Gut bacteria determine speed of tumor growth in pancreatic cancer

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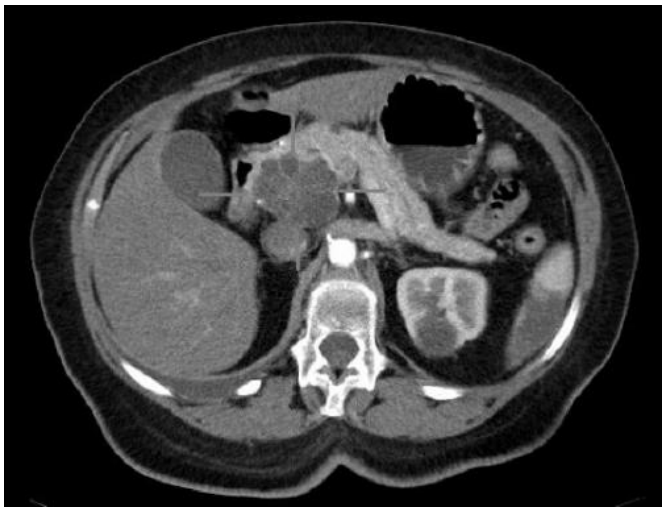

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

The population of bacteria in the pancreas increases more than a thousand fold in patients with pancreatic cancer, and becomes dominated by species that prevent the immune system from attacking tumor cells.

These are the findings of a study conducted in mice and in patients with pancreatic ductal adenocarcinoma (PDA), a form of cancer that is usually fatal within two years. Led by researchers at NYU School of Medicine, Perlmutter Cancer Center, and NYU College of Dentistry, the study published online March 22 in *Cancer Discovery*, a journal of the American Association for Cancer Research.

Specifically, the study found that removing bacteria from the gut and pancreas by treating mice with antibiotics slowed cancer growth and reprogrammed immune cells to again "take notice" of cancer cells. Oral antibiotics also increased roughly threefold the efficacy of checkpoint inhibitors, a form of immunotherapy that had previously failed in pancreatic cancer clinical trials, to bring about a strong anti-tumor shift in immunity.

Experiments found that in patients with PDA, pathogenic gut bacteria migrate to the pancreas through the pancreatic duct, a tube that normally drains digestive juices from the pancreas into the intestines. Once in the pancreas, this abnormal bacterial mix (microbiome) gives off cellular components that shut down the immune system to promote cancer growth, say the authors.

"While combinations of changes in genes like KRAS cause cells to grow abnormally and form pancreatic tumors, our study shows that bacteria change the immune environment around cancer cells to let them grow faster in some patients than others, despite their having the same genetics," says senior study co-author George Miller, MD, co-leader of the Tumor Immunology Research Program at Perlmutter, the H. Leon Pachter, MD, Professor in the Department of Surgery, and professor of Cell Biology at NYU Langone Health.

"Our results have implications for understanding immune-suppression in pancreatic cancer and its reversal in the clinic," says senior co-author Deepak Saxena, PhD, associate professor of Basic Science and Craniofacial Biology at NYU College of Dentistry. "Studies already underway in our labs seek to confirm the bacterial species most able to shut down the immune reaction to cancer cells, setting the stage for new bacteria-based diagnostic tests, combinations of antibiotics and immunotherapies, and perhaps for probiotics that prevent cancer in high-risk patients."

On the one hand, the research team theorizes that changes in the genes that cause abnormal cell growth in the pancreas might also change the immune response in ways that favor the growth of different bacterial species than are found in normal

individuals.

Alternatively, environmental factors like diet, other diseases, or common medications might cause bacterial changes in the gut that are reflected in the pancreatic microbiome.

Whatever the cause, the new study found that bacteria that are more abundant in pancreatic cancers - including groups of species called proteobacteria, actinobacteria, and fusobacteria - release cell membrane components (e.g. lipopolysaccharides) and proteins (e.g. flagellins) that shift macrophages, the key immune cells in the pancreas, into immune suppression.

Experiments showed that eliminating bacteria using antibiotics restored the ability of immune cells to recognize cancer cells, slowed pancreatic tumor growth, and reduced the number of cancer cells present (tumor burden) by 50 percent in study mice.

The researchers found that "bad" bacteria in pancreas tumors trigger immune cell "checkpoints" - sensors on immune cells that turn them off when they receive the right signal. These checkpoints normally function to prevent the immune system from attacking the body's own cells, but cancer cells hijack checkpoints to turn off immune responses that would otherwise destroy them. Checkpoint inhibitors are therapeutic antibodies that shut down checkpoint proteins to make tumors "visible" again to the immune system.

"Adding antibiotics improved the performance of a checkpoint inhibitor in a mouse model of PDA, as shown by an increase in T cells that could attack the tumors," says first co-author Mautin Hundeyin, MD, a postdoctoral fellow in Miller's lab. "Our study confirmed that, similar to what has been observed in patients with pancreatic cancer, checkpoint inhibition alone did not protect mice. This may be because, in the immunosuppressive environment of the tumor, there are too few immune cells around to be activated."

As a next step, the research team plans to soon begin recruiting patients into a clinical trial at Perlmutter Cancer Center to test whether a combination of antibiotics (ciprofloxacin and metronidazole) can improve the effectiveness of a checkpoint inhibitor (an anti-programmed death receptor 1 (PD-1) antibody) in PDA patients.

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