

Scientists Show How Molecular Switch Helps Pancreatic Cancer Beat Drugs

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Researchers at the Moores Cancer Center at the University of California, San Diego, have found one reason that pancreatic cancer tumors are so difficult to treat with drugs. They have shown how a molecular switch steps up pancreatic cancer cell survival as well as resistance to a standard chemotherapy drug, and have identified alternate routes cancer cells take to avoid the effects of the therapy.

The findings, by a group led by Andrew M. Lowy, MD, professor of surgery and chief of surgical oncology at the UCSD School of Medicine and the Moores UCSD Cancer Center, are reported online and will appear February 1 in the journal *Cancer Research*. The study provides new insights into pancreatic cancer development and new potential drug targets and treatment strategies against the disease.

"To understand how to treat pancreatic cancer tumors, we need to better understand their circuitry and behavior," Lowy said.

Pancreatic cancer is a particularly deadly cancer, fast-moving and difficult to detect early. It's estimated that more than 35,000 people died from pancreatic cancer last year in the United States.

RON is a signaling protein known as a tyrosine kinase, essentially a switch that turns on various activities in cells. Previous work in Lowy's lab showed that RON is overexpressed in a majority of precancerous and pancreatic cancer cells, and could also help cells resist dying. The researchers wanted to find out what role, if any, RON played in pancreatic cancer development and progression.

In a series of experiments, the researchers showed that RON sends signals that regulate the activity of genes that help tumors cells survive, "implying RON is a potent survival signal for pancreatic cancer cells," Lowy said.

To see the effects of reducing or blocking RON activity, the team shut down RON expression in pancreatic cancer cells using a molecular technique called "gene silencing," and then used those cells to establish tumors in mice. Those tumors were treated with gemcitabine, the most common chemotherapy drug used to treat pancreatic cancer patients. Tumors in which RON was silenced were much more sensitive to the chemotherapy than the RON-expressing cancer cells.

"This is the first demonstration that RON-directed therapy in an animal model can sensitize tumors to chemotherapy," Lowy said. Yet, the scientists found that the cancer cells and tumors were eventually able to bypass the silencing agent as well as the drug's effects, and continued to grow.

About 50 percent of the tumor cells re-expressed RON. The researchers also found that the tumor cells activated other growth proteins, including epidermal growth factor receptor (EGFR), to enable them to continue to grow. "This is what most tumors do," Lowy said, explaining that clinically, pancreatic cancer tumors often respond to therapy at first, only to begin growing again. "We know that diseases such as pancreatic cancer are

too complex for one drug to be effective. If we can learn to predict the results of RON-directed therapy, maybe we can combine it with an EGFR-directed therapy, for example, to take away tumor escape routes."

Lowy explained that scientists still need far more information about RON's part in pancreatic cancer development and progression. "We need to figure out which tumors are relying on RON," he said. "If we could develop biomarkers to identify which tumors are going to be susceptible to RON-targeted therapy, then we can begin to figure out what tumors do to escape such treatments."

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The Moores UCSD Cancer Center is one of the nation's 40 National Cancer Institute-designated Comprehensive Cancer Centers, combining research, clinical care and community outreach to advance the prevention, treatment and cure of cancer. For more information, visit <http://health.ucsd.edu/cancer>. The Ludwig Institute for Cancer Research (www.licr.org) is an international organization with branches in 10 countries.

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