Pancreatic cancer genetic marker may predict outcomes with radiation therapy

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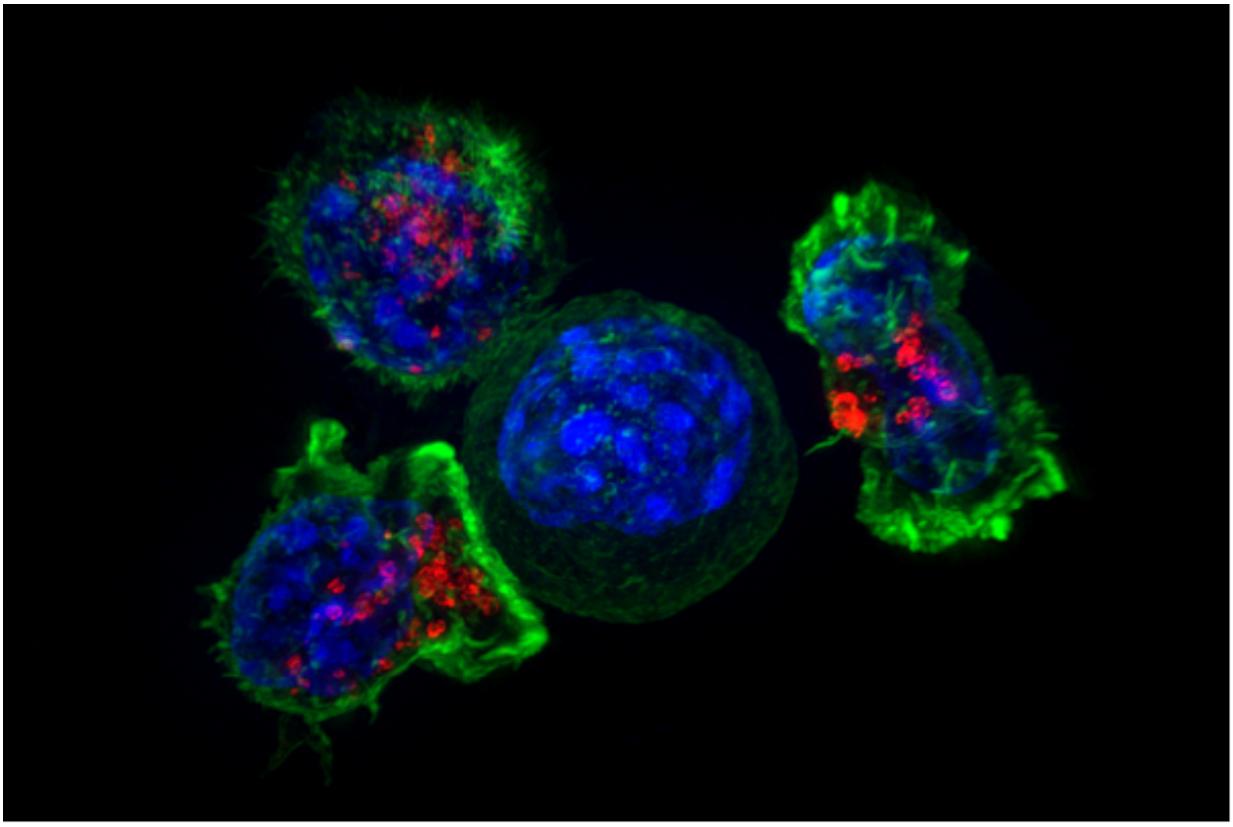

Killer T cells surround a cancer cell. Credit: NIH

Pancreatic cancer is one of the most difficult cancers to treat and is a leading cause of cancer-related deaths. Now, Sidney Kimmel Cancer Center—Jefferson Health and Lankenau Institute for Medical Research

scientists find that a gene involved in the immune system called IDO2 plays a significant role in pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer. The discovery may help physicians provide better treatment options for patients.

"The findings could point to a therapeutic target or an important prognostic biomarker," said George Prendergast, Ph.D., President and CEO of the Lankenau Institute for Medical Research (LIMR) of Main Line Health who co-led the study with Jonathan Brody, Ph.D., Director of the Research Division and Professor of Surgery at Thomas Jefferson University, both of whom are members of the Sidney Kimmel Cancer Center—Jefferson Health.

The team published the new work September 28 in the journal *Clinical Cancer Research.*

The IDO2 gene, which was first discovered by LIMR researchers in 2006, produces an enzyme that helps manage the immune system. During pregnancy, IDO2 and a related gene, IDO1, tone down the mother's immune system so it will not attack the fetus, for example. Cancer, however, hijacks the IDO genes' function. It uses IDO1 and 2 to conceal itself from the immune system. The researchers thought that shutting down the IDO enzymes could make the cancer visible to the immune system, thereby allowing the body's defenses the opportunity to fight the cancer. In fact, in previous research, the team found that mice lacking the IDO genes did not develop pancreatic cancer in a rodent model of the disease. The results suggested IDO genes are essential to pancreatic cancer progression.

Now, Drs. Brody and Prendergast find IDO2 spurs the formation of PDAC tumors. When the researchers induced the development of pancreatic cancer in mice, they found nearly 30 percent of rodents developed the invasive cancer. In mice that lack the IDO2 gene,

however, the cancer grew in only 15 percent of the animals. Strikingly, all the mice lacking IDO2 that developed cancer were male. The results suggest IDO2's involvement in pancreatic cancer may affect females differently from males.

The researchers knew that many people in the general population have inherited, or germline, alterations in the IDO2 gene that turn off the gene's ability to mediate the immune system. So the scientists examined the IDO2 gene in a subgroup of pancreatic cancer patients from Thomas Jefferson University Hospital. Genetic testing is easy and cost effective, since researchers need only a sample of blood or cheek swab to detect this DNA.

"Besides IDO2's involvement in development of pancreatic cancer, we wanted to know whether IDO2 affects how patients respond to treatment," said Dr. Brody.

When the team compared patients' IDO2 genes with their prognosis, they found that patients with defunct IDO2 genes had more favorable outcomes.

"The patients in our small cohort actually do better in specific treatment settings," said Dr. Brody. "They have improved disease-free survival when they receive radiotherapy."

Patients with nonfunctional IDO2 who also received adjuvant radiation treatment lived cancer-free for almost twice as long as patients with a working version of the gene, the researchers found. The results suggest that people with a specific IDO2 gene status may respond better to radiotherapy for their disease. In fact, patients who had deficient IDO2 gene status and received radiotherapy had a markedly improved survival. Patients with a functioning IDO2 gene who had received radiation treatment did not demonstrate such benefits and nor did patients with an

inactive IDO2 gene who did not receive radiotherapy.

Together, these initial findings suggest that IDO2 gene status has the potential to influence pancreatic care decision-making (i.e., precision therapy). In the future, physicians may be able to use the gene's status as a biomarker to inform their treatment recommendations.

"Developing new strategies to refine therapeutic options has been a top priority of our nationally recognized pancreatic cancer team at the Sidney Kimmel Cancer Center," says cancer researcher Karen Knudsen, Ph.D., Director of the Sidney Kimmel Cancer Center—Jefferson Health. "This breakthrough in understanding lays the foundation for determining what patients might most benefit from radiotherapy, and represents a major step forward toward the goal of precision oncology."

Although the researchers are excited about these findings, Dr. Brody suggests a lot of work needs to be done to validate the study in additional, larger cohorts, and ultimately, in a prospective clinical trial. If confirmed, Brody states, "With a simple blood test, physicians could determine a patient's IDO2 gene status and determine whether they should go on radiotherapy."

More information: Avinoam Nevler et al, Host IDO2 gene status influences tumor progression and radiotherapy response in KRAS-driven sporadic pancreatic cancers, *Clinical Cancer Research* (2018). DOI: 10.1158/1078-0432.CCR-18-0814

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