CHIEF SCIENTIST OFFICE

CODE: PCL/22/03

RESEARCH PROJECT BRIEFING

The Role of Cancer Associated Fibroblast Heterogeneity in Determining Metastatic Patterns in Pancreatic and Oesophageal Adenocarcinoma.

AIMS

This research project set out to determine whether types of non-cancerous cells, called fibroblasts, can influence the ability of cancers to spread to other sites. Fibroblasts are cells that are involved in producing proteins that are the building blocks for scaffolding tissue and producing scars. We are also now learning that they have important roles in regulating immune cells.
I wanted to see whether the type of fibroblast can influence where in the body pancreas and oesophageal cancer spreads to.

KEY FINDINGS

- Fibroblasts exist in various subtypes in pancreas and oesophageal cancers
- These fibroblast cells can change which subtype they are
- The type of fibroblast subtypes that are most dominant in pancreas cancers, predict how likely the cancer is to come back or spread after it has been removed.

WHAT DID THE STUDY INVOLVE?

To perform this study, I selected 2 types of cancers that arises from the gastro-intestinal tract (or gut), called pancreas and oesophageal cancer. These commonly spread to other sites in the body. I believed that there may exist similarities in the non-cancerous fibroblasts that may help them to spread.

To study this, I used tissue from cancers that have been surgically removed. Using the help of another team in the University of Glasgow, led by Professor John Le Quesne, and my PhD student (Adam Bryce), we designed a panel of markers that help us characterise fibroblasts. These 8 markers (including aSMA, FAP, S100A4, CTGF, LIF, IL6, PDGFR) can help differentiate the type of fibroblast. It also allowed us to see how these fibroblasts organise themselves in the cancer, and whether that has any influence on how the cancer behaves.

Following this, we have performed a further analysis, using a panel that include >50 markers in pancreas cancer (using a system called the Akoya Phenocycler). We designed this panel ourselves, and this took nearly 2 years to do. This is a unique, custom designed panel which is extremely valuable for this type of study. This will allow us to see in detail how fibroblasts interact with cancer and immune cells, and how this influences whether the cancer spreads or not.

Lastly, to make this study more detailed, I have done the above experiments on pancreas cancers that have spread to the liver and lung. This includes the original cancer in the pancreas, as well as the paired metastases (area where it has spread to).

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

Thus far, we have performed the experiments on oesophageal and pancreas cancers, but only been able to analyse the pancreas experiments. These will be the results discussed.

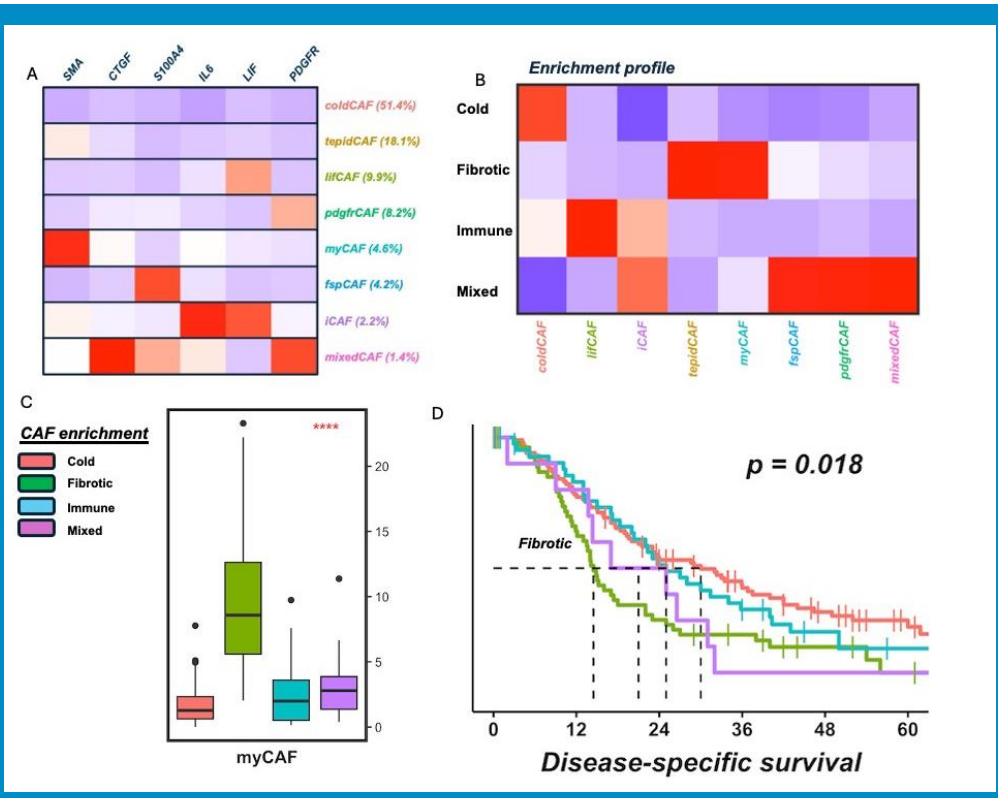
The first analysis we did looked at how fibroblasts organise themselves with cancer cells. We found that the more ‘mixed up’ cancer cells and fibroblasts are, the worse patients’ survival is after the pancreas cancer has been removed. This suggests that when fibroblasts and cancer cells interact more, they can lead to the cancer being more aggressive.

Next, we looked at the type of fibroblasts using the markers I mentioned. We found that they can exist in many different subtypes or states, but that these can group together to have similar consequences on how the cancer behaves. The most interesting was that if the cancer was rich of fibroblasts that have higher levels of 2 markers (aSMA, CTGF) then patients had a worse prognosis. It also suggested that these were more likely to spread to other sites of the body. We were able to characterise the architecture of each patient's cancer based on the subtypes of fibroblasts. We found that a type, that we called *fibrotic*, had lots of fibroblasts with high levels of aSMA and CTGF. These had worse prognosis after surgery.

Currently, we are analysing the differences in fibroblast types between patients that have had no treatment vs those that had chemo- or radiotherapy before they had surgery. This will allow us to see whether treatment changes how the fibroblasts behave.

We are also analysing the large (>50 marker) panel and the comparison of the lung and liver metastases. These are large and complex datasets. Analysing these will require many more months, but we are very excited about the results of these.

This figure shows the differences of each marker in subtype of fibroblasts we defined (A) and how they organise into types of tumour architecture (B). The fibrotic type has lots of fibroblasts called myCAFS (C) and is associated with worse prognosis after surgery.



WHAT IMPACT COULD THE FINDINGS HAVE?

- This study is the first, to our knowledge to compare paired pancreas cancers with the sites where they have spread to in this detail.
- This could identify new treatments for patients to stop, or control, pancreas and other cancers from spreading to sites such as the liver.
- This has also led to more studies using these experimental techniques. This includes a large international study of which I am part of called Team SAMBAI – which investigates the role of social deprivation on pancreas, prostate and breast cancer.

HOW WILL THE OUTCOMES BE DISSEMINATED?

Results from this study has already been presented internationally. At present, the analysis is still ongoing. Once this is complete, I envisage we will have at least 2 manuscripts to contain these results.

I was able to generate so many results and data from this, that it is impossible for 1 person or group to analyse. As a result, I am collaborating with other groups to share my data so that they can complement their own studies with the results I generated during this project.

I have already used these results to apply for more funding to continue my research into this topic to improve outcomes for patients.

CONCLUSION

Fibroblasts exists in many different states, and the subtype of fibroblast influences how aggressive pancreas and oesophageal cancers are, and how likely they are to spread. The next steps are to understand how they help the cancers growing once they have spread to other sites.

RESEARCH TEAM & CONTACT

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