes of the young 5 (*MODY5*) gene, is activated downstream of Hnf6 (47), and Hnf1β expression is diminished in pancreatic cystic structures of *Hnf6*^{-/-} mice. (43). To examine the role of Hnf1β in pancreas development, Haumaitre et al. generated chimeric mice by tetraploid aggregation, since *Hnf1b*^{-/-} mice die before gastrulation (48). These mice display agenesis of the ventral bud and rudimentary development of the dorsal pancreas, which overlaps with some features of *Ptf1a*^{-/-} mice. In part, this may be due to direct regulation of Ptf1a by Hnf1β; however, the more severe picture of perturbed pancreatic organ formation in *Ptf1a*^{-/-} mice indicates Ptf1a-independent effects of Hnf1β (48).

Yet another critical transcriptional factor is the Sry/HMG box transcription factor Sox9, which is essential for the maintenance of the pancreatic progenitor pool, because it stimulates proliferation and survival of progenitors. Therefore, pancreas-specific *Sox9* ablation leads to hypoplasia of the gland (49). One study positions SOX9 upstream of HNF6 and HNF1β at the time of

secondary transition (50). Interestingly, the authors show also that Sox9 directly regulates the expression of *ngn3*, highlighting the role of Sox9 in controlling a bipotent (ductal and endocrine) progenitor population (50).

In contrast to the aforementioned gene ablation models, more recent studies have used direct cell lineage tracing to understand pancreatic lineage specification (Figure 2). Labeling Hnf1β-expressing cells before secondary transition (E11.5–E13.5) reveals that this population gives rise to all pancreatic lineages, whereas, shortly afterward (E13.5–E15.5), Hnf1β cells differentiate into ductal and endocrine lineages, and labeling around E18 labels only the ductal compartment (51). More recently, Furuyama et al. (52) used a knockin lineage tracing approach to show that even after secondary transition (E16.5 or as late as P1), Sox9-positive cells contribute to the ductal, acinar, and endocrine lineages. After induction at P7, labeled cells were found exclusively within the ductal and acinar compartments. This holds true in their model system even in older mice (eight weeks), suggesting Sox9-positive ductal cells or centro-acinar cells maintain the exocrine compartment (52).



Sander and colleagues obtained different results with a *Sox9CreER^{T2}* transgenic mouse model. Indeed, their pulse-chase experiments confirmed that inducing at any time between E8.5 and E18.5 labels all pancreatic lineages (53). By contrast, at P5, Sox9-positive cells give rise to ductal cells and to few endocrine cells. However, although a small percentage of insulin-positive cells are lineage labeled, these fail to give rise to new β cells in the time course of the experiment. Therefore, Sox9-positive cells do not contribute to the β cell compartment during this early postnatal period in these experiments (53). Overall, these discordant results are likely due to differences between the two mouse models and leave some room for differing interpretations of the role of Sox9 in the specification of pancreatic lineages.

It seems to some extent that the HNF1 β -positive population differs from the Sox9-positive population. Kopp et al. demonstrated that some of the Sox9-positive cells at E14.5 are HNF1 β negative; however, they coexpress Ptf1a, Nkx6.1, and Pdx1 and are localized at the interface between the trunk and tip, a region that might represent a niche for progenitor cells (53). Of note, evidence from in vitro experiments shows that Sox9 interacts with Hnf1 β , Hnf6, and Foxa2, and these interactions could modulate the action of each transcription factor in pancreatic development. In turn, both *Foxa2* and *Hnf1b* regulate Sox9 expression, demonstrating feedback loops between these genes (49, 50).

Plasticity of ductal cells: a source of islet cells?

Of intense interest in the study of ductal cells has been their potential capacity to give rise to islet cells. If possible, this would be another vehicle to generate islet cells for transplantation as well as a potential treatment of diabetes mellitus. Insights into ductal cell plasticity have been gained through in vitro and in vivo approaches. For example, ligation of the pancreatic duct in the adult rat fosters duct- to islet-cell differentiation (54). Human ductal tissue in vitro can be expanded to insulin-positive cells (55). However, genetically based in vivo studies have yielded divergent results. One study concluded that β cell progenitors can be activated in the injured adult mouse pancreas and are located in the ductal lining (56). Differentiation of these adult endocrine pancreatic progenitor cells was *ngn3* dependent, and all islet cell types emerged from this population. The authors demonstrated β cell proliferation both in situ and in embryonic explant culture systems (56). Another study used the pancreatic ductal-specific human carbonic anhydrase II (CAII) promoter with an inducible Cre/lox model in lineage tracing studies. CAII-expressing cells within the pancreas appear to act as progenitors that give rise to both new islets and acini, normally after birth and after injury (pancreatic duct ligation [PDL]) (57).

These findings, however, have been challenged. For example, Hnf1 β -positive cells do not give rise to acinar or endocrine cells during the neonatal period, during a 6-month period, or during induction of different types of injury (51). In another study, a subset of Sox9-positive cells start to express *ngn3* after PDL; however, this population fails to contribute to the emergence of the endocrine lineage (53). One possible conclusion that emerges from these divergent studies is that a subpopulation of ductal cells or cells lining the ductal epithelium, marked by endocrine marker(s), is able to give rise to islet cells in the adult, but this activation requires some form of injury, and such a population is not genetically labeled by either Hnf1 β or Sox9. Additionally, preexisting β cells are the major source of new β cells during adult life and after partial pancreatectomy in mice (54–58), supporting the premise that β cells arise from self-duplication (58–62). These results sug-

gest that major hurdles remain before the potential plasticity of ductal cells can be exploited as a source of new β cells.

ADM: insights into ductal cell reprogramming and neoplastic transformation

Metaplasia is defined by the conversion or replacement of one differentiated cell type with another in the context of a given tissue. In some tissues, metaplasia is associated with an increased risk of cancer. Investigation of metaplasia might also provide clues to the cell of origin of cancer. To that end, pancreatic acinar cells have the capacity to undergo metaplasia to a ductal cell phenotype in the setting of acute or chronic inflammation, representing an important link to pancreatic ductal adenocarcinoma (PDAC). ADM might represent reprogramming of a progenitor population, direct transdifferentiation of acinar cells to ductal cells, or transdifferentiation via an intermediate cell type (potentially a progenitor cell). Lineage tracing suggests ADM occurs in vivo but occurs only in a subset of metaplastic lesions (63). Exocrine epithelial explants lose acinar cells in culture with expansion of ductal cells (64–67); however, these results could be due to potential survival advantages of ductal cells in culture.

The molecular basis underlying the development of ADM involves a number of seemingly diverse pathways and molecules. One common theme in divergent studies of ADM is the importance of TGF- α and EGFR signaling. Transgenic mice with *Tgfa* overexpression in the exocrine pancreas progress to a phenotype marked by duct-like cells and tubular structures (64). The importance of EGFR signaling in ADM has been underscored in other studies as well (68–70). Acinar-enriched epithelial explants were isolated from a mouse model designed for acinar-specific lineage tracing, involving Cre/lox-mediated β -gal expression, and cultured subsequently in the presence of recombinant human TGF- α (71). At the time of isolation, β -gal staining was observed exclusively in acinar cells, and no β -gal activity was observed in cells expressing duct-specific keratins. After culturing epithelial explants for five days in the presence of TGF- α , cystic ductal epithelial structures formed that were positive for β -gal activity (71). Houbracken and colleagues very recently showed that human acinar cells display an equal amount of plasticity through lineage tracing (72). Interestingly, after one week of culture, almost all of the surviving acinar cells expressed ductal markers. This could be prevented partially by inhibiting MAPK signaling (72).

TGF- α -mediated engagement of EGFR results in the activation of downstream signaling cascades that might involve Kras activation. Preneoplastic and neoplastic lesions in the pancreas harbor mutations in the Kras oncogene, resulting in constitutive activation of downstream signaling cascades (73, 74). Such mutations are critical in the induction of neoplastic lesions. Acinar-specific expression of activated Kras is one of several mouse models of PDAC. Analysis of such mice (*LSL-Kras^{G12D}/+*/*Ptf1aCre/+* mice) at four weeks of age reveals that the predominant cellular alteration in the exocrine pancreas is acinar metaplasia, in which individual acini consist of acinar cells and duct-like cells (75). Metaplastic acinar structures are highly proliferative, express Notch target genes, and exhibit mosaic expression patterns for EGFR, ErbB2, and pErk, reminiscent of the PDAC precursors, pancreatic intraepithelial neoplasia (PanIN) lesions (71, 75, 76). Kras activation in mature acinar cells induces PanIN lesions identical to those observed upon ubiquitous Kras activation, and Notch signaling promotes both initiation and progression of these acinar-derived PanINs (77). At the cellular level, Notch/Kras coactivation promotes rapid reprogramming of acinar cells to a duct-like phenotype.

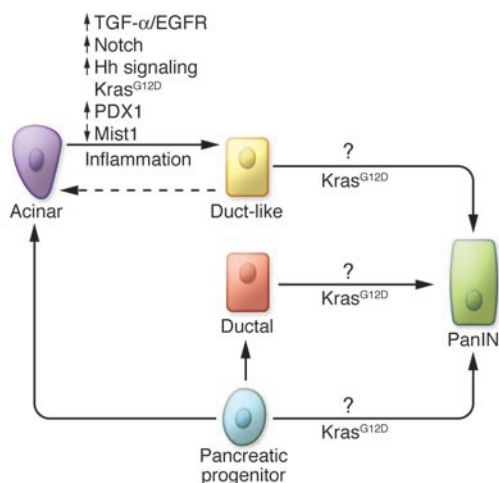


Figure 3 ADM and PanIN — roles of potential pathways. In the adult mouse pancreas, ADM may be triggered by inflammation and other factors. Known associations with ADM include, but are not limited to, extracellular cues — TGF- α , Hedgehog signaling, Notch signaling — and intracellular alterations mediated by Kras^{G12D} activation, including induction of Pdx1, induction of TNF- α , and decreased Mist1 expression. Ductal cells or duct-like cells are replaced by healthy acinar cells during recovery from injury. ADM might represent a precursor lesion to PanIN and constitute a cell of origin for PanIN. The cell of origin for PanIN might be a ductal cell or a distinct yet-to-be-identified progenitor cell.

Another theme in ADM involves changes in the transcriptional network. Spontaneous ADM has been described in vitro, accompanied by the induction of Pdx1 expression during culture of acinar cells (66). Based upon the finding that transgenic mice with *Tgfa* overexpression develop ADM and an expansion of Pdx1-positive epithelial cells (70), a more direct role for Pdx1 in ADM has been suggested. Indeed, transgenic expression of Pdx1 in the Ptf1a domain (35) results in the replacement of acinar cells by duct-like structures, and, furthermore, this requires Stat3 activation (78).

Another relevant transcription factor is Mist1. Mist1 functions as a homodimer, and its loss results in ADM in vitro, with accompanying induction of K19 and K20 (79). Transgenic mice expressing a dominant-negative Mist1 undergo ADM in vivo (79). Collectively, these studies suggest that loss of Mist1 initiates metaplasia and that Pdx1 expression fosters ADM, perhaps mediated by Stat3 as a potential target of Pdx1.

One unifying (perhaps simplified) model underlying ADM involves TGF- α engagement of EGFR, subsequent EGFR-mediated activation of downstream signaling effectors (e.g., Kras, MAPK, Pten) (80), and, ultimately, alteration (induction or suppression) of key transcription factors, such as Mist1, Pdx1, and Stat3. In addition to EGFR signaling, Notch signaling (manifested by Hes1 expression) suppresses the acinar cell phenotype (16) and favors ADM (75). It is also known that Notch is required for TGF- α -mediated effects in the pancreas (76). Thus, the acinar cell state is Mist1 positive, Pdx1 negative, and Hes1 negative, and, with the transition to the ductal state, metaplastic cells are increasingly Mist1 negative, Pdx1 positive, and Hes1 positive. This model would presuppose that ADM is critical in neoplastic transformation, abetted by a proinflammatory state (81, 82).

Ductal cells and their relationship to PanIN and PDAC

The most common subtype of human pancreatic malignancy is PDAC. It has been established that PDAC is preceded by the evolution of precursor lesions, PanIN 1A/B, 2, and 3 (83, 84), and, under certain conditions, ADM might be critical for the development of PanIN lesions (70, 71). PanIN lesions can occur in the setting of chronic pancreatitis and might also be age dependent in the background of otherwise normal pancreatic architecture at the time of autopsy. An unresolved question relates to the cell of origin for PanIN and PDAC. Genetically engineered mouse models using mutant Kras support the notion that ADM might represent a prerequisite for PanIN and PDAC development (70, 71). In addition, the chronic administration of cerulein to mutant Kras mice accelerates PDAC lesions, suggesting that inflammation is important in mediating tumorigenesis (80), which is influenced by different cell types in the tumor microenvironment (85).

Conceivably, ADM yields a cell type with ductal features that is susceptible to the effects of Kras activation and other genetic alterations (Figure 3). Intriguingly, spontaneous conversion of acinar cells to PanIN lesions in the mouse can occur by direct targeting of acinar cells with Kras^{G12D} in the absence of injury or inflammation (86). However, the development of PanIN lesions in vivo may involve the emergence of a progenitor population that is either an indirect or direct precursor to cells that will contribute to a PanIN (Figure 3). This progenitor population would necessarily express Pdx1, which is normally low or absent in ductal cells. It is possible that a resident progenitor population exists among ductal cells or centroacinar cells, which undergoes neoplastic transformation without ADM. The existence of such a population is suggested by the finding that a subset of adult mouse centroacinar cells/terminal duct cells harbor high aldehyde dehydrogenase isoform 1 (ALDH1) enzymatic activity, which is important in retinoic acid metabolism and has been associated with stem and progenitor cells in a variety of tissue types (87). Isolation of Aldh1-positive cells by flow cytometry reveals enrichment of Sca1, Sdf1, c-Met, Nestin, and Sox 9 (87). These cells form “pancreatospheres” in culture, with a capacity for endocrine and exocrine differentiation (suggesting plasticity), and independently expand in the face of chronic epithelial injury. As a related but separate consideration, whether such a population may participate in the eventual development of pancreatic cancer stem cells, marked by CD133, CXCR4, CD44, CD24, and epithelial-specific antigen (ESA) expression (88, 89), is not clear. While it is believed that non-islet cells are the cells of origin for PanIN and PDAC lesions, it has been suggested that chronic pancreatic injury can alter the endocrine fate of β cells, which are usually resistant to the effects of oncogenic insults, and allow them to serve as the cells of origin for exocrine neoplasia (90).

Definitive proof for a ductal cell or centroacinar cell of origin for PanIN and PDAC will require the generation and characterization of appropriate cell-type specific promoters with endogenous Kras activation (with lineage tracing strategies), possibly coupled to other genetic alterations (e.g., mutant p53). These approaches could then be placed into the context of existing genetically engineered mouse models of PDAC that use *Pdx1-cre* or *Ptf1a-cre*.

Summary and future directions

The ductal tree evolves during mouse embryogenesis from a common progenitor pool that is fated to evolve into the endocrine and exocrine lineages. First evident at E14–E15, the ductal structures mature by E17–E18 (42). Pdx1, EphB signaling, and Cdc42 are important in pancreatic ductal branching morphogenesis (42,



91, 92). Elegant genetically engineered mouse models capitalizing upon the expression patterns of *Hnf1 β* , *Hnf6*, and *Sox9* have yielded somewhat divergent results for the capacity of ductal cells to give rise to other lineages during development in the postnatal period and in young mice. In the adult mouse pancreas, it is clear that ductal cells, like islet and acinar cells, are relatively quiescent under homeostatic conditions. However, injurious conditions may reveal a restricted or transient capacity of acinar cells to evolve into ductal cells or ADM. ADM is an important precursor to PanIN lesions, and PanIN lesions progress to PDAC, at least in the mouse. Whether ADM results from direct metaplasia or perhaps transdifferentiation, or whether either process occurs through an intermediate progenitor cell, remains unresolved. It should be noted that the development of PanIN lesions may not require ADM. The adult pancreas may well harbor a low-frequency progenitor population, perhaps resident among centroacinar cells or among ductal cells, a population that may be unmasked during injury and inflammation and may even have the capacity to give rise to islet cells.

Questions remain about the transcriptional regulation of gene expression in ductal cells, which might have shared mechanisms with genes expressed in acinar and islet cells (93–95), and the differences between terminal ducts and the main duct as well as about whether ductal cells can serve as the cells of origin for PanIN/PDAC and whether progenitor cells might reside in the ductal

tree itself. Furthermore, in recent years, insights have been gained into the clinical, histopathological, and genetic characteristics of mucinous cystic lesions in the pancreas (intraductal papillary mucinous neoplasm [IPMN], mucinous cystic neoplasm), which carry a low malignant potential and might represent developmental derangements in the ductal tree, although they manifest in late adulthood (96–101). For example, comparisons between IPMN and PDAC might help to elucidate whether the location of the lesion within the ductal system contributes to the pathogenesis of the type of malignancy. These studies underscore the necessity for an increased understanding of ductal cell biology to inform our research in fields as diverse as development and tumorigenesis.

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Address correspondence to: Anil K. Rustgi, GI Division, 600 CRB, 415 Curie Blvd., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA. Phone: 215.898.0154; Fax: 215.573.5412; E-mail: anil2@mail.med.upenn.edu.

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