IMMUNE CELLS AND METASTASIS

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Our lab focuses on a type of immune cell, called a 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 2023, our lab contributed to three scientific papers, and we were asked to write two commentaries on the works of other researchers. Rob successfully completed his PhD. We said good-bye to Anna, and we welcomed Heather, Muhammad, Elizabeth, Cai, Amy and Yasmin.

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 express different co-inhibitory molecules on their surface. One subset (Vγ6$^+$ cells) express constitute levels of PD-1, while another subset (Vγ4$^+$ cells) upregulate TIM-3 in response to tumour-derived factors. Blocking either PD-1 or TIM-3 signaling in mammary tumour-bearing mice increases proliferation of Vγ6$^+$ or Vγ4$^+$ cells, respectively. This increase in Vγ6$^+$ or Vγ4$^+$ cell number counteracts T cell checkpoint inhibitor immunotherapy, as genetic deletion of γδ T cells sensitizes metastatic mammary cancer cells to anti-PD-1 or anti-TIM-3 and prevents lung metastasis. Second, the scRNAseq highlighted different subsets of IFNγ-producing γδ T cells, identifiable by the differential expression of Ly6C. These subsets have cancer-killing functions. We have found that Ly6C$^+$ γδ T cells are maintained by the cytokine, IL-27, which amplifies their cancer-killing ability. In adoptive transfer experiments, Ly6C$^+$ γδ T cells delay mammary tumour growth, while Ly6C— γδ T cells do 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 counteract intestinal adenoma formation and kill transformed enterocytes in mice. When tumours develop, however, these cells are 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, is 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* induces the down-regulation of *Btnl1* mRNA using organoids derived from our mouse models. This down-regulation of *Btnl1* is accompanied by decreased expression by gut-specific transcription factors, such as HNF4A and HNF4G. Interestingly, inhibition of β-catenin in mouse models reverses the down-regulation of *Hnf4a*, *Hnf4g*, and *Btnl1* in tumours, which is associated with higher numbers of γδ T cells in the tumour micronenvironment.

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 promote cancer progression in mouse models driven by oncogenic β-catenin and MYC. We performed scRNAseq on these cells to gain an in-depth perspective of how their phenotype changes in the presence of a tumour (Figure 1).

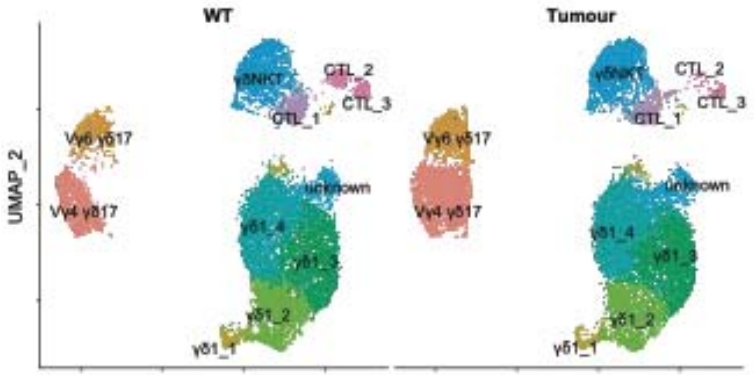

Figure 1. Diversity of gamma delta T cells in normal liver and tumour-bearing livers. scRNAseq analysis of liver gamma delta T cells by Chromium 10X technology.

Data were analysed by Sarina Raven's lab (Hannover, Germany).

This analysis has provided important clues about their behaviour and function.

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 has been focused on overcovering the mechanism by which γδ T cells promote metastasis. We discovered that macrophages and fibroblasts are reduced in pancreatic tumours from γδ T cell-deficient mice, indicating that γδ T cells regulate these cells in some way to support metastasis. Currently, we are investigating the mechanisms by which this occurs.

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