MedicalXpress

# Advanced pancreatic tumors depend on continued oncogene activity

April 26 2012

Researchers at Dana-Farber Cancer Institute have shown that advanced pancreatic cancers in mice can't survive without continued expression of a mutant oncogene that "rewires" key metabolic pathways to fuel the cancer cells.

The findings, published in the April 27 issue of the journal *Cell*, suggest that some of these altered metabolic pathways might be potential targets for future drugs to treat the deadly cancer.

The investigators report that when they experimentally shut down the expression of the Kras oncogene in mice, the pancreatic tumors rapidly shrank, and, in some cases, left no visible signs of cancer. This outcome, they said, provides evidence that advanced pancreatic cancers are "addicted" to the Kras oncogene for their continued growth.

"This experiment allowed us to demonstrate that pancreatic cancers in their native setting are dependent on continued oncogenic Kras expression for tumor maintenance," says Alec Kimmelman, MD, PhD, co-corresponding author of the report along with Ronald DePinho, MD, formerly at Dana-Farber and now at M.D. Anderson Cancer Center in Houston.

Kimmelman said they also discovered that oncogenic Kras "basically reprograms the glucose metabolism of the cell by regulating the expression of key metabolic enzymes, some of which might provide novel therapeutic targets." If that is the case, then attacking these

pathways might be more feasible than attempting to block KRAS directly, since KRAS has proven frustratingly difficult to hit with designer drugs.

It is estimated that pancreatic ductal adenocarcinoma will be diagnosed in more than 43,000 people in the United States in 2012, according to the American Cancer Society, and more than 37,300 will die from the disease, which has a 5-year survival rate of only 5 percent.

It has been known that the Kras oncogene is an important driver of pancreatic cancer, unleashing chaotic proliferation of cancer cells, but a key question remained as to whether cancer cells that developed spontaneously in the pancreas needed Kras to survive.

To clarify this point, Kimmelman and colleagues created a genetically engineered mouse model in which the mutant Kras gene in the pancreas could be turned on and off at will through dietary manipulation. In addition, the tumor suppressor gene p53 was "knocked out" to model the loss of p53 that occurs in pancreatic cancer.

Next, the scientists removed an antibiotic from some of the rodents' feed, which inactivated the Kras oncogene. Scans and histology showed tumors beginning to shrink within two or three days and were diminished by an average of 50 percent after a week. PET scans revealed that the remaining tumors were no longer consuming glucose, meaning they were inactive. In addition, malignant changes in the tumors' tissue environment caused by the Kras oncogene had been reversed.

In collaboration with the laboratory of Lewis Cantley, PhD, of Beth Israel Deaconess Medical Center, the investigators then determined how Kras oncogene activity enabled the tumors to survive and grow. "We found that Kras is regulating glucose metabolism in pancreatic cancer," Kimmelman says.

The researchers showed that the oncogene – which regulates the activity of multiple genes in cells -- "reprogrammed" gene pathways that are involved in utilizing and processing glucose, which serves as fuel for cells. For example, experiments revealed that Kras activity shunted glucose building blocks into a pathway called the non-oxidative pentose phosphate pathway (PPP) -- a previously unknown connection. Importantly, suppressing these key metabolic enzymes regulated by Kras resulted in a significant impairment of tumor growth.

"These results suggest that it may be possible to attack tumors by inhibiting some of these enzymes," Kimmelman explains, though he cautions that it remains to be seen whether the enzymes can be reduced without having unwanted effects on the body.

Still, this research may ultimately yield new avenues for treating various cancers that are driven by the hard-to-target Kras oncogene.

Provided by Dana-Farber Cancer Institute