CHIEF SCIENTIST OFFICE

CODE: TCS/21/25

RESEARCH PROJECT BRIEFING

The role of myeloid immune cells in driving chemotherapy resistance in bile duct cancers.

AIMS

Resistance to chemotherapy greatly limits the benefit patients with bile duct cancer (cholangiocarcinoma, CCA) gain from standard anti-cancer treatment. We had preliminary evidence that immune cells (which are usually involved in fighting foreign insults within our body) can also affect how cancer cells respond to chemotherapy. These studies aimed to gain a deep knowledge on how a subtype of circulating immune cells, monocytes, can change the response of cholangiocarcinoma cells to chemotherapy and understand how these monocytes can change and evolve during the course of chemotherapy to drive resistance.

KEY FINDINGS

- We have established a laboratory platform to monitor cell growth in 2D & 3D while we cultured together cholangiocarcinoma cells and monocytes.
- We showed that selected monocytes collected from cholangiocarcinoma patients can alter cancer sensitivity to chemotherapy.

- We showed that there was a consistency between the chemoresistance observed in clinic in the patients and that observed in our laboratory models, suggesting that monocytes could be responsible for the loss of benefit from chemotherapy that is observed in patients.
- Monocytes undergo a rewiring of their gene expression over the course of chemotherapy treatment.
- In the tumours, recruited monocytes can be found in close contact with CCA cells and other tumour-supportive cells, including FAP+ fibroblasts, which creates an immunosuppressive micro-environment that can be disrupted with combination strategies.
- We have established a biobank of 3D patient-derived organoids (Mini-tumours) that can be used to test responsiveness to drugs for a number of drugs for each given patient.

WHAT DID THE STUDY INVOLVE?

Monocytes are circulating immune cells in the blood stream that can be recruited to the tumour and become adapted to sustain tumour growth. In these studies, we investigated the role of monocytes in inducing resistance to chemotherapy in CCA patients. We developed a co-clinical trial within the REG-bil platform involving 50 CCA patients, where monocytes were collected at several time points during the course of chemotherapy. Monocytes were 1) studied for detailed gene expression and 2) cultured alongside CCA models to investigate the effect on sensitivity of CCA to chemotherapy drugs (Figure 1). The project was developed together with patients and patient representatives, and was regularly presented at conferences where lay public was involved. Regular patient meetings were held as part of the REG-bil platform to receive feedback on the progress of the projects, and the burden for those enrolled.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

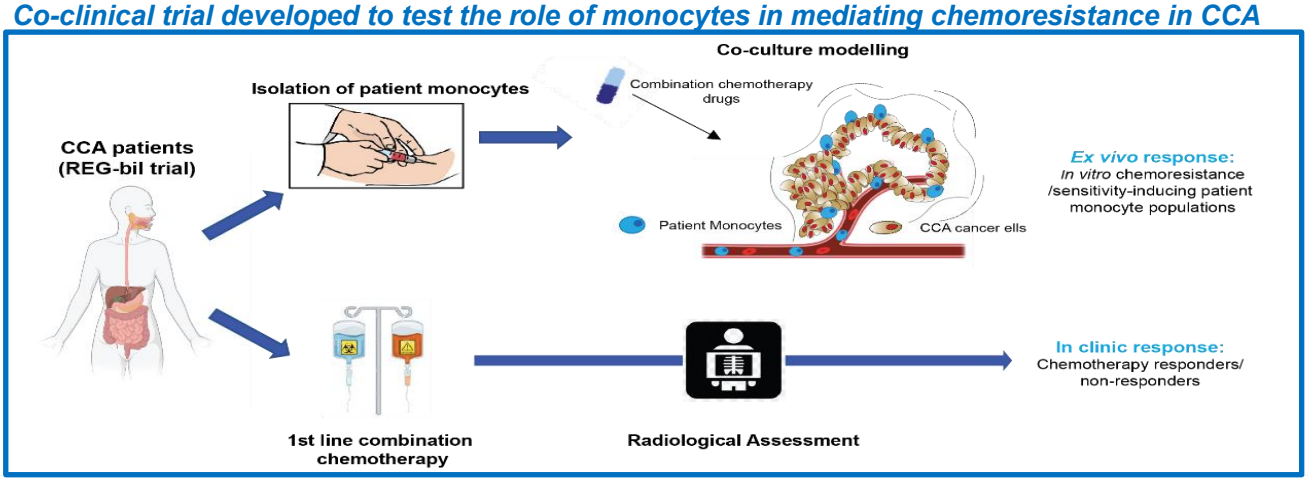
For the first time, these findings highlight the role of monocytes in changing how CCA cells respond to chemotherapy. This new knowledge will be important for the development of novel therapeutics, which will need to be aimed at preventing the evolution of monocytes towards a

chemoresistance-inducing state as well at disrupting the crosstalk between monocyte and cancer cells after they are recruited in the tumour. As part of this project we have also developed a biobank of patient-derived organoids that can be used to support drug discovery and testing.

WHAT IMPACT COULD THE FINDINGS HAVE?

- Development of novel therapeutics that aim to improve ***CCA patient*** response to chemotherapy.
- Provide the ***research community*** with novel disease models that can support investigation of biological mechanisms and drug testing.
- Lead to new anti-cancer therapies that can change the guidelines for the management of CCA patients and be introduced in the ***clinical practice***.

Figure 1.
Co-clinical trial developed to test the role of monocytes in mediating chemoresistance in CCA



HOW WILL THE OUTCOMES BE DISSEMINATED?

The findings from these studies have been presented to several international conferences, including those with a focus on clinical management, drug discovery and basic research as well as those organized by patient charities to enable dissemination to the lay public. The data are currently organized in multiple scientific manuscripts which are going to be submitted to peer review scientific

journals. Once publication of these manuscripts is finalized, we will use additional means (i.e. social media and press releases) to disseminate these findings to the public.

The next phase of this project includes mechanistic dissection of the gene expression and biological processes associated with monocyte-induced CCA chemoresistance, followed by the trial of novel therapeutics that can target monocytes to disrupt their chemoresistance-induction.

CONCLUSION

Using patient centric disease modelling, we have identified a novel monocyte-driven mechanism of CCA chemoresistance which can support development of more effective therapeutics. We would like to thank all the patients involved who have donated their samples to advance our knowledge of CCA.

RESEARCH TEAM & CONTACT

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Additional Information
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