tion-specific inhibitors. Patient stratification and matching the drug to the mutation will be an important strategy to ensure successful treatment of malignancies such as NSCLC. Furthermore, most patients on prolonged gefitinib and erlotinib treatment develop secondary mutations in the EGFR kinase domain that block drug binding, leading to clinical resistance and therapy failure (Kobayashi et al., 2005; Kwak et al., 2005; Pao et al., 2005). The ability to synthesize drugs that inhibit through different binding modes will be crucial if we are to tackle this increasingly important clinical problem. Finally, the information learned for the EGFR will have important ramifications for other kinases, such as BCR-ABL, which also binds to drugs in either the active and inactive conformations (Liu and Gray, 2006; Schindler et al., 2000).

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A Case of Mistaken Identity? Nonductal Origins of Pancreatic "Ductal" Cancers

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In this issue of *Cancer Cell*, Guerra and colleagues provide important new insights regarding the ability of specific pancreatic cell types to generate invasive pancreatic cancer. First, they demonstrate that classical pancreatic "ductal" neoplasia can be induced by activation of oncogenic *Kras* in nonductal exocrine cells. Second, they show that, while *Kras* activation in immature acinar and centroacinar cells is readily able to induce ductal neoplasia, *Kras*-mediated tumorigenesis in mature exocrine pancreas requires the induction of chronic epithelial injury. The results shed new light on the "cell of origin" of pancreatic ductal cancer and demonstrate that chronic pancreatitis provides a permissive environment for *Kras*-induced pancreatic neoplasia.

Among the many problems of cancer research, "cell-of-origin" questions may occasionally be viewed as trivial or semantic. Yet tumors are not born equal: for example, pancreatic ductal adenocarcinomas (PDACs) nearly always arise from precursors that sustain activating *KRAS* mutations, while such mutations are almost never seen in less common pancreatic cancers such as islet cell carcinomas. Some of these differences may reflect the internal wiring of the initiating cell types, such that *KRAS* activation favors transformation in one cell but not another. Deciphering these interactions between epigenetic determinants of cell identity and genetic changes leading to tumor formation might identify new targets for cancer treatment and prevention. In this issue of *Cancer Cell*, Guerra et al. (2007) make an important and surprising advance in clarifying the adult cell of origin for PDAC.

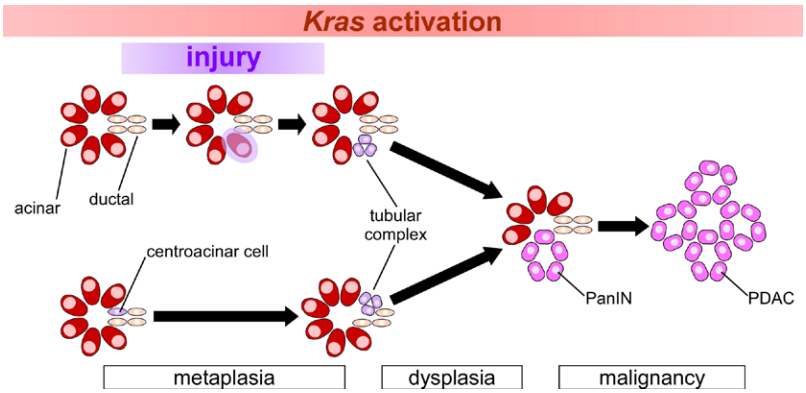

Figure 1. Potential Cellular Sources of Pancreatic Cancer
The study of Guerra et al. (2007) indicates that $Kras^{G12V}$ mutations arising in acinar (top) or centroacinar (bottom) cells of the adult pancreas can give rise to pancreatic intraepithelial neoplasia (PanIN) lesions and invasive pancreatic ductal adenocarcinoma (PDAC). In the mature pancreas, the vast majority of both cell types appear to tolerate expression of activated *Kras* without effect. Chronic injury, however, dramatically sensitizes the adult pancreas to $Kras^{G12V}$-driven dysplasia, possibly by evoking the formation of metaplastic tubular complexes that are uniquely sensitive to the effects of the oncogene. Such complexes might arise from the transdifferentiation of mature acinar cells, from the expansion of a pre-existing centroacinar cell population, or both.

What are the possible cellular compartments in which PDAC-producing *KRAS* mutations might occur? PDAC is often assumed to arise from preexisting duct cells, based on the fact that the two known pancreatic cancer precursor lesions—pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasia (IPMN)—both exhibit features of ductal differentiation. This hypothesis has been surprisingly difficult to prove: direct targeting of oncogenic *Kras* to mature ductal cells, using the *Cytokeratin 19* promoter, fails to induce neoplasia (Brembeck et al., 2003). In contrast, similar transgenic studies reveal that acinar cells, which comprise the most abundant cell type in mature pancreas, are susceptible to transformation by a variety of oncogenes (including *Kras*) and give rise to tumors that often contain ductal elements (Hruban et al., 2006). In addition to acini and ducts, of course, the pancreas is also comprised of endocrine islets, as well as several less common cell types, including centroacinar cells and clear ("Helle Zelle") cells. Centroacinar cells have recently been implicated as the apparent source of ductal tumors induced by pancreas-specific *Pten* deletion (Stanger et al., 2005), and chemical carcinogenesis studies in rat and hamster have suggested that hyperplastic lesions leading to ductal tumors may be initiated among a variety of nonductal cell types (Bockman et al., 2003; Pour et al., 2003). Although all of these studies have provided fascinating insights into cellular plasticity in the setting of neoplastic transformation, it has been difficult to reconcile their conclusions, or extrapolate to the human form of the disease. Chemical carcinogenesis can, in principle, affect multiple pancreatic cell types, making it almost impossible to establish a lineage relationship between normal cells, precancerous lesions, and invasive tumors. Transgenic constructs are likely to produce nonphysiological levels of oncogene expression, and use of heterologous cell type-specific promoters essentially limits the ability of a tumor to change its cellular phenotype. Perhaps for this reason, most of these models have failed to recapitulate the PanIN/PDAC progression seen in humans (Hruban et al., 2006).

A recent breakthrough in PDAC modeling came with the development of conditionally activatable *Kras* alleles in the mouse (Aguirre et al., 2003; Hingorani et al., 2003). These alleles are silent in the majority of cells, yet can be heritably activated by Cre-loxP recombination, mimicking the somatic *KRAS* point mutations that initiate PDAC formation in human pancreas. When this system is used to activate *Kras* throughout the developing pancreas, adult mice develop a PanIN/PDAC progression that is almost indistinguishable from its human counterpart (Hruban et al., 2006). Because the initial applications of this system relied on pan-pancreatic *Kras* activation, they could not address the cell-of-origin question, and it is into this breach that Guerra et al. (2007) now step. These authors have developed a tetracycline-regulated system in which Cre recombinase is conditionally expressed under control of the acinar-specific *Elastase* promoter. Using this system, they demonstrate the formation of classic PanINs, and eventual invasive PDAC, following Cre-mediated activation of a conditional $Kras^{G12V}$ allele in nonductal exocrine cells.

Unfortunately, this system does not fully resolve the cell-of-origin question for PDAC, as the authors observe Cre-loxP recombination in centroacinar as well as acinar cells. Centroacinar cells lie at the junction between acinar cells and adjacent ductal epithelium, and as noted above have previously been proposed as a potential source for ductal neoplasia (Stanger et al., 2005). In addition, centroacinar cells have been suggested to represent a stem- or progenitor-like population for the adult pancreas, particularly following injury. Although the resting pancreas is a relatively quiescent organ, with little evidence for dedicated stem cells, experimental injury elicits the transient appearance and proliferation of progenitor-like cells, variously termed "tubular complexes" or "acinar-ductal metaplasia" (Bockman, 1997). The origin of these cells is no better understood than that of PDAC (indeed, experimental PDAC models are often associated with similar metaplastic structures): do

they arise from dedifferentiation of acinar cells, or from the expansion of centroacinar or duct cells?

This question bears on another provocative finding of Guerra et al. (2007), that experimental pancreatitis dramatically sensitizes mice to $Kras^{G12V}$-driven PanIN/PDAC formation. Human patients suffering from chronic pancreatitis, especially its hereditary form, are at increased risk for pancreatic cancer (Lowenfels et al., 1997), and this mouse model may allow us to establish exactly why this is the case, and what can be done about it. Indeed, although chronic inflammatory conditions in numerous tissues are associated with increased cancer risk, untangling causes, effects, and mechanisms has proven very difficult in humans. Genetically tractable model systems for inflammation-associated cancer make it possible to unravel basic mechanisms and may also provide a preclinical test bed for therapeutics targeting the relevant components of the inflammatory process.

Here, the authors create a chronic pancreatitis-like state by long-term treatment with caerulein, an acinar cell secretagogue. Much prior research into caerulein-induced pancreatitis has focused on two important questions: what are the molecular mechanisms determining the severity of injury, and what are the cellular mechanisms of postinjury repair? With regard to the determinants of injury, caerulein treatment induces rapid activation of the NF-κB transcription factor; as in other organ inflammation models, blocking this activation appears to blunt subsequent pancreatitis (Gukovsky et al., 1998). As expected, Guerra et al. (2007) observe NF-κB activation in acinar cells of caerulein-treated mice, although this activation occurs to the same extent in wild-type and $Kras^{G12V}$-expressing pancreata, and little or no NF-κB activation is seen in the actual PanIN lesions or tumors induced by $Kras^{G12V}$. Thus, while the current results fail to definitively characterize the role of NF-κB in PDAC initiation and progression, this unique system for the study of pancreatitis-associated cancer should provide new opportunities to resolve this important issue.

The second question regarding caerulein-induced pancreatitis is also likely to be relevant here: how does injured pancreatic tissue repair itself? Caerulein-induced pancreatitis is one of the experimental insults known to provoke expansion of metaplastic tubular complexes, and one school of thought suggests that metaplastic epithelial cells serve as progenitors to replace lost acinar tissue (Jensen et al., 2005). In in vitro culture systems, activation of the Notch and/or EGF receptor pathways causes acinar cells to dedifferentiate and assume a metaplastic phenotype (Miyamoto et al., 2003), potentially mimicking a process induced by injury in vivo. Alternatively, metaplasia may represent the induced expansion of centroacinar cells (Stanger et al., 2005), and it is important to recognize that acinar cell dedifferentiation and centroacinar expansion are in no way mutually exclusive events (Figure 1). Whatever the source, one might imagine that pancreatitis causes otherwise quiescent adult cells to assume a progenitor-like phenotype, in which they are more susceptible to transformation by oncogenic *Kras*. It should be emphasized that this possibility is not strictly academic, as it implies that interfering with injury-induced metaplasia might prevent the earliest stages of pancreatic cancer.

This work represents the first direct demonstration that cells in adult mouse pancreas are susceptible to transformation by activated *Kras*, and the first model for pancreatitis-associated tumor promotion. Further work, using Cre lines with stricter specificity for duct, centroacinar, or acinar cells, will be required to more definitively resolve the cell-of-origin problem for PDAC, and it may yet turn out that the precise cell of origin matters less than the context in which that cell finds itself—i.e., whether *Kras* mutations occur in the context of inflammation and/or regenerative metaplasia. Nonetheless, the results of Guerra et al. (2007) represent a major advance in the field of pancreatic cancer modeling and provide an important foundation for future studies of pancreatic cancer initiation and progression.

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