Study reveals disparity between fibroblasts of different pancreatic diseases

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Fibroblasts present in different pancreatic diseases are genetically distinct and their functions are 'programmed' by the unique environment of each disease, according to new research from the University of Liverpool (UK).

As well as different genetic profiles, the team found to their surprise, that disease-specific fibroblasts retain their unique gene expression following isolation and culture. As fibroblasts are a key drug development target for these diseases, the findings have important implications for how research is conducted.

Fibroblasts are the most common cells within the body's connective tissues and play a critical role in wound healing. But they can also be recruited by cancer cells to help them grow, spread and evade the body's immune system.

Funded in part by the UK charity Pancreatic Cancer Research Fund, the Liverpool team is the first to isolate, characterise and compare the properties of fibroblasts found in pancreatic cancer, chronic pancreatitis and periampullary tumours (a rare cancer affecting the area between the bile duct, pancreas and small intestine).

Lead researcher Professor Eithne Costello said: "It's long been thought that fibroblasts from different pancreatic diseases were very alike and have similar functions. But we've been able to show for the first time that this is absolutely not the case. While fibroblasts from distinct

diseases share many properties, each disease changes the fibroblast in a different way and it's clear that researchers using fibroblasts for disease-specific research should ensure they use appropriate ones for their work."

The study, published in the journal *Cancer Research*, found that less than one quarter of activated genes were shared between fibroblasts isolated from different disease groups, compared to fibroblasts found in normal tissue. When comparisons were restricted to disease-associated fibroblasts only, less than one per cent of differentially expressed genes were common across disease types.

Fibroblasts are particularly abundant in pancreatic cancer, secreting growth factors and other chemicals to promote the growth of a fibrous scar-like coating around the tumour—the stroma—which prevents drugs from reaching the cancer cells within. It is this key role in the microenvironment of pancreatic cancer tumours and their complex interaction with surrounding cells that makes fibroblasts an important focus of research for finding potential drug targets.

When the team analysed blood samples from 230 patients with different pancreatic diseases and healthy donors, they found that pancreatic cancer patients had much higher levels of a protein produced by fibroblasts in the samples, compared to patients with chronic pancreatitis.

The protein—known as TNC—is one of the main proteins produced by fibroblasts to aid the growth of the stroma in pancreatic cancer. But intriguingly, when the team knocked down this protein from fibroblasts, and assessed its effect on the migration of pancreatic cancer cells, the cancer cells began to migrate more.

"It suggests that TNC in fibroblasts is somehow inhibiting the migration of cancer cells which is something that has not been reported before and

warrants further investigation. It also underlines just how complex the interaction between fibroblasts and pancreatic cancer cells is," said co-researcher Dr. Lawrence Barrera.

However, while TNC's potential as a therapeutic target remains unclear, the research team believes that the distinct difference in the levels of TNC found in the blood of patients with pancreatic cancer and those with chronic pancreatitis may be a potential biomarker to distinguish between the two diseases—something that currently can only be determined clinically or by a tissue biopsy.

More information: Lawrence N Barrera et al, Fibroblasts from distinct pancreatic pathologies exhibit disease-specific properties, *Cancer Research* (2020). DOI: 10.1158/0008-5472.CAN-19-3534

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