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Mutated Kras spins a molecular loop that launches pancreatic cancer

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Scientists have connected two signature characteristics of pancreatic cancer, identifying a self-perpetuating "vicious cycle" of molecular activity and a new potential target for drugs to treat one of the most lehal forms of cancer.

The research, reported in the journal *Cancer Cell* and led by scientists at The University of Texas MD Anderson Cancer Center, connected the molecular dots between:

- Mutated versions of Kras, a gene that acts as a molecular on-off switch but gets stuck in the "on" position when mutated.
- Heightened activity of a protein complex called NF-kB that controls activation of genes.

"Kras is mutated in 80 to 95 percent of pancreatic ductal adenocarcinomas, and is the most frequent mutation among all cancers," said senior author Paul Chiao, Ph.D., professor in MD Anderson's Department of Molecular and Cellular Oncology.

About 42,000 new cases of pancreatic ductal adenocarcinoma are diagnosed in the United States each year. Estimates vary, but the 5-year survival rate has been 1 to 3 percent for decades and median survival after diagnosis is six months, the researchers note.

Interleukin-1α is a new potential drug target

"There have been many attempts to inhibit mutated Kras, but it's an elusive target that so far has defied treatment," Chiao said. "So if we can't hit Kras, maybe we can target one of its downstream genes. This research identifies some of those genes and suggests that interleukin-1apha (IL-1α) is a potential therapeutic target."

Chiao and colleagues identified IL-1α as a crucial player in a feed-forward loop that:

- Begins with mutationally activated Kras triggering a chain reaction that induces IL-1α expression;
- This in turn activates NF-κB via the protein kinase IKK2/β, which blocks the inhibitor of NF-κB.
- In the cell nucleus, NF-κB oversees gene transcription and regulates a number of inflammation-promoting genes, including IL-1α.
- IL-1α and another protein called p62 activate NF-κB which in turn cycles back to perpetuate the loop by activating its activators.

"It's a vicious cycle," Chiao said. The overactive NF-κB fuels pancreatic cancer by activating genes that promote inflammation, the growth of new blood vessels and block programmed cell death.

Chiao has three research grants from the National Cancer Institute to study pancreatic cancer. "We study signaling transduction pathways to try to find out why it's such a bad disease and to find a weak point for targeted therapy," he said.

In the Cancer Cell paper, the authors conclude: "Our findings suggest

that the prime mover responsible for cancer-related inflammatory response and the development of pancreatic intraepithelial neoplasia (precancerous lesions) and pancreatic ductal adenocarcinoma is the mutant Kras-initiated constitutive activation of NF-κB."

This process, they further noted, creates a pro-tumor microenvironment by promoting inflammation, creation of new blood vessels and tissue repair that is similar to conditions found in inherited pancreatitis, inflammation of the pancreas that is linked to the development of cancer.

Kras mutation, IL-1α, NF-κB go together with poor survival

The team analyzed mouse and human tumors and mouse strains with mutated Kras expressed in their pancreases. In a series of experiments they found:

- Active IKK2/β – the activator of NF-κB – was required for the Kras-mutated mice to develop either pancreatic cancer or precancerous legions.
- Deletion of IKK2/Beta interrupted Kras-stimulated inflammation and cell proliferation, suggesting that chronic inflammation is a key factor in promoting pancreatic cancer development.
- Microarray profiles of gene expression showed that several NF-κB-regulated inflammatory genes were present in high levels in mice with mutated Kras and active IKK2/β but only found at lower levels in mice with IKK2/β knocked out.

- In human pancreatic tumors, high expression of the same inflammatory genes in the mutated Kras mice were associated

with positive lymph node status, high-risk, late tumor stage and poor survival.

- Expression of several genes regulated by NF-κB progressed from low levels in normal pancreases to higher levels in precancerous lesions and tumors, including IL-α.
- IL-1α was known to be both a target of and an inducer of NF-κB, but its expression had not previously been connected to mutated Kras. The team found that downstream targets of Kras, including IL-1α, are interrupted when IKK2/β is inactivated.
- Analysis of 14 human pancreatic cancer tumor samples showed that overexpression of IL-1α, the presence of Kras mutation and the activation of NF-kB are correlated and are associated with poor survival.

- Continued activation of NF-κB and its gene transcription activity are sustained by IL-1α and p62.

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