Age-related changes in fibroblast cells promote pancreatic cancer growth and spread

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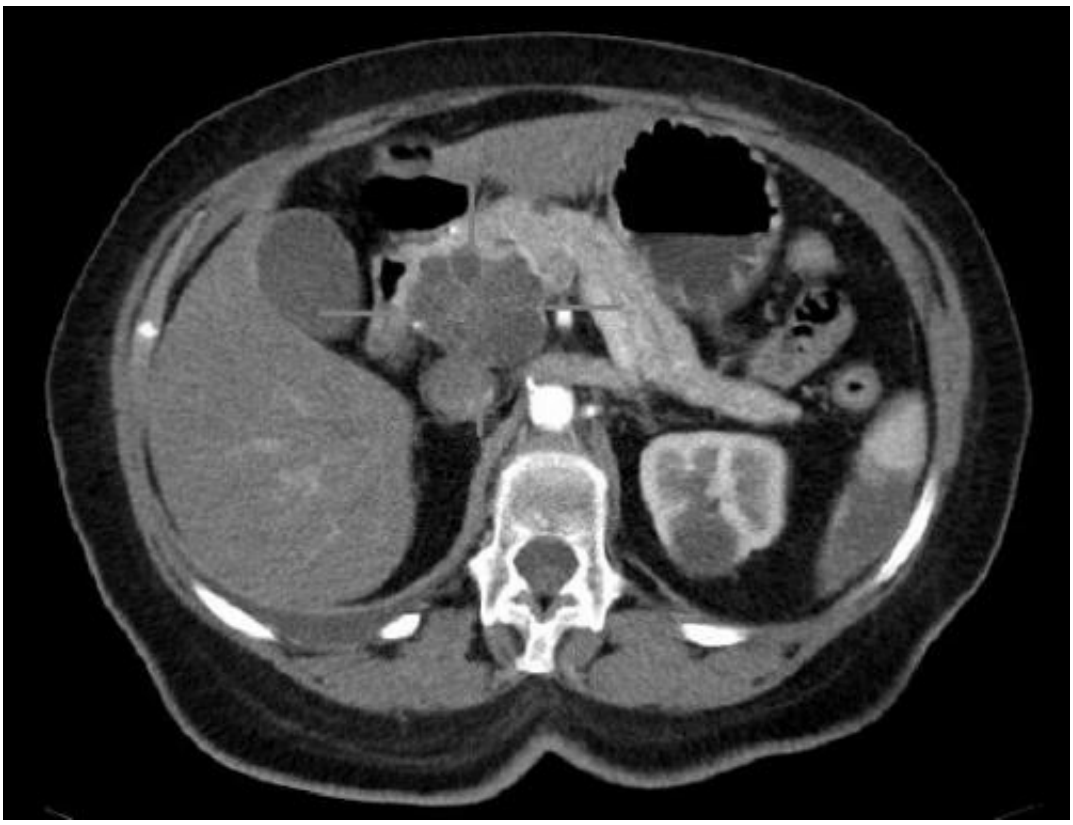

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Older people may be at greater risk of developing pancreatic cancer and have poorer prognoses because of age-related changes in cells in the

pancreas called fibroblasts, according to research led by investigators from the Johns Hopkins Kimmel Cancer Center, the Johns Hopkins Bloomberg School of Public Health and the Bloomberg~Kimmel Institute for Cancer Immunotherapy.

The study, published in *Cancer Research*, provides clues as to why pancreatic cancer is more common and aggressive in older people. It may also help scientists develop new therapeutic approaches for this difficult-to-treat cancer. The study showed that aging alters fibroblasts in ways that enable them to promote pancreatic cancer tumor growth.

"Older fibroblasts release proteins that directly affect pancreatic cancer cells and ultimately lead to the growth and spread of pancreatic cancer tumors," says the study's lead author, Daniel Zabransky, M.D., Ph.D., assistant professor of oncology at the Johns Hopkins University School of Medicine. "The younger fibroblasts did not have these capabilities. We think this is a key reason why we see pancreatic cancer more commonly in older patients."

Zabransky and his colleagues compared samples of pancreatic fibroblasts from patients older than 55 with pancreatic fibroblasts from patients younger than 35. They discovered that the cells from older patients behave very differently than younger ones. To find out why, they compared the proteins released by the younger and older cells and noted profound differences.

They determined that a critical change in older pancreatic fibroblasts is that they release more of a protein called growth/differentiation factor 15 (GDF-15). When the team treated young mice with pancreatic tumors with GDF-15, it caused the tumors to grow more rapidly, just as they do in older mice. Older mice that were genetically engineered to lack the gene encoding GDF-15 had reduced pancreatic tumor growth.

Experiments in human cells and mouse models revealed that GDF-15 activates the AKT signaling pathway in an age-dependent manner. The discovery was a surprise because the AKT pathway is typically not very active in mouse models of pancreatic cancer, Zabransky says.

However, most studies look only at young mice. Experimental drugs already exist that inhibit the AKT pathway. When the team tested AKT-inhibiting drugs in mouse models of pancreatic cancer, they found the drugs reduced tumor growth in mice with aged fibroblasts. However, it had no effect in mice with young fibroblasts. Zabransky and his colleagues next plan to study age-related changes in other cells found in pancreatic cancer tumors, including immune cells, and their impact on pancreatic cancer.

Previous work by senior study author Ashani Weeraratna, Ph.D., co-chair of the Cancer Invasion and Metastasis Program and associate director for laboratory research for the Johns Hopkins Kimmel Cancer Center, demonstrated the importance of age-related changes in melanoma, a finding the team has now extended to pancreatic cancer.

Weeraratna also is the E.V. McCollum Professor and chair of the Department of Biochemistry and Molecular Biology a Bloomberg Distinguished Professor at the Johns Hopkins Bloomberg School of Public Health, and a professor of oncology at the Johns Hopkins University School of Medicine.

"We have very few treatment options for pancreatic cancer," Weeraratna says. "Trying to understand how the aging microenvironment contributes to pancreatic cancer progression might open up new avenues for therapies."

"Precision cancer therapy just got more complicated," adds study co-author Elizabeth Jaffee, M.D., deputy director of the cancer center, co-

director of the gastrointestinal cancers program, and the Dana and Albert "Cubby" Broccoli Professor of Oncology at Johns Hopkins.

"This work by Dr. Zabransky and his team points out for the first time in pancreatic cancer that there are aging-specific signals in tumors that may need to be modulated to realize the potential of current and future treatments for this deadly disease."

Zabransky says age-related changes may also be critical in other types of cancers. He noted scientists test most cancer drugs in young mice, and drugs that target age-specific cancerous changes may not work in these young mouse models. It also may be vital to examine the results of clinical trials of cancer drugs to see if the effects vary in different age groups, he says.

More information: Daniel J. Zabransky et al, Fibroblasts in the aged pancreas drive pancreatic cancer progression, *Cancer Research* (2024). DOI: 10.1158/0008-5472.CAN-24-0086

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