Pancreatic cancer subtypes discovered in largest gene expression analysis to date

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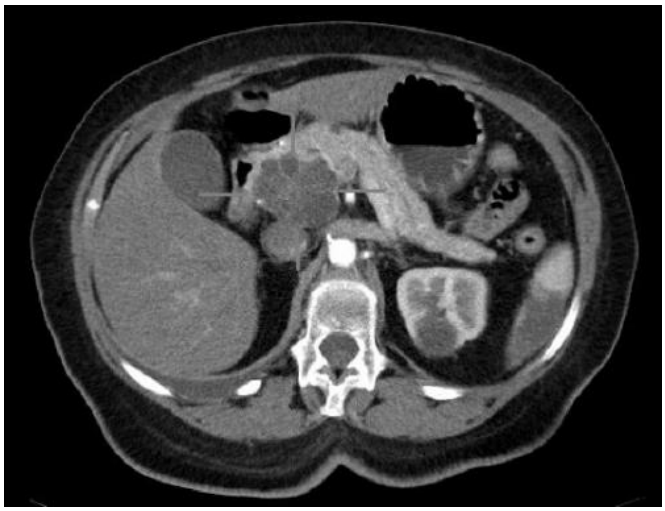

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Dense surrounding tissue can block drugs from reaching pancreatic cancer tumors, but it can also help prevent the cancer from spreading. Now a new study by UNC Lineberger Comprehensive Cancer Center researchers and collaborators helps explain the conflicting role of the surrounding tissue known as stroma. In the study, the researchers revealed that based on molecular characteristics, there are two subtypes of pancreatic cancer stroma.

In the study published in *Nature Genetics* today, researchers reveal findings of both new subtypes of stroma and two subtypes of pancreatic cancer tumors. The findings could help doctors tailor treatments to individual patients. And the researchers say that could be particularly important for a disease that has only a 7 percent five-year survival rate.

"Right now, we still treat pancreatic cancers as one entity, while for some other cancers, we personalize treatment based on an individual patient's tumor genetics or other characteristics," said the study's senior author Jen Jen Yeh, MD, a UNC Lineberger member and an associate professor and the vice chair for research in the UNC School of Medicine Department of Surgery. "We believe these results will set the groundwork for future clinical trials, allow treatments to be assigned based on the subtypes, and guide the development of new therapies."

The study reveals the most rigorously validated classification system for pancreatic ductal adenocarcinoma to-date. Previous studies, such as a 2011 study led by Eric A. Collisson, MD, an assistant professor at the UCSF School of Medicine, have identified subtypes of pancreatic cancer. But the researchers believe those attempts were confounded by the large amount of surrounding stroma that is intermixed with both normal and cancerous pancreatic tissue.

To solve that problem, UNC Lineberger researchers used a mathematical approach led by Richard Moffitt, PhD, a postdoctoral research associate at UNC Lineberger, to separate the tissue. That approach, called blind source separation, allowed the researchers to separate the normal from the cancerous tissue and the stroma. They were then able to examine gene expression patterns for each type in tissue samples from five different institutions. They analyzed 145 primary and 61 metastatic tumors, 17 cell lines, as well as 46 normal pancreatic samples and 88 samples of normal, non-cancerous tissue outside of the pancreas.

"The issue is that pancreatic cancer is a particularly difficult cancer to analyze because of its confounding stroma, so we needed to marry the right data analysis technique to the right problem," Moffitt said.

The researchers uncovered two subtypes of pancreatic stroma that they called "normal" and "activated." Patients with the activated subtype had worse survival outcomes.

"This study helps make sense of researchers' conflicting findings about stroma – that it can either promote or be a barrier to tumor spread," Yeh said. "We are seeing two distinct types of stroma in patients."

Their analysis also revealed two subtypes of pancreatic cancer tumors. One subtype, called "basal-like," is linked to worse outcomes for patients. Forty-four percent of patients with the basal-like subtype lived one year after surgery, compared to a 70 percent survival for patients with other subtype, which they called "classical." Basal-like tumors also trended toward a better response to adjuvant therapy.

"If we know that your tumor is aggressive, then it may be important to treat your whole body first with neoadjuvant therapy, which is therapy given prior to surgery, as opposed to just trying to remove the tumor with surgery at the outset," said Yeh, who, in addition to her role in the Department of Surgery, also has an appointment in the UNC School of Medicine Pharmacology Department. "

In addition, the basal-like subtype is very similar to basal breast and bladder cancers, which respond to therapies differently than other tumor subtypes, so we are very interested in seeing whether or not this is true for pancreatic cancer as well."

Overall, the findings suggest that treatment decisions should be based on both a patient's stroma and tumor subtype. Yeh said the researchers will be launching clinical trials to investigate how patients with the different subtypes respond to treatment.

"For pancreatic cancer in particular, it's a race against the clock, every therapy counts, so you want your first therapy to work," she said. "With this cancer, you don't have a lot of time to try different therapies. If a patient is given a therapy that is unsuccessful, that is time in which the patient's disease has progressed. So the goal is to start patients on the right therapy from the get-go."

More information: "Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma." *Nature Genetics* (2015) DOI: 10.1038/ng.3398

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