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Disputed Paternity: The Uncertain Ancestry of Pancreatic Ductal Neoplasia

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In this issue of *Cancer Cell*, Kopp and colleagues report that pancreatic ductal cells are largely refractory to the induction of pancreatic neoplasia. Whereas a rare ductal subpopulation may still prove capable of neoplastic transformation, these findings refocus attention on acinar and other non-ductal cell types as initiators of this deadly neoplasm.

While malignant tumors of the pancreas can display a variety of histologic forms, the term "pancreatic cancer" is usually synonymous with a pathological diagnosis of pancreatic ductal adenocarcinoma (PDAC). As its name implies, PDAC has long been presumed to arise from pancreatic ductal epithelial cells. Along with its noninvasive precursor, pancreatic intraepithelial neoplasia (PanIN), these tumors typically display a distinctly duct-like histology, and express markers of ductal differentiation. As demonstrated for other tumor types, however, tumor histology is often misleading in determining tumor lineage, and work from Kopp et al. (2012) published in this issue of *Cancer Cell* reinforces the disputed paternity of pancreatic "ductal" neoplasia.

Initial clues suggesting that non-ductal cells might serve as effective cells of origin for pancreatic ductal neoplasia were provided by studies involving transgenic misexpression of individual oncogenes under the regulation of non-ductal promoter elements, in which a subset of resulting tumors displayed histologic resemblance to adult ductal epithelium (Sandgren et al., 1991). However, these similarities were ultimately proven to be only skin-deep, as additional studies of PanIN and PDAC revealed activation of transcriptional programs typically observed in embryonic pancreatic epithelium, but not in differentiated duct cells (Miyamoto et al., 2003; Park et al., 2011).

With the advent of autochthonous mouse models of pancreatic neoplasia, more recent studies have interrogated individual pancreatic cell types for the ability to generate PanIN, based upon Cre/lox-mediated activation of oncogenic *Kras*. Initial seminal work in this arena utilized either *Pdx1*^{Cre} or *Ptf1a*^{Cre} alleles to activate *Kras* in embryonic pancreatic progenitor cells (Aguirre et al., 2003; Hingorani et al., 2003). While these studies demonstrated that embryonic activation of oncogenic *Kras* effectively initiated pancreatic ductal neoplasia, they provided considerably less information regarding the capacity of individual adult cell lineages to similarly serve as effective cells of origin. Based on the availability of appropriate Cre driver lines, this adult capacity was first interrogated in pancreatic acinar cells. Using either a Nestin-Cre driver to activate oncogenic *Kras* in exocrine progenitor cells and their acinar cell descendants (Carrière et al., 2007) or a variety of inducible Cre lines to activate *Kras* in adult acinar cells (De La O et al., 2008; Guerra et al., 2007; Habbe et al., 2008), these studies provided strong evidence that acinar cells could indeed serve as effective biologic parents for pancreatic ductal neoplasia. In these studies, the ability of adult acinar cells to generate PanIN was dramatically accelerated in the context of associated pancreatitis, a known risk factor for the human disease. Additional studies suggested that a permissive inflammatory microenvironment could broadly bestow PanIN-parenting capabilities, as even insulin-expressing cells

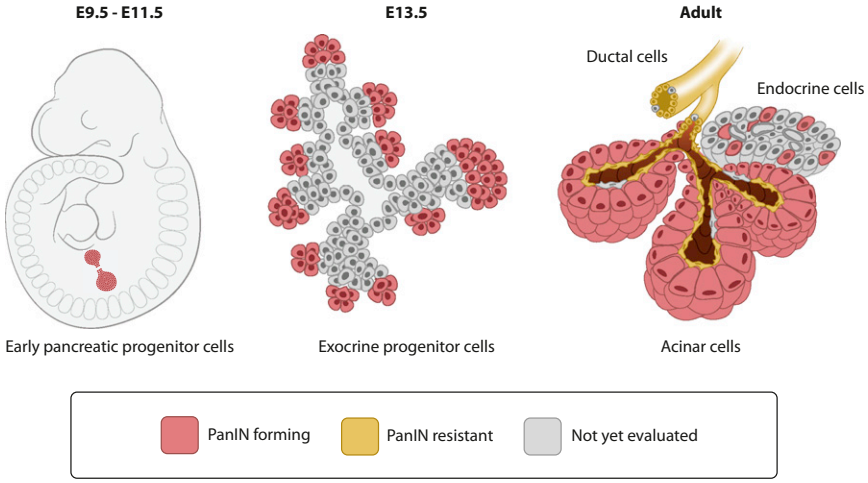

Figure 1. Competence of Individual Pancreatic Cell Types to Generate Pancreatic Intraepithelial Neoplasia in Response to Oncogenic *Kras* Activation

(A) *Kras* activation in early pancreatic progenitor cells and their progeny leads to effective pancreatic intraepithelial neoplasia (PanIN) initiation.

(B) *Kras* activation in later exocrine-dedicated progenitor cells and their acinar cell progeny also results in PanIN.

(C) *Kras* activation in differentiated acinar cells, but not the most common ductal epithelial lineage, leads to effective PanIN initiation. In an inflammatory microenvironment, insulin-expressing endocrine cells can also generate PanIN. Low-abundance pancreatic ductal/centroacinar subpopulations may still remain to be evaluated as effective cells of origin. Red indicates cell types capable of forming PanIN; yellow indicates cells resistant to PanIN; and gray indicates known and potentially unknown cell populations still unevaluated.

were shown to be capable of generating PanIN in the context of associated pancreatitis (Gidekel Friedlander et al., 2009).

Ironically, these studies demonstrating that pancreatic ductal neoplasia could be generated from a variety of non-ductal cell types were all completed prior to a similar definitive evaluation in actual ductal epithelial cells. However, a long-awaited detailed glimpse at the parental capacities of the ductal epithelial lineage is now available. In this new study, Kopp et al. (2012) directly compare the efficiency of PanIN formation following cell type-specific activation of oncogenic *Kras* in the acinar lineage using a *Ptf1a*^{CreER} line and in the ductal/centroacinar lineage using a *Sox9*^{CreER} line. For both lines, postnatal tamoxifen administration induced recombination in a similar proportion of target cells. Similar to prior studies using other acinar cell-specific Cre driver lines, the authors observed potent induction of PanIN lesions in *Ptf1a*^{CreER}; *Kras*^{G12D} mice, an effect that was further accelerated by concomitant pancreatitis. However there was minimal-to-no PanIN induction in *Sox9*^{CreER}; *Kras*^{G12D} mice, even in the presence of pancreatitis. Even when discrepant PanIN frequencies were normalized based on the greater abundance of acinar cells, the difference in PanIN-generating capabilities between the two lineages remained striking, with acinar cells at least 100-fold more effective than ductal/centroacinar cells in generating PanIN. In addition, the authors demonstrated that, within the acinar lineage, *Sox9* itself was required for efficient PanIN induction, and that *Sox9* overexpression enhanced both pancreatitis-associated metaplasia and *Kras*-induced PanIN formation within the acinar lineage.

Together, these comprehensive studies demonstrate that, while differentiated acinar cells are fully capable of generating PanIN through requisite *Kras*-induced *Sox9* activation, ductal and centroacinar cells already expressing *Sox9* are dramatically resistant to *Kras*-induced neoplastic transformation. In conjunction with prior studies, these findings lead to the startling recognition that the predominant *Sox9*-expressing ductal epithelial lineage represents the only pancreatic epithelial lineage evaluated to date that is unable to efficiently generate PanIN (Figure 1).

Before entirely disqualifying ductal and centroacinar cells from consideration as capable PanIN parents, it is necessary to consider a broad number of remaining questions and possibilities. First, it must be recognized that, while *Sox9* appears to be expressed in a substantial majority of pancreatic ductal and centroacinar cells, there is considerable heterogeneity in gene expression along the ductal epithelial tree, and the distinct possibility remains that PanIN can effectively originate from a subpopulation of *Sox9*-negative ductal epithelial cells. In addition, the study by Kopp et al. (2012) relied on tamoxifen-induced recombination in only 12% of all *Sox9*-expressing cells. As acknowledged by the authors, this fraction, when further reduced by a less than uniform response to *Kras* even among competent cell types, means that rare *Sox9*-expressing cells (i.e., centroacinar cells) might not have been effectively interrogated in large numbers; perhaps these cells account for the rare PanIN lesion observed in these mice. In spite of these caveats, it remains difficult to escape the authors' primary conclusion that the predominant ductal lineage in adult mouse pancreas remains largely refractory to *Kras*-mediated transformation.

While it is tempting to extend these findings to the human disease, appropriate caution is warranted. In particular, the current experimental paradigm only evaluates what can happen, i.e., the competence of individual adult murine cell types to generate PanIN in response to oncogenic *Kras*, as opposed to what actually does happen under conditions of spontaneous or carcinogen-induced human *KRAS* mutations. Certainly, murine PanIN induced by *Kras* activation in either embryonic pancreas or in adult acinar cells seems to bear exquisite resemblance to human PanIN, both histologically and with respect to gene expression patterns. However, prior analysis of *KRAS* sequences in acinar cells adjacent to human PanIN failed to identify mutant alleles (Shi et al., 2009), suggesting that acinar cell *KRAS* mutations are either extremely rare or rapidly induce metaplastic or neoplastic conversion to a non-acinar morphology. On the other hand, cells with features of acinar differentiation can often be identified in human PanIN, and a subset of acinar to ductal

metaplasia (ADM) do, indeed, harbor *KRAS* mutations identical to those observed in adjacent PanIN (Shi et al., 2009). These findings might be consistent with *KRAS* mutations arising in either acinar cells themselves or in areas of ADM, with subsequent rapid progression to PanIN.

Assuming that these findings are indeed relevant to the human disease, what are the ramifications of the current findings? Certainly, they suggest that future chemoprevention strategies might be best targeted at early events in acinar rather than ductal cells; blocking acinar cell activation of *Sox9* now joins Notch pathway inhibition and maintenance of *Mist1* expression as examples of such approaches. In addition, these findings underscore an increasingly recognized disconnect between *Kras* mutations and Kras activity. Along these lines, it will be fascinating to determine the presumably epigenetic determinants underlying the differential responsiveness to oncogenic *Kras* observed in acinar and ductal cell types; manipulating such determinants may convert acinar cells into less capable parents, hopefully eliminating PanIN from the pancreatic family tree.

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Chemokine to the Rescue: Interleukin-8 Mediates Resistance to PI3K-Pathway-Targeted Therapy in Breast Cancer

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Adaptive resistance to PI3K-mTOR inhibitors potentially limits the clinical antitumor activities of these agents. In this issue of *Cancer Cell*, Britschgi and coworkers show that certain tumors acquire resistance to PI3K-mTOR inhibitors through activation of a JAK2-dependent pathway, leading to interleukin-8 secretion.

More than 25 years have passed since the discovery of phosphoinositide 3-kinase (PI3K) as an oncoprotein-associated enzymatic activity. The term "PI3K" in this context designates the Class I subset of phosphoinositide kinases (comprising the α, β, γ, and δ isoforms), which convert phosphatidylinositol-4,5-bisphosphate to the bioactive second messenger phosphatidylinositol-3,4,5-trisphosphate (Vanhaesebroeck et al., 2012). These PI3Ks are activated, directly or indirectly, by a variety of cell surface receptors that include receptor tyrosine kinases (RTKs) and G protein-coupled receptors. Several cardinal alterations elicited by PI3K activation include changes in cell proliferation, survival, migration, and metabolism, and are highly aligned with the "hallmarks of cancer" discussed by Hanahan and Weinberg (2011). Indeed, inappropriate activation of the PI3K pathway has been observed in a remarkably broad array of human cancers. Nested within this pro-oncogenic signaling network are two pivotal protein serine-threonine kinases, AKT (also termed protein kinase B) and mTOR, both of which represent druggable targets, like PI3K itself. This combination of biological relevance and pharmacological tractability rendered the PI3K pathway an irresistible target for cancer drug discovery. The ensuing efforts in