

Hard-to-treat pancreatic cancer hijacks immune system and could be targeted with immunotherapies

3 September 2020



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

Scientists have used artificial intelligence (AI) to reveal an aggressive form of pancreatic cancer that is more likely to respond to immunotherapy, in the most extensive analysis of the immune landscape of these tumours to date.

Pancreatic neuroendocrine [cancer](#) starts in cells that produce hormones such as insulin. Once it spreads, only one in four people will survive for more than five years, and new treatment options are desperately needed.

The new study found that a particularly aggressive type of these tumours can evade [immune attack](#) by hijacking the [immune system](#)'s response to viral infections, and reveals possible targets for immunotherapy for this rare, hard-to-treat form of [pancreatic cancer](#).

Next, the researchers plan to translate their findings into new clinical trials to test the possible benefit of immunotherapies in those patients most likely to respond.

Changes in immune system genes

Scientists at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, working with colleagues at the University and Hospital Trust of Verona, Italy, used AI and genetic analysis to study 207 [tumour](#) samples from patients with pancreatic neuroendocrine tumours for the levels of 600 immune-related genes.

Comparing four separate forms of the disease, they found that samples of the most aggressive form, known as metastases-like primary tumours, saw changes in activity of 74 immune-related genes, compared with changes in only 12 immune system genes in the more benign insulinoma-like tumours.

The study was published in the journal *Gut* today, and was funded by the NIHR Biomedical Research Centre at The Royal Marsden and The Institute of Cancer Research (ICR), the ICR itself, and by Italian charities including the AIRC Foundation for Cancer Research.

Hijacking a damage-alert system

The scientists found that 83 percent of aggressive, metastatic-like tumours contained particularly high levels of a gene called TLR3, part of a damage-alert system that mimics the infection response triggered by viruses, drawing immune cells to the tumour.

This damage response is related to a form of programmed [cell death](#) that occurs when there's not enough oxygen—which can happen inside

metastatic-like tumours, which tend to be larger in size.

The researchers believe that by hijacking the damage response through TLR3—which helps flag tumour cells to the immune system—cancer cells can escape from the immune system, leading to the tumour's ability to grow and evolve.

The ICR, a charity and research institute, is raising the final £2 million for its revolutionary new Centre for Cancer Drug Discovery, dedicated to overcoming cancer's ability to evolve resistance to treatment.

Targets for existing immunotherapies

Importantly, the ICR team also studied the presence of known targets for existing immunotherapies in all four kinds of pancreatic neuroendocrine tumours.

They found that the most aggressive type had the highest levels of an immune marker known as PD-L1, which suggests they can be targeted with immunotherapies designed to take the brakes off the immune system so it can attack tumour cells, known as checkpoint inhibitors.

Immunotherapy treatments have been shown to work very well in some tumour types—but they don't work for everyone and have only shown modest benefits in this form of pancreatic cancer, so it is important to be able to identify the patients who are most likely to benefit from immunotherapy.

The researchers now hope their results will lead to clinical trials to test the benefit of immunotherapies, either alone or in combination with other treatments, for patients with the metastatic-like form of pancreatic neuroendocrine tumours.

Complex interplay of cancer and immune cells

Dr. Anguraj Sadanandam, Team Leader in Systems and Precision Cancer Medicine at the ICR, said:

"Our new study offers an important basis from which to start developing new treatment strategies

for a rare form of cancer, which starts in the hormone-producing cells of the pancreas.

"We found that there is a complex interplay between cancer and [immune cells](#) in the most aggressive type of pancreatic neuroendocrine tumours, which suggests immunotherapy could work for patients with this form of the disease.

"Our findings could help to pick out those patients most likely to benefit from immunotherapy—and we're keen to translate our work into clinical trials to test the benefit of different immunotherapeutic strategies to tackle this hard-to-treat form of pancreatic cancer."

Understanding cancer's ability to evolve

Professor Paul Workman, Chief Executive of the ICR, said:

"Pancreatic cancers have some of the poorest survival rates—so it's hugely encouraging to see such an extensive study of the immune landscape of a rare form of pancreatic cancer, looking at the underlying biology to inform the best way forward in treating the disease.

"It's fascinating to see a mechanism unveiled by which these tumours develop the activity of a highly distinct set of immune-related genes, as this could not only underlie the immune escape of these tumours, but also feed into their ability to evolve—one of the biggest challenges in [cancer research](#) and treatment today.

"Immunotherapy has transformed the outlook for a range of different cancer types, and I look forward to seeing these new findings progress to clinical trials, which might lead to a more personalised way of treating people with pancreatic neuroendocrine tumours."

More information: *Gut* (2020). doi.org/10.1136/gutjnl-2020-321016

Provided by Institute of Cancer Research

APA citation: Hard-to-treat pancreatic cancer hijacks immune system and could be targeted with immunotherapies (2020, September 3) retrieved 9 May 2021 from <https://medicalxpress.com/news/2020-09-hard-to-treat-pancreatic-cancer-hijacks-immune.html>

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