CHIEF SCIENTIST OFFICE

CODE: PCL/21/03

RESEARCH PROJECT BRIEFING

The role of NFKB signalling in immune checkpoint expression and myeloid cell function in colorectal cancer

AIMS

This project aimed to study how the immune system behaves in bowel cancer, focusing on specific signals and immune cells called macrophages. We also looked at certain markers that help cancer cells hide from the immune system, to see how these factors are linked to patient outcomes

KEY FINDINGS

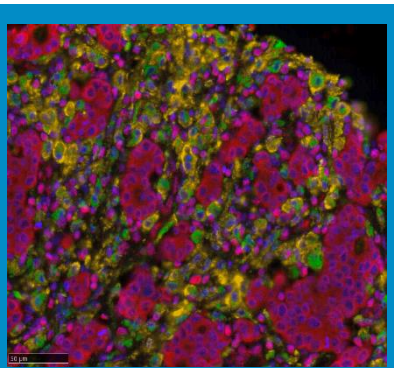
1. We discovered that certain immune signals in bowel cancer, particularly a pathway called NFKB (which is an “on-switch” for inflammation), were linked to proteins (PD-1 and PD-L1) that cancer uses to avoid being attacked by the immune system.
2. This was especially important in a type of bowel cancer called microsatellite stable (MSS) colorectal cancer, which usually does not respond to current immunotherapy.
3. We also found that tumours with and without PD-L1 (an immune “brake” protein) had different types of immune cells (called macrophages, which can “eat” tumor cells) in the tumour environment.
4. Interestingly, when macrophages inside the tumour showed signs of strong immune activation (by using the NFKB “on-switch”), patients tended to do better—they had improved outcomes.
5. Younger patients with colorectal cancer had higher levels of certain macrophage types, and their blood contained different immune signals (including IL-10 and IP-10) during treatment, suggesting the disease may behave differently in younger people.
6. Patients who didn’t respond well to treatment had higher levels of TNF and PD-L1 in their blood, suggesting these immune signals might be involved in resistance to therapy where in the future treatments might be needed for these patients.

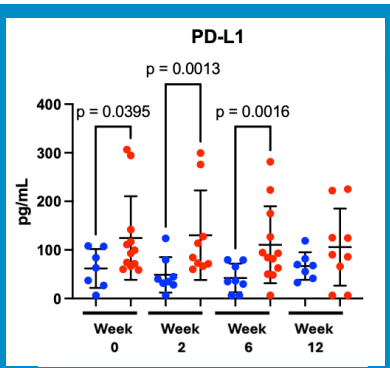
WHAT DID THE STUDY INVOLVE?

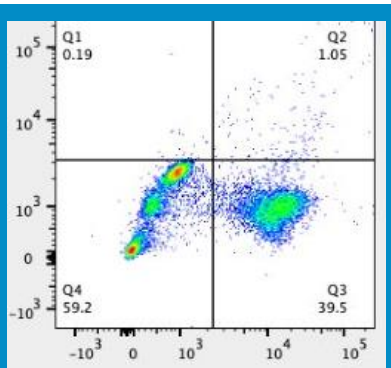
In this study, I looked at tissue samples from patients with bowel cancer to better understand how certain immune cells, called macrophages, behave inside tumours. I worked with lab scientists to carefully develop a method to highlight these cells using special stains, so we could study them under the microscope and see how they relate to patient survival. I also worked with immunologists to test patients' blood samples for immune signals using a technique that can measure many proteins at once. In addition to lab work, I learned how to analyse large sets of gene data from tumours to help confirm our findings.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

1. We found that high levels of a protein called TAK1 (part of the NFKB "on-switch" immune pathway) were linked with PD-L1, a protein that helps cancer hide from the immune system. This was seen in bowel cancer samples taken from patients after surgery.
2. A specific pattern of TAK1 called "punctate staining" was more common in aggressive, nasty tumours. These cancers also had lower levels of a growth-related protein (IGF2) and were more likely to come back after surgery, especially in the more common type of bowel cancer that usually doesn't respond to immunotherapy.
3. Among patients receiving chemoradiotherapy for advanced rectal cancer, those with higher levels of proteins TNF-alpha and PD-L1 in their blood did not respond as well to treatment
4. Younger patients (under 50) with rectal cancer had lower levels of immune signals called IL-10 and IP-10 in their blood compared to older patients, suggesting that younger people may have a different immune response to cancer.
5. In the lab, we treated bowel cancer cells with a drug that blocks part of the NFKB pathway (IKK beta inhibitor), which caused a drop in PD-L1 levels—suggesting that this drug could make the cancer more visible to the immune system.
6. When we studied immune cells in tumours, we found that younger patients had more macrophages, especially a type called M2, which can sometimes help cancer grow.
7. Other factors we found that may predict better survival after surgery include:
    1. More "fighting" type M1 macrophages
    2. Positive PD-L1 staining
    3. Macrophages inside the tumour showing strong immune activation (NFKB-positive)







WHAT IMPACT COULD THE FINDINGS HAVE?

- These findings help us better understand what controls PD-L1, a protein that allows cancer to hide from the immune system and is a key target for immunotherapy in bowel cancer.
- They show how important immune cells behave inside tumours, especially in patients whose cancer comes back after treatment.
- With more young people being diagnosed with bowel cancer, this research highlights key biological differences in their tumours and immune responses compared to older patients.
- These results could help in developing new treatments, especially for patients who don't respond well to standard therapy, by targeting mechanisms like high PD-L1 in the blood using immunotherapy.

HOW WILL THE OUTCOMES BE DISSEMINATED?

- National and International presentations
    - e.g. ASCO GI, 2023, San Francisco and ASCRS 2022, Florida
- Regionally e.g. Scottish clinical academic development meetings, University of Glasgow meetings
- Peer reviewed publications

CONCLUSION

The CSO funding has helped develop the interrogation of the important interactions of colorectal cancer tumour cells, NFKB signalling, PD-L1 expression and recurrence of cancer after resection

Furthermore, it has helped develop my academic career, helping with further funding streams (RCSEd, NHSGGC), collaboration with disciplines of immunology, cancer sciences and clinical surgeons, and collaboration with other institutions such as MD Anderson. I am now doing a Colon and Rectal Cancer Surgery Fellowship at MD Anderson in Texas, US, and hope to bring new knowledge and skills to Scotland as a clinical academic.

RESEARCH TEAM & CONTACT

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Additional Information

This helped support supervision of students (1xMSc Immunlogy student, 2x Intercalating BSc students, all at University of Glasgow)