IMMUNE CELLS AND METASTASIS

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Our lab focuses on a type of immune cell, called gamma delta (γδ) T cell. γδ T cell refers to a variety of cell subsets with distinct properties and anatomical locations. There are γδ T cell subsets that kill cancer cells and other subsets that promote cancer progression. Our lab has ongoing projects aimed at understanding when and where these diverse γδ T cell subsets are important. We are exploring the involvement of γδ T cells in breast, colon, liver, and pancreatic cancers.

In 2022, our lab contributed to six scientific papers; two of these publications highlighted our work on IL-17A-producing γδ T cells. We deposited data from other studies as preprints on *BioRxiv*, which centre around tissue-resident subsets of γδ T cells. We attended several conferences to disseminate this work, including the 2nd International workshop on "Receiving and Transmitting Signals via the γδ TCR" in Cefalu, Sicily, and the British Society for Immunology annual congress in Liverpool. Mark and Hannah successfully completed their PhD studies. We welcomed three new members of the group: Kyi Lai, Federico, and Anna.

Breast cancer

In previous years, we generated a single cell RNA sequencing (scRNAseq) dataset of γδ T cells isolated from the lungs of tumour-free and tumour-bearing mice. This analysis uncovered two new avenues of research in the lab. First, we found that subsets of IL-17A-producing γδ T cells expressed different co-inhibitory molecules on their surface. One subset (Vγ6$^+$ cells) expressed constitute levels of PD-1, while another subset (Vγ4+ cells) upregulated TIM-3 in response to tumour-derived factors. Blocking either PD-1 or TIM-3 signalling in mammary tumour-bearing mice increased proliferation of Vγ6$^+$ or Vγ4$^+$ cells, respectively. This increase in Vγ6$^+$ or Vγ4$^+$ cell number counteracted T cell checkpoint inhibitor immunotherapy, as genetic deletion of γδ T cells sensitized metastatic mammary cancer cells to anti-PD-1 or anti-TIM-3 and prevents lung metastasis (Figure 1). Second, the scRNAseq highlighted different subsets of IFNγ-producing γδ T cells, identifiable by the differential expression of Ly6C. These subsets had cancer-killing functions. We have found that Ly6C+ γδ T cells were maintained by the cytokine, IL-27, which amplified their cancer-killing ability. In adoptive transfer experiments, Ly6C+ γδ T cells delayed mammary tumour growth, while Ly6C$^-$ γδ T cells did not. Future efforts will focus on the endogenous role of these cells in breast cancer progression.

Colorectal cancer

We have continued our collaboration with Owen Sansom and Adrian Hayday (Francis Crick Institute) to investigate the role of γδ T cells in mouse models of bowel cancer. We are particularly interested in the gut-resident γδ T cell population that express the Vγ7 chain T cell receptor chain and their role in cancer progression. We have found that these cells counteracted intestinal adenoma formation and killed transformed enterocytes in mice. When tumours developed, however, these cells were largely excluded from the tumour microenvironment. We have found that Butyrophilin-like 1 (BTNL1), a molecule expressed on gut epithelial cells required for survival of Vγ7 cells, was absent from tumours in the bowel. This observation has led to an examination into the mechanism of BTNL1 loss. We have found that deletion of the tumour suppressor Apc induced the downregulation of *Btnl1* mRNA using organoids derived from our mouse models. This down-regulation of *Btnl1* was accompanied by decreased expression by gut-specific transcription factors, such as HNF4A and HNF4G. Interestingly, inhibition of β-catenin in mouse models reversed the downregulation of *Hnf4a*, *Hnf4g*, and *Btnl1* in tumours, which was associated with higher numbers of γδ T cells in the tumour microenvironment.

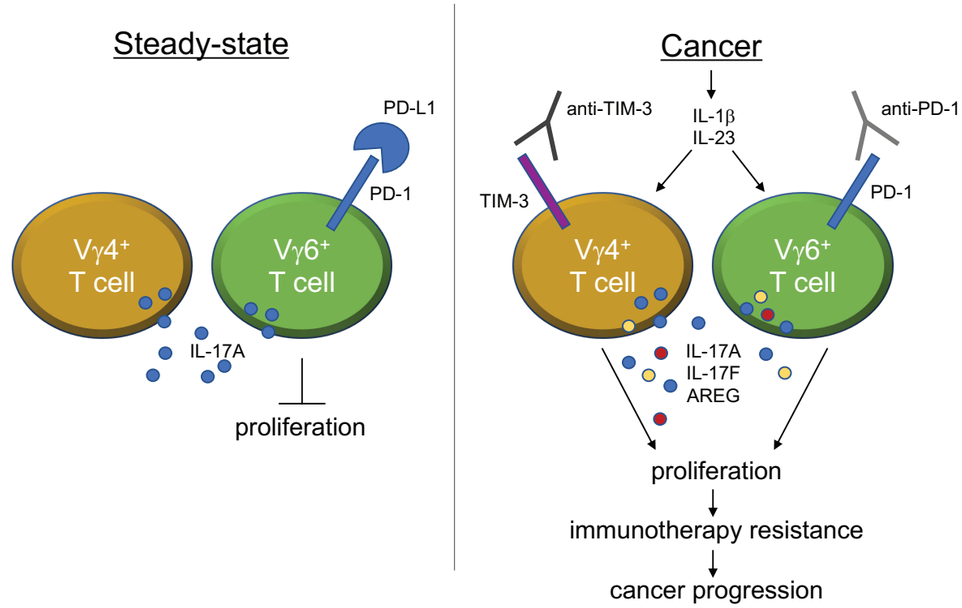

Figure 1
Phenotypic analysis of gamma delta T cells from lungs of mice shows that subsets of IL-17A-producing cells express distinct co-inhibitory molecules (i.e. PD-1 and TIM-3) that regulate cell expansion and counteract immunotherapy.

Liver cancer

Together with Tom Bird's lab, we have started to address the role of γδ T cells in hepatocellular carcinoma. We have discovered that γδ T cells promoted cancer progression in mouse models driven by oncogenic β-catenin and MYC. Unlike our data in breast cancer, γδ T cells in the liver failed to express IL-17A. For the future, we will undertake a deep phenotypic analysis of these γδ T cells in the liver and perform experiments to understand how they perpetuate tumour growth.

Pancreatic cancer

We have found that γδ T cells drive metastasis in the *Kras$^{G12D/+}$;Trp53$^{R172H/+}$;Pdx1-Cre* (KPC) mouse model of pancreatic cancer, and our work over the past three years has been focused on overcovering the mechanism by which γδ T cells promote metastasis. During lockdown, we discovered that macrophages and fibroblasts were reduced in pancreatic tumours from γδ T cell-deficient mice, indicating that γδ T cells regulated these cells in some way to support metastasis. Currently, we were investigating the mechanisms by which this occurs.

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