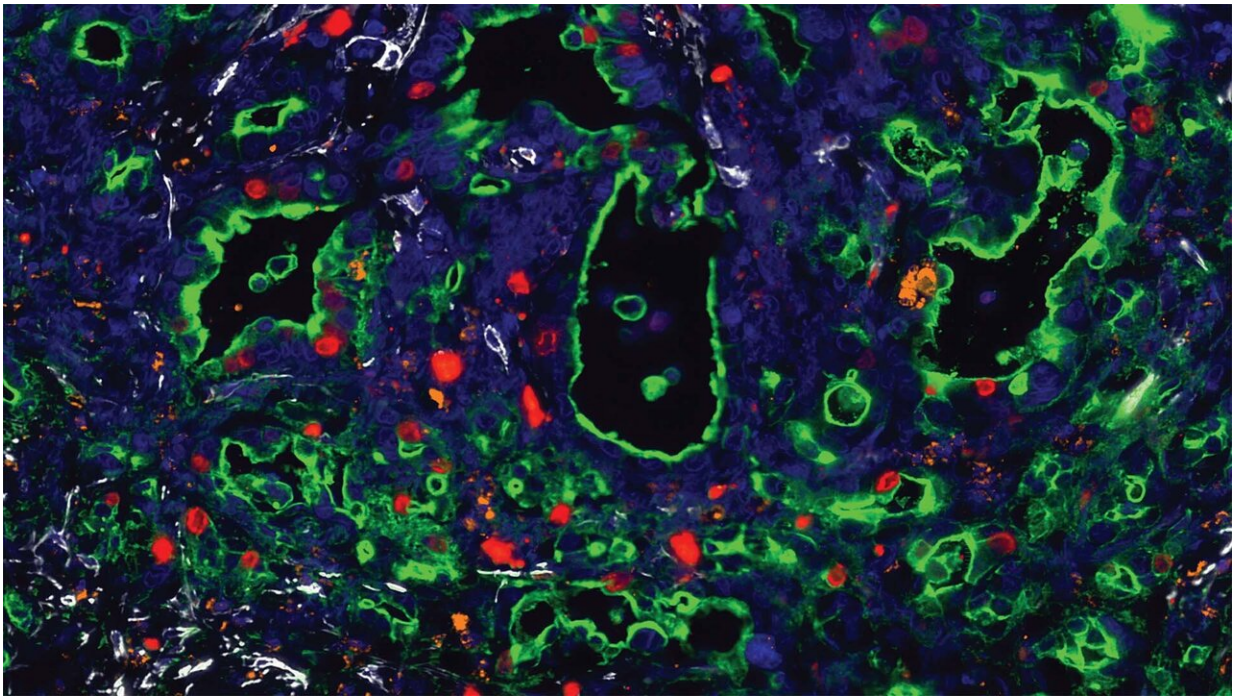
Why pancreatic ductal adenocarcinoma is so lethal

May 19 2020, by Judy Gelman Myers



Photomicrograph of a human pancreatic cancer tumor showing a mixture of different kinds of cells in close proximity to each other. Tumor-promoting, p63-positive cancer cells are stained red, neutrophils orange, fibroblasts white, and other p63-negative cancer cells are green. Given that p63-positive pancreatic cancer cells secrete inflammatory factors, this image demonstrates how these cancer cells can communicate with surrounding cells and promote inflammatory processes in human patients. The sample was stained by multiplexed immunofluorescence. Credit: Vakoc lab/CSHL, 2020

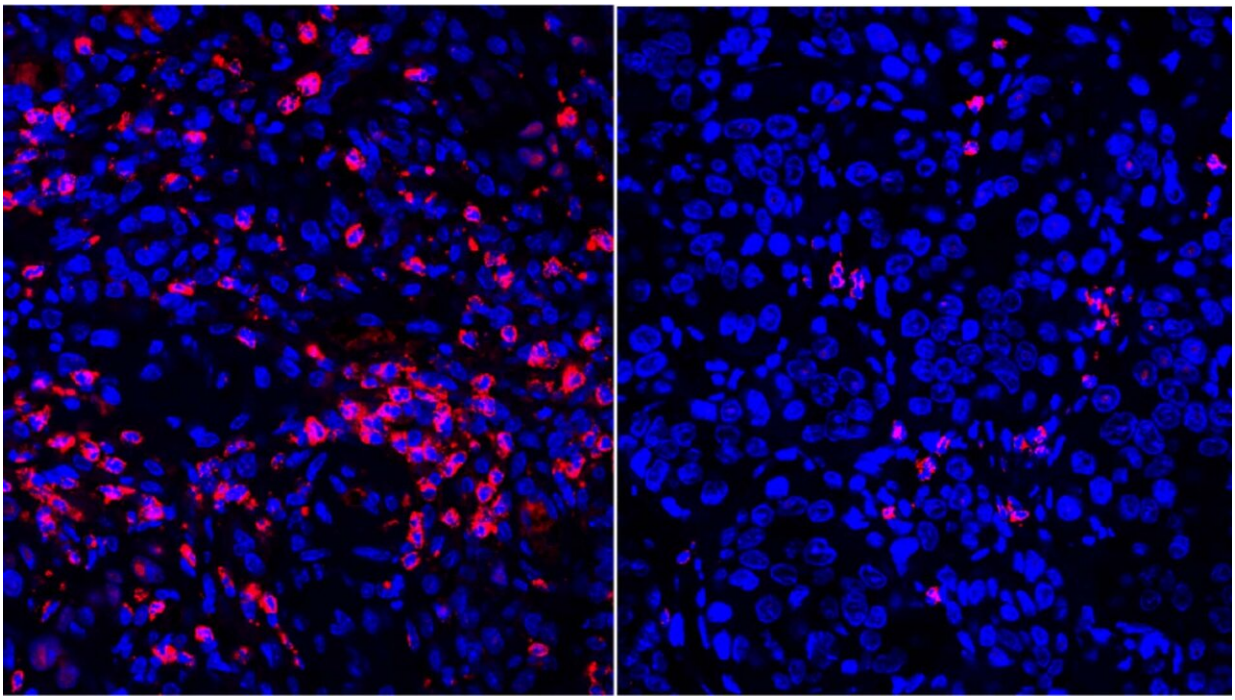
Pancreatic ductal adenocarcinoma (PDA) is a deadly cancer, killing patients within a year. CSHL Professor Christopher Vakoc and his former postdoc Timothy Somerville discovered how pancreatic cells lose their identity, acquire a deadly new identity, and recruit nearby cells to help them grow, promote inflammation, and invade nearby tissues. This understanding could lead to new therapies similar to ones developed for other cancers.

Vakoc says, "We think part of the reason why these tumors are so aggressive is that they exploit normal cells. The normal cells that are in the vicinity of these tumors, are actually co-conspirators in this disease, and are being co-opted to kind of create a community of cells that are kind of teaming up with one another to drive this aggressive cancer to expand and metastasize. Ultimately, we think we sort of learned why this tumor is so aggressive through understanding these two mechanisms."

Somerville found two transcription factors that were highly abundant in PDA but not in a normal pancreas: ZBED2 (pronounced Z-bed too) and p63.

ZBED2 confuses the pancreas cell about its own identity. It displaces another transcription factor that is required for the pancreas cell to perform its normal functions as a pancreas cell. ZBED2 turns pancreas cells into squamous cells—a type of cell found in the skin. Patients with the worst outcomes have the highest levels of squamous cells in their tumors.

Little was known about ZBED2 when Somerville began his research. He says, "ZBED2 is a gene. It makes a protein, which is transcription factor ZBED2. What was completely unknown was what this protein ZBED2 was actually doing. We were able to demonstrate that it is a transcription factor, which means that it can bind to DNA and regulate other genes. And we were able to show what types of genes it regulates."



Fewer neutrophils lead to less inflammation in pancreatic tumors. In this photomicrograph of pancreatic tumor specimens taken from mice, neutrophils are shown in red and all other cells in blue. The image on the left shows a tumor formed by p63-positive pancreatic cancer cells and the image on the right shows the same pancreatic cancer cells but where the researchers used a genetic technique, CRISPR, to prevent cells from expressing p63. Note that there are far fewer neutrophils in the p63-negative tumor (right). Specimens were stained by immunofluorescence. Credit: Vakoc lab/CSHL, 2020

p63 recruits nearby cells—mostly neutrophils and fibroblasts—to support the cancerous squamous cells. They "alter the tumor microenvironment, making it more inflammatory and more aggressive. This is what we think is contributing to the particularly poor outcomes of this group of pancreatic patients," says Somerville.

PDA is notoriously resistant to chemotherapy. The wall of inflammatory

cells makes it difficult for anti-tumor drugs to access the tumor. Somerville believes that understanding what ZBED2 and p63 are doing to make this cancer so aggressive will uncover ways that scientists can prevent or at least slow its growth. Somerville notes, "It's about exploiting transcription factors. If we understand their functions, we can use them to show us how to think about different ways to treat this disease."

The FDA has already approved drugs that target transcription factors in breast cancer, leukemia, and prostate cancer. Vakoc's lab is seeking to advance this concept for other types of cancer, such as PDA.

More information: Somerville, T.D.D. et. al, "ZBED2 is an antagonist of interferon regulatory factor 1 and modifies cell identity in pancreatic cancer" *PNAS*, May 8, 2020. DOI: 10.1073/pnas.1921484117 , www.pnas.org/content/early/2020/05/07/1921484117

Somerville, T.D.D. et. al, "Squamous trans-differentiation of pancreatic cancer cells promotes stromal inflammation" *eLife*, April 24, 2020. DOI: 10.7554/eLife.53381

Provided by Cold Spring Harbor Laboratory