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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Putting the Cell of Origin for Pancreatic Cancer Into its Proper Context

Some might consider the ongoing debate about the cell of origin of pancreatic cancer as a drama without a stage. After all, pancreatic ductal adenocarcinoma (PDA) patients almost always present with advanced, usually metastatic, disease. In the years since its initiation, the cancer has gone on to acquire additional mutations, increasing both its aggressiveness and refraction to treatment, with the almost inevitable outcome that it will kill the patient. Beyond satisfying our own curiosity, what impact does knowing its cell of origin provide? In this issue, Shi et al[1] show that the cell of origin has a major impact on how PDA can develop, and that gene expression programs vary depending on the cell of origin. Thus, mouse models of PDA derived from different cells of origin may provide insights into the drivers and therapeutic targets in the resulting tumors.

In some organs, such as lung, cancers that arise within them can be quite heterogeneous, with one common hypothesis explaining this phenomenon being that different tumor types arise from different cells of origin.[2] Regardless of their similar appearance, it is possible that an acinar-derived PDA and a duct-derived PDA are different cancers entirely, ultimately affecting how we should treat them. By using cell-type–specific Cre drivers to initiate the expression of oncogenic Kras, the initiating mutation of most PDAs, previous studies have concluded that both duct and acinar cells can give rise to neoplasia,[3,4] with the acinar cell being much more susceptible to transformation and therefore the more likely cell of origin in mice.[4] Other studies have layered additional mutations that rarely are found in human pancreatic cancer to show that duct cells also can be transformed rapidly.[5,6] What makes the current study by Shi et al[1] unique is the discovery that, in the context of obstructive pancreatitis, Kras mutation alone can both initiate rapidly progressing PDA from duct cells and suppress transformation of the acinar cells. However, within the proximal unobstructed portion of the pancreas, acinar cells more commonly give rise to precancerous neoplasia whereas the ducts rarely do, consistent with previous studies.

By maintaining a consistent genetic background, with a single common initiating mutation, Shi et al[1] have made the clear case that when it comes to the cell of origin, context is king. However, what, precisely, is the determining context? After all, other models of experimental pancreatitis, usually induced by supramaximal doses of the cholecystokinin orthologue cerulein, clearly promote transformation within the acinar cell compartment. However, unlike the duct obstruction model used in this study, cerulein is a signaling molecule that acts directly on the murine acinar cell, promoting not just acinar cell stress, but also Ras pathway activation.[7] Cerulein also induces primarily necrotic acinar cell death, as opposed to apoptotic acinar cell death induced in the duct obstruction model. The mode of cell death in inflammatory disease can have a profound effect on the nature of the inflammatory response[8] and, in these contexts, on the mechanisms of transformation. Also, Shi et al[1] themselves point out that surgical obstruction of the main pancreatic duct induces pancreatitis distal of the obstruction, in the tail portion of the pancreas, whereas pancreatic tumors form more commonly in the head of the pancreas in both patients and mouse PDA models. Although the reasons for this location bias remaining unclear, it may contribute to the relevant transformation-permissive context.

Inspired by the promise of personalized medicine, -omics have confirmed that not all pancreatic cancers are the same. Genomic analysis has shown that a small, but relevant, portion of pancreatic cancers harbor actionable mutations in addition to the currently undruggable driver mutations (KRAS, TP53, CDKN2A, and SMAD4).[9] Transcriptomic analysis has further divided pancreatic cancers into 2 consensus subtypes, termed classic and basal,[10] roughly reflecting the well-differentiated and undifferentiated phenotypes long-recognized by pathologists. Although these subtyping efforts were performed with the hope of identifying the best treatment options for each patient's tumor, responsiveness to at least standard chemotherapies does not correlate with these transcriptomic subtypes.[11] The study by Shi et al[1] suggests that it is possible that the cell of origin and the context in which it arises imprint an epigenetic memory on the cancer, predetermining the specific pathways of plasticity available to each cancer as it evades treatment and immunity. Perhaps by defining the epigenetic and transcriptomic signatures unique to acinar and duct-derived mouse PDA and better understanding their potentially unique biologies, we can overlay these signatures onto data from human tumors and not only surmise their cell of origin, but the therapies with which to best treat them.

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Conflicts of interest
The author discloses no conflicts.


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