

CANCER SYSTEMS BIOLOGY AND TUMOUR EVOLUTION



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Cancer remains one of the most complex, and devastating diseases of our time, characterized by its ability to evade treatment and adapt to an ever-changing biological landscape with diverse selective pressures. At the forefront of this challenge, our laboratory is pioneering the use of next-generation single-cell and spatial biology tools, paired with functional genomic technologies and relevant murine models, to unravel the developmental origins of cancer. Specifically, we investigate how damage-associated regenerative programs, activated in the context of chronic inflammatory diseases (fatty liver/MASLD, viral hepatitis, colitis, IBD) contribute to cancer initiation and progression.

The Origins of Cancer: A Crossroads of Regeneration and Dysfunction

Recent work from our laboratory and others has elucidated remarkable foetal-like, developmental remodelling of the tumour microenvironment (TME) in human hepatocellular carcinoma (HCC) (Sharma *et al.*, 2020, *Cell*; Nguyen *et al.*, 2022, *Nat Commun*). Our current research is rooted in understanding how chronic inflammation, a hallmark of diseases such as colitis, chronic hepatitis, or pancreatitis, can activate similar developmental programs to establish a “pro-tumorigenic niche” or a fertile soil for tumourigenesis (Balakrishnan *et al.*, 2024, *J Hepatol*; Cappellesso *et al.*, 2022, *Nat Cancer*; Scolaro *et al.*, 2024, *Nat Cancer*). During these inflammatory processes, regenerative programs are activated to repair damaged tissues. However, when dysregulated, these programs can lead to aberrant cell growth, epithelial damage, endothelial-immune dysfunction, fibrosis and eventually tumour formation. Using advanced single-cell and spatial biology tools (single cell RNA-seq, scATAC-seq, spatial transcriptomics, proteomics and metabolomics, and multi-parametric flow cytometry), we study the cellular and molecular mechanisms underlying this transition from chronic non-healing wounds to cancer. These technologies allow us to map cellular interactions at unprecedented resolution, providing insight into how damaged epithelial cells communicate with their surrounding microenvironment, including immune cells, stromal cells, and endothelial cells. Finally, our understanding of the molecular mechanisms of cross-regulatory interactions between tumour cells and their ecosystem is paving the way for innovative

therapeutic approaches that we, in close collaborations with clinicians, are implementing as part of clinical trials aimed at interrogating the efficacy of combining drugs targeting the tumour stroma (anti-angiogenics) along with immune checkpoint inhibitors. Initial data from these clinical studies on nasopharyngeal carcinomas (NPC) show striking improvement in anti-PD1 response when combined with anti-VEGFa therapy, compared to the use of anti-PD1 alone as monotherapy (Chong *et al.*, 2024, *Lancet Oncol*).

A Focus on Co-Evolutionary Mechanisms in the Tumour Microenvironment

Cancers do not evolve in isolation. It emerges and thrives in the context of its microenvironment, engaging in dynamic cross-regulatory interactions with surrounding cells. Our work centres on uncovering these co-evolutionary mechanisms that shape tumour initiation, tissue remodelling, and progression.

Key areas of focus include:

- **Endothelial Dysfunction:** Endothelial cells play a critical role in maintaining vascular integrity and regulating tissue homeostasis. In chronic inflammation, persistent endothelial dysfunction can promote abnormal angiogenesis, hypoxia, and endothelial anergy, fostering tumour growth and metastasis.
- **Fibrosis:** Fibroblasts, activated during tissue repair, can become cancer-associated fibroblasts (CAFs) that contribute to a fibrotic tumour microenvironment. This fibrosis not only supports tumour growth but also serves

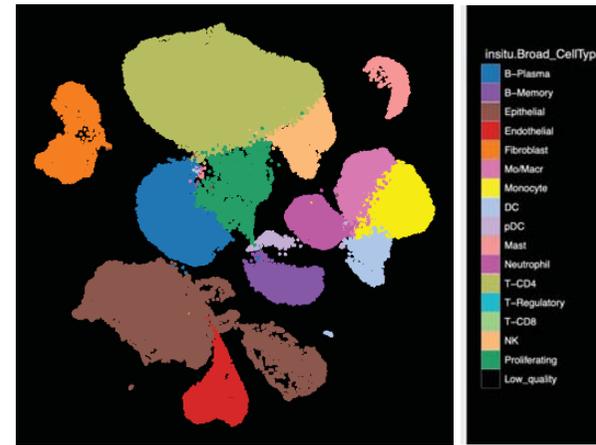


Figure 1. Cells to location: localizing cell types and cell states to their spatial coordinates in NPC

as a barrier to effective drug delivery, or immune-cell infiltration, making tumours more resistant to treatment.

- **Immune Dysregulation:** Chronic inflammation disrupts immune homeostasis, leading to immune suppression and the recruitment of tumour-promoting immune cells, such as pro-remodelling macrophages and regulatory T cells (Tregs). By studying how tumours exploit immune-stromal interactions, we aim to identify new therapeutic strategies targeting the tumour ecosystem to restore immune balance.

Bridging Technologies to Decode Tumour Evolution

Our laboratory employs an integrated approach, leveraging cutting-edge single cell and spatial multi-Omics technologies to study mechanisms of damage-associated chronic disease progression to cancer:

- **Single-Cell Analysis:** Tools like single-cell RNA sequencing (scRNA-seq, ATAC-seq) allow us to dissect cellular heterogeneity of disease-associated cell states (DACs) within tumours and their microenvironments, as well as gene regulatory networks and signalling pathways that specify the transcriptomic signatures of DACs
- **Spatial Biology:** Advanced imaging technologies enable us to visualize the geo-spatial organization and cellular interactions within tissue architecture, capturing the spatial dynamics of DACs or tumour cells with their ecosystem, including endothelial cells, fibroblasts and immune cells.
- **Functional Genomics:** CRISPR-based screens and drug libraries in relevant murine and patient-derived cell line/organoid models enable the identification of genes and pathways that drive tumour evolution, offering insights into potential therapeutic vulnerabilities.

From Discovery to Clinical Translation

Our ultimate goal is to translate these discoveries into tangible clinical benefits. By understanding the developmental origins of cancer and the role of co-evolutionary mechanisms, we aim to:

- Identify early biomarkers that predict tumour initiation and progression.
- Develop preventative therapies targeting the regenerative programs (especially those targeting the tissue/tumour ecosystem) that are hijacked during chronic inflammation.
- Create strategies to disrupt tumour-immune-stromal cross-regulatory interactions in order to prevent tumour progression into treatment-resistant, metastatic disease.

Publications listed on page 119

Figure 2. Spatial organization of individual cell type within a tumour (left); spatial distribution of distinct neighbourhoods of interacting cells (niches) identified within tumour biopsies

