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EDITORIAL

PYK2 at the Intersection of Signaling Pathways in Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer, has few consistent mutations in oncogenes or tumor suppressor genes compared with other cancers, and most of those are not therapeutically targetable at this time. Although a wide variety of other driver mutations that vary considerably patient to patient is one potential reason for this paucity of consistent driver gene mutations, another possibility is that epigenetic changes play a major role in tumor development and maintenance in the pancreas. Whereas the former suggests that any targeted therapeutic is likely to work on only a small subset of PDAC patients, the latter suggests that there may be targets common to many patients that are not associated with mutations. To this end, a number of signaling molecules and transcription factors that are either up-regulated or down-regulated have been implicated in PDAC development and maintenance. One question that arises from all these studies is whether each of these many molecules has a distinct, independent function in tumorigenesis, or whether they reflect a coordinated interplay of signaling pathways that coalesce on specific downstream targets. Answering that question is crucial to understand tumor biology and, more importantly, to identify the most likely targets for therapeutic interventions. In the current article by Gao et al,[1] multiple seemingly disparate signaling molecules, both previously published and novel, are shown to lie within a direct pathway that regulates PDAC development and tumor growth.

Gao et al[1] investigated the role of PYK2 in PDAC development and maintenance. PYK2 is closely related to the non-receptor tyrosine kinase FAK and was overexpressed in more than half of PDAC tissues examined. Using *Pyk2*$^{-/-}$ mice, the authors show that eliminating PYK2 greatly decreased the ability of *Kras* mutation, with or without inflammation, to induce transition from normal tissue to abnormal lesions called acinar-to-ductal metaplasia or pancreatic intraepithelial neoplasms, thought to be benign precursors of PDAC. In human cell lines, knocking down PYK2 levels greatly decreased growth of xenograft tumors. Although this novel role for PYK2 is intriguing, the authors extended this study to identify how PYK2 was regulated and what its targets might be. They built on results in the literature that showed that PYK2 was regulated by STAT3[2] and that the Hippo pathway regulated STAT3 levels.[3] They found that reducing Hippo signaling or STAT3 level was sufficient to reduce PYK2 levels. They also examined potential downstream targets of PYK2 phosphorylation and found that β-catenin is a direct target of PYK2 kinase activity and that levels of PYK2 correlated with the extent of nuclear β-catenin accumulation and target gene expression. Furthermore, overexpression of a constitutively active β-catenin was able to restore tumor growth in xenograft tumors with decreased PYK2 expression. Thus, Gao et al were able to demonstrate that a number of previously identified regulators of PDAC development actually lie in the same molecular pathway, with Hippo signaling leading to STAT3 activation, which then up-regulates PYK2 expression. PYK2 then phosphorylates and activates β-catenin, which in turn regulates expression of many growth promoting genes. Targeting any of these points along this pathway was sufficient to inhibit transformation.

At face value, understanding how PDAC develops seems irrelevant to treating this deadly cancer. Most patients are not diagnosed until much later stages when the tumor has already spread locally or metastatically. However, it is becoming clear that early mutations may result in a dependence, or "addiction," of the tumor to the results of that mutation. For example, even though *KRAS* mutation is thought to be one of the earliest mutations in pancreatic cancer initiation, both mouse and human cell models indicate that at least some tumors continue to rely on mutant KRAS activity for growth and survival. Similarly, inflammation is critical for initiation of PDAC but continues to play roles in tumor development, maintenance, and spread. Gao et al[1] found that PYK2 responds to inflammation as well as KRAS activation and has a continuing role in tumorigenesis from initiation to tumor maintenance. Although mutant KRAS appears to be resistant to therapeutic intervention and inflammation in the pancreas is perhaps too complex for effective targeting at present, it may be possible to target pathways downstream of KRAS and inflammation. By understanding a pathway critical to tumor development, Gao et al may have identified a pathway to which the tumor remains addicted for the life of the tumor. Thus, by understanding how a tumor develops, potentially actionable regulators of the established cancer can be uncovered.

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Conflicts of interest
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