Metabolism Drives Carcinogenesis and Maintenance of Pancreatic Tumors

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Summary: In this issue of Cancer Discovery, Carrer and colleagues find that early events in pancreatic tumorigenesis are driven by altered acetyl-CoA metabolism, where targeting this axis in established cancer models impairs tumor growth. This work provides new insights into the roles of acetyl-CoA in pancreatic cancer and underscores the value of studying early events in carcinogenesis to yield new treatment strategies.

See related article by Carrer et al., p. 416 [1].

Pancreatic ductal adenocarcinoma (PDA) is one of the deadliest human malignancies. This is largely due to a lack of early-detection methods and limited therapeutic options. Mutations in the KRAS oncogene are a near-universal feature in PDA, and despite considerable efforts it remains an “undruggable” target. Thus, an alternative strategy to identify new therapeutic targets has focused on examining events that occur downstream of KRAS early in the pancreatic tumorigenesis process. In this issue of Cancer Discovery, Carrer and colleagues use this strategy to study how KRAS regulates acetyl-CoA metabolism during pancreatic tumor formation and the impacts on biosynthetic metabolism and epigenetics [1].

In the past decade, significant progress has been made in uncovering the mechanisms that initiate and drive PDA (2) using genetically engineered mouse models. Namely, expression of oncogenic KRASG12D in the pancreas of mice, using organ-specific cre recombinases, is sufficient to drive the formation of precursor lesions known as pancreatic intraepithelial neoplasia (PanIN; ref. 3). These can then be engineered to progress to invasive PDA in combination with loss of tumor suppressor function. Lineage tracing with these models has revealed that mutant KRAS expression readily transforms acinar cells of the exocrine pancreas to PanIN lesions (3). This occurs as a result of mutant KRAS hijacking a wound-healing process known as acinar-to-ductal metaplasia (ADM). In normal pancreatic physiology, acinar cells lost in response to an injury are replaced by other acinar cells transdifferentiating to a proliferative progenitor-like state resembling ductal architecture. This occurs in a MAPK-dependent manner, where the ductal-like cells then redifferentiate back to quiescent acinar cells after replication (4, 5). However, chronic MAPK stimulation by oncogenic KRAS signaling prevents acinar cell redifferentiation, locking these cells into a malignant state (6).

Although many studies have demonstrated that blocking ADM can inhibit tumorigenesis, they have focused mainly on RAS-mediated signal transduction (5). However, in the transdifferentiation process, acinar cells shift their identity from professional protein-producing cells to a proliferative progenitor-like state, which requires a corresponding shift in the gene expression and metabolism. Previous work led by the Wellen group demonstrated that AKT activation of ATP citrate lyase (ACLY) increased the levels of histone H4 acetylation in pancreatic acinar cells expressing oncogenic KRAS (7). This was presumed to result through the ACLY-mediated increase in acetyl-CoA levels.

Carrer and colleagues now expand on their previous observation to demonstrate that AKT activity is responsible for maintenance of global histone acetylation in both acinar cells and PanIN lesions (1). Consistent with the previously observed increase in global histone acetylation, the authors now find increased levels of acetyl-CoA in KRASG12D-expressing acinar cells. In addition to higher pool sizes of acetyl-CoA, oncogenic KRAS also diversified the carbon sources used by acinar cells to generate acetyl-CoA. Beyond its role in histone acetylation, acetyl-CoA is also a substrate for de novo fatty-acid and sterol biosynthesis. Along these lines, further investigation into acetyl-CoA metabolism in acinar cells revealed that expression of sterol biosynthesis pathway components was highly upregulated by mutant KRAS. Correspondingly, the sterol biosynthetic intermediate HMG-CoA was actively produced from acetyl-CoA by acinar cells.

These observations suggested at least two non-mutually exclusive roles for ACLY-generated acetyl-CoA in ADM, the modification of histones and/or sterol biosynthesis. The authors then tested the requirement for these pathways with inhibitors. To accomplish this, the “reading” of histone acetylation was blocked with the BET inhibitor JQ1, and sterol biosynthesis was inhibited with atorvastatin (Fig. 1).

Here, they determined that both pathways were required for KRASG12D-expressing acinar cells to successfully undergo transdifferentiation. Furthermore, the inhibition of ADM through blockade of sterol biosynthesis could
be rescued with the downstream metabolites mevalonate and cholesterol, suggesting a requirement for de novo cholesterol synthesis by acinar cells, as opposed to myriad alternate roles of this pathway in biosynthesis and signal transduction.

To study the necessity of ACLY-generated acetyl-CoA in pancreatic homeostasis and pancreatic cancer, the authors generated mice in which Acly was conditionally deleted from the pancreas. Somewhat surprisingly, given its central role in acetyl-CoA generation, they observed no obvious global metabolic defects in development or in the metabolism of adult mice with pancreatic Acly knockout. However, by crossing the conditional Acly allele into a pancreatic carcinogenesis model (Aclyfl/fl;KrasLSL-G12D+/−;Pdx1-Cre), the authors discovered that genetic ablation of Acly blocked ADM in vitro and slowed pancreatic tumorigenesis in vivo. Given that ADM could progress in vivo, in contrast to the in vitro results, the authors posit that heterocellular signaling in the pancreas could provide bypass of ACLY. Indeed, they noted that PanIN lesions in mice, which developed in the presence or absence of Acly, had high expression of the alternative acetyl-CoA production pathway enzyme ACSS2 (Fig. 1). These results suggested that neoplastic lesions may utilize this alternative pathway to generate acetyl-CoA during carcinogenesis and maintenance in vivo. Finally, the authors determined that loss of ACLY significantly extended survival of mice in a more aggressive PDA model that combines oncogenic KRASG12D expression with p53 loss of heterozygosity. Taken together, these data show that ACLY can be produced from acetate by the ACSS2 reaction. The acetyl-CoA is used to fuel increased sterol synthesis and histone acetylation during acinar-to-ductal metaplasia (ADM). Targeting these processes with atorvastatin or JQ1, respectively, blocks the ADM process. In established PDA cells, the AKT–ACLY pathway dynamically regulates epigenetic programming, and combined atorvastatin + JQ1 treatment to block this axis inhibits cancer cell growth. Metabolite names in blue; enzymes in green; inhibitors in purple.

**Figure 1.** Oncogenic KRAS mutations activate downstream signaling through the AKT–ACLY pathway, enhancing the conversion of citrate to acetyl-CoA. Alternatively, acetyl-CoA can be produced from acetate by the ACSS2 reaction. The acetyl-CoA is used to fuel increased sterol synthesis and histone acetylation during acinar-to-ductal metaplasia (ADM). Targeting these processes with atorvastatin or JQ1, respectively, blocks the ADM process. In established PDA cells, the AKT–ACLY pathway dynamically regulates epigenetic programming, and combined atorvastatin + JQ1 treatment to block this axis inhibits cancer cell growth. Metabolite names in blue; enzymes in green; inhibitors in purple.
Beyond epigenetic consequences, the authors also demonstrated that reprogrammed acetyl-CoA metabolism is not only necessary during early tumorigenesis, it is also an important part of the PDA cell identity. Studying metabolism in established PDA has uncovered several mechanisms by which the cancer cells are rewired to survive the nutrient-poor pancreatic tumor microenvironment (2). By comparison, relatively little is known about the initial events in priming this metabolic transition or how many of these processes are maintained through carcinogenesis. Thus, the insights provided by Carrer and colleagues, beyond their direct implications, demonstrate the value of studying tumor origins as a means to understand established cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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