How targeting healthy cells could help develop treatments for pancreatic cancer

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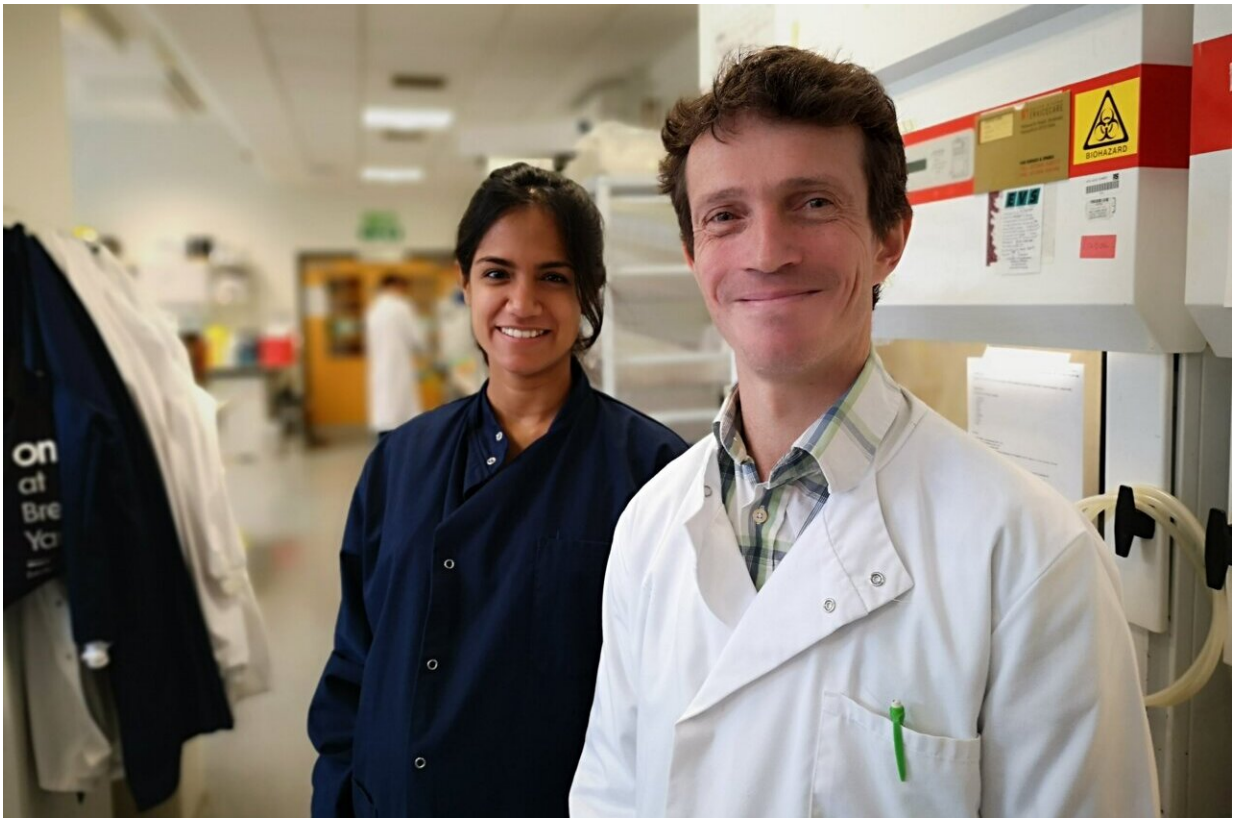

Dr Angus Cameron & Dr Shinelle Menzes at Barts Cancer Institute. Credit: Please credit: Worldwide Cancer Research

Researchers at Barts Cancer Institute at Queen Mary University of London, supported by a partnership between the UK charities

Worldwide Cancer Research and Pancreatic Cancer Research Fund, have made a discovery that reveals new insight into how healthy cells help pancreatic tumors develop, which they hope will lead to the development of new drugs for this hard to treat cancer.

The research, led by Dr. Angus Cameron, found that blocking expression of a protein, called PKN2, changed the behavior of healthy cells around the tumor. These cells, called fibroblasts, which are highly mobile and invasive, not only protect pancreatic cancer from treatment, but also aid in spreading it around the body. The researchers therefore hope that targeting fibroblasts to change their behavior could affect how pancreatic cancer develops.

When the researchers blocked expression of PKN2 in the healthy cells of a pre-clinical model of pancreatic cancer, the tumor grew more aggressively. However, the fibroblasts switched to a less mobile and invasive state and instead promoted inflammation—this is known to make tumors more aggressive but can also make them more responsive to immunotherapy.

The research is published today in the journal *Cell Reports*.

Pancreatic cancer remains one of the hardest to treat types of cancer—fewer than 1 in 10 people in the UK are expected to survive five years or more after diagnosis. Pancreatic tumors are often surrounded by a dense stroma, or 'scar tissue,' produced by cells called fibroblasts. The stroma blocks chemotherapy from reaching the tumor and suppresses the immune system, making immunotherapy ineffective.

Dr. Shinelle Menezes, Postdoctoral Researcher in Dr. Cameron's laboratory and joint first author of the study said: "Fibroblasts are like the gatekeepers of pancreatic cancer tumors, and our findings suggest that they can have both positive and negative roles to play in cancer

progression."

"We found that, when activated through PKN2, fibroblasts can actually act as a defense mechanism to limit cancer spread by keeping the cancer cells tightly compacted within the tumor. Blocking PKN2 suppresses the ability of fibroblasts to contain the cancer cells; however, it also means that they may let more immune cells into the tumor. This novel finding could have broad implications for how we target stromal fibroblasts to treat cancer."

The findings of this study expose PKN2 as a potential new drug target to alter the development and treatment sensitivity of pancreatic cancer. Dr. Cameron and his team are now studying the altered profile of immune cells within pancreatic cancer tumors. In future, the right combination of immunotherapy and a PKN2-targeting drug could be an effective way of treating pancreatic cancer.

Dr. Angus Cameron, lead author of the study, said: "To improve the outcomes for patients, we need to identify new strategies to target cancer cells as well as the normal cells supporting cancer growth, and find ways to help the body's immune system fight back against cancer.

"Our study contributes to the understanding of the biology of the invasive process in pancreatic cancer, and the roles that fibroblasts play. In our future work, we hope to identify effective drugs to target PKN2, which can be used in laboratory models of pancreatic and other cancers. This will allow us to test how targeting this pathway changes the way cancers develop, which is a key step towards clinical application."

Dr. Helen Rippon, Chief Executive at Worldwide Cancer Research said: "Pancreatic cancer remains stubbornly stuck as one of the least survivable cancers, with fewer than 1 in 10 people living five years after diagnosis. It is difficult to treat because current cancer drugs do not work

well, so for people with pancreatic cancer to have a better outlook we must find completely new ways to treat it.

"By supporting innovative cancer research projects like that of Dr. Cameron and enabling the brightest minds around the world to investigate new ideas, we can have hope for new cancer cures in future."

Maggie Blanks, CEO at Pancreatic Cancer Research Fund, said: "Anything we can do to find a way to improve the effect of immunotherapy on pancreatic cancer would be a major step forward, so it's encouraging that this research is contributing to the knowledge in this area. We're looking forward to hearing more about how this research progresses."

More information: Elizabeth R. Murray et al, Disruption of pancreatic stellate cell myofibroblast phenotype promotes pancreatic tumor invasion, *Cell Reports* (2022). DOI: 10.1016/j.celrep.2021.110227

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