Kras, Pten, NF-κB, and Inflammation: Dangerous Liaisons

Paul J. Chiao and Jianhua Ling

Summary: Ying and colleagues identify a novel function of Pten as a haploinsufficient tumor suppressor in human pancreatic cancer development. Genomic, genetic, and biochemical data reveal that Pten loss and Kras mutation cooperate to accelerate pancreatic cancer development by altering PI3K regulation to enhance NF-κB activation and upregulate downstream cytokine genes; this provides a protumorigenic and metastatic microenvironment. Cancer Discovery; 1(2): 103-5. ©2011 AACR.

In this issue of Cancer Discovery, Ying and colleagues (1) report that human genome analyses of pancreatic ductal adenocarcinoma (PDAC) and modeling PDAC in the mouse have identified Pten as a haploinsufficient tumor suppressor in metastatic PDAC development. Alterations in PI3K regulation caused by Pten loss and mutational activation of Kras enhances NF-κB activation and upregulation of downstream cytokine genes, which in turn promotes stromal activation and immune cell infiltration, shaping a pro-tumorigenic and pro-metastatic microenvironment.

Pancreatic cancer, which strikes 43,000 Americans annually (killing 36,800), is the fourth leading cause of adult cancer mortality in the United States (2). The 5-year survival rate has remained between 1% and 3% for the past 25 years (2). At the time of diagnosis, approximately 80% of PDAC patients present with locally advanced or metastatic therapy-resistant disease, and the median survival after diagnosis is <6 months (3). Even when stage I or II pancreatic cancer is localized to the pancreas and surgically removed, 70% of patients develop liver metastases in the absence of primary PDAC within 2 years of surgery (3). The onset of liver metastasis in the absence of primary PDAC is thought to be due to early neoplastic cell dissemination (3). Despite research advances, current chemotherapy and radiation therapy regimens are largely ineffective because most PDAC tumors are resistant to standard therapy and no useful drug targets have been identified. Hence, a better understanding of the molecular basis of PDAC inception and development is the key to identifying prevention strategies and therapeutic targets that will ultimately increase patient survival rates, one of the greatest challenges in current cancer research.

A genetic profile of PDAC is emerging on the basis of the most commonly detected mutations (Fig. 1; ref. 4, 5). For example, mutational Kras activation is an early event in pancreatic carcinogenesis and is detected in 80% to 95% of PDAC cases; inactivation of the p16/Ink4a and p53 tumor-suppressor genes is identified in approximately 50% and 75% of PDAC cases; and NF-κB is constitutively activated in nearly 70% of PDAC tumors, most PDAC cell lines (4, 6), and in many other tumor types as well (7). NF-κB activation in Ras-transformed cells is mediated through both the mitogen-activated protein kinase (MAPK) and PI3K pathways (7). NF-κB integrates pro-inflammatory signals and orchestrates anti-apoptotic responses (8); thus, NF-κB signaling has been implicated as a hallmark of cancer development (9). However, significant gaps still exist in our understanding of how such genetic alterations act in concert to induce NF-κB activation and PDAC development and progression. This question has now been answered in part by the findings of Ying and colleagues (1).

The Pten tumor suppressor gene is frequently deleted or mutated in human solid cancers. In genetically engineered mouse models of PDAC, mice harboring Pten deletions in the pancreas develop widespread ductal metaplasia and invasive pancreatic adenocarcinoma at a low frequency (10). In this report, Ying and colleagues (1) identified Pten as a haploinsufficient tumor suppressor that cooperated with Kras to induce PDAC in their Pdx1-cre;KrasG12D;PtenL/+ genetically engineered mouse model, which is consistent with an earlier report from the Wu group (11). Furthermore, Ying and colleagues (1) found frequent loss of at least one allele of the Pten gene in PDAC patient samples through high-resolution genome analyses of human PDAC; this result was supported by evidence that Pten heterozygosity was retained in the majority of mouse PDAC, suggesting Pten loss is a key genetic alteration in human PDAC progression (Fig. 1). In biochemical studies, the authors demonstrated that activation of the NF-κB pathway was associated with the expression of various cytokines and chemokines, which may play a role in recruiting inflammatory cell infiltrates into pancreatic tumors. The combined human PDAC genomic, mouse genetic, and functional studies have revealed that Pten functions as a haploinsufficient tumor suppressor in PDAC development. Moreover, frequent Pten loss and activation of the PI3K pathway, a common event in PDAC development, plays a key role in the progression of Kras-initiated PDAC in the Pdx1-Cre;KrasG12D;Pten1/2 PDAC mouse model by enhancing activation...
of the NF-κB signaling pathway, which in turn increases the expression of proinflammatory cytokines and chemokines that modulate the PDAC tumor microenvironment.

These new findings raise several important questions. What is the primus movens responsible for development of cancer-related inflammatory responses? What are the underlying mechanisms by which mutant Kras induces NF-κB activation? Is activation of PI3K the principal pathway that cooperates with mutant Kras to induce NF-κB activation? What is the expression profile of various NF-κB–dependent cytokines and chemokines in the epithelial cells expressing mutant Kras? How is the cooperation between tumor cells and their inflammatory surroundings orchestrated? Do the high levels of cytokines and chemokines in the tumor microenvironment further amplify the NF-κB pathway, reaching a crescendo in a feed-forward loop, in Pten-deficient cells to promote PDAC development? Can the NF-κB–activating pathways be targeted for preventive and therapeutic intervention for cancers harboring mutant Kras?

The findings by Ying and colleagues (1) suggest the need to obtain a more comprehensive mutational analysis of the PDAC genome and to evaluate the profiles of various signaling pathways, such as the PI3K and NF-κB pathways, in a large human PDAC sample set through the Cancer Genome Atlas projects. Kras mutation has been found in 80% to 95% of PDAC cases and has been shown to induce PDAC in mouse models (4, 12). However, targeting mutant Ras proteins directly with small-molecule inhibitors has thus far proven unsuccessful. Therefore, the discovery and inhibition of important signaling pathways that function downstream of mutant Ras may lead to the identification of novel and effective therapeutic targets (7). As a result of close cooperation between Pten deficiency and oncogenic Kras during PDAC development, the activation of the PI3K and NF-κB signaling pathways are such potential therapeutic targets. Thus, targeting multiple signaling pathways downstream of mutant Kras, including the PI3K, Raf, and MAPK pathways, may lead to effective treatment (7). For example, combined treatment of Kras-induced lung cancer in a genetically engineered mouse model with a dual pan-PI3K and mTOR inhibitor (NVP-BEZ235) and a mitogen-activated protein kinase (MEK) inhibitor (ARRY-142886) resulted in marked synergy in inhibiting the lung cancer (13). It is also possible that directly inhibiting the key cytokine signaling pathways in PDAC harboring Pten deficiency and Kras mutation may represent additional opportunities for targeted therapy.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

Published online July 18, 2011.

**REFERENCES**


Kras, Pten, NF-κB, and Inflammation: Dangerous Liaisons

Paul J. Chiao and Jianhua Ling


Updated version
Access the most recent version of this article at:
http://cancerdiscovery.aacrjournals.org/content/1/2/103

Cited articles
This article cites 13 articles, 6 of which you can access for free at:
http://cancerdiscovery.aacrjournals.org/content/1/2/103.full.html#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.