Immune system infighting explains pancreatic cancer's aggression

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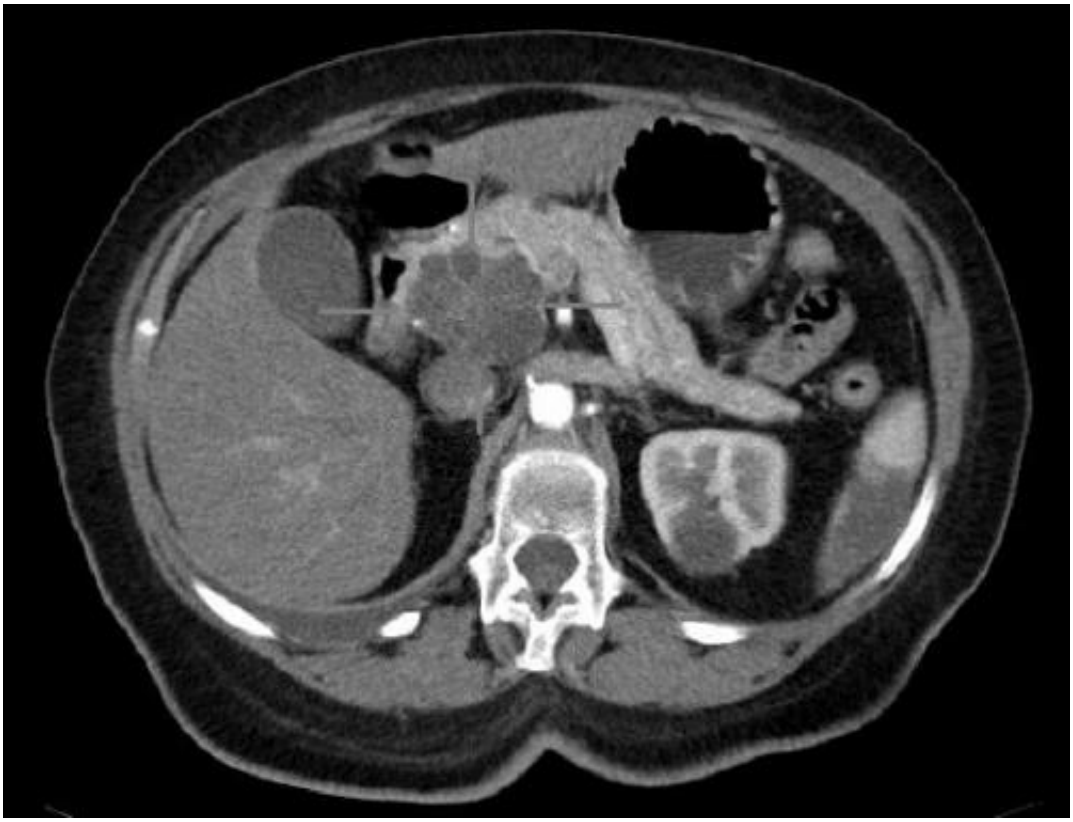

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Internal conflict between cell types explains why the immune system struggles to recognize and attack pancreatic cancer. Curbing this infighting has the potential to make treatment more effective, according

to a study led by researchers from NYU Langone Medical Center and its Perlmutter Cancer Center.

The study, which published Aug. 25 in *Cell*, describes how a powerful subset of immune cells, known as "gamma delta T cells," prevents other tumor-fighting T cells from entering pancreatic tumors. Without interference from gamma delta T-cells, CD4 and CD8 cells multiply and actively attack tumors the way they attack invading viruses or bacteria. Unfortunately, the immune system generates a large number of pro-tumor gamma delta T cells that infiltrate pancreatic tumors.

Recent advances in immunotherapy, an approach that activates a patient's immune system to combat cancer, boost the effects of CD4 or CD8 T cells. Results of the newly published study argue that this kind of immunotherapy must be more rigidly targeted in pancreatic cancer. Unless the gamma delta T-cells are blocked, CD4 and CD8 cells are unable to function or thwart cancer growth, the study finds.

"Standard immunotherapy does not work in pancreatic cancer, which is especially deadly. Now we have more information to help us understand why," says senior author George Miller, MD, head of the Immunology Program at Perlmutter, vice chair for research in the Department of Surgery, and associate professor in the Department of Cell Biology at NYU Langone. "The main anti-tumor defense mechanism is rendered completely useless in pancreatic cancer."

Miller's study focused on pancreatic ductal adenocarcinoma (PDA), which is nearly always fatal. While overall cancer survival rates have improved dramatically with the advent of modern therapies in the past two decades, only about 8 percent of people survive five years after their diagnosis with any form of pancreatic cancer.

Gamma delta T-cells are prolific in human PDA tumors, making up

about 40 percent of T cells on average. This prompted Miller and lead author Donnele Daley, MD, a postdoctoral fellow and surgery resident at NYU Langone, to theorize that gamma delta T cells play a unique role in the promotion of pancreatic cancer, as the new study shows. Separate tests revealed that gamma delta cells alone do not promote tumor growth - they simply prevent the tumor-fighting immune cells from working.

The findings also underscore the complexity of the immune system, says Miller. The same gamma delta T-cells that enable pancreatic cancer tumors to grow unchecked have been shown to fight other kinds of cancers, such as melanoma, some kidney cancers, and colon cancer. Not all immune cells have the same roles in different cancers, and they sometimes work against each other.

The research has important implications for the development of better diagnostics and treatment for pancreatic cancer. However, Miller cautions that translating it to humans may be challenging, because there is currently no known drug or other method that can block the action of gamma delta T-cells in humans.

In the current study, Miller's team analyzed tumor size and the quantity and type of immune cells present over time in mice bred with pancreatic cancer and lower numbers of gamma delta T-cells. Mice harboring pancreatic cancer with fewer than normal gamma delta cells survived nearly a year longer on average than mice with a normal number.

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