Project abstract

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PROJECT PROPOSAL (1)

In the Dermal Oncoimmunology lab, we aim to understand the contribution of stroma on anti-tumour. We strive to identify stromal mediated roadblocks that mediate resistance to anti-cancer therapy.

The role of the tumour draining lymph node (TDLN) has been the subject of intense study, particularly in melanoma, over the past decade. These studies, performed primarily in mouse models, have highlighted a critical role for the TDLN in the initiation and development of the anti-tumour immune response and are often the first site for metastasis. The TDLN has been shown to undergo significant stromal (lymphangiogenesis and fibroblast proliferation) and matrix (altered collagen deposition) remodelling as tumours evolve. Stromal changes in the TDLN have been correlated with suppression of the anti-tumour immune response and promote tumour survival. While a large body of, mainly *in vivo*, work has focused on the role of TDLNs in mounting an immune response against the tumour, the role of non-draining lymph nodes (NDLNs), in close proximity to the tumour, have been largely overlooked.

In this project, we will perform a systematic characterisation of the immune and stromal compartments of these NDLNs from patients. In addition, we will compare the T cell receptor (TCR) repertoire found in the NDLNs with those in the peripheral blood to assess the "immunosuppression/antigen-deletion" capacity of the T cells in the different sites. We will quantify cytokine production, activation marker expression, proliferation and cytotoxic capacity of NDLN and peripheral blood-derived T cells to determine whether the cells are anergic in the presence of the tumour. This study could provide novel insight into the differences in the type and activation status of immune cells in LNs found nearby but not directly connected to the tumour. The precise annotation of the clinical situation together with the unprecedented in-depth stromal and immune analyses will provide a new perspective on the role of NDLNs in tumour growth and metastasis. It will also provide a translational trajectory for further stratification of "high-risk" patients versus "medium-risk".

PROJECT PROPOSAL (2)

The tumour microenvironment (TME) is a complex niche of cancer cells, immune cells, and stromal cells with extracellular matrix. Studies show that TME components, especially cancer-associated fibroblasts (CAFs), regulate tumour growth and invasion. CAF subsets vary across tumour types and evolve as tumours progress. Overall, CAF infiltration is linked to therapy resistance, recurrence, and poor prognosis. Consequently, research now focuses on characterising CAF origins and functions to develop treatments that overcome CAF-driven resistance. In the Dermal Oncoimmunology lab, we place fibroblasts at the centre of immune-regulatory networks in melanoma. We strive to elucidate and compare the phenotype and function of fibroblasts in these disease contexts in order to target these subsets therapeutically.

While the role of fibroblasts in established tumours has been well documented, evidence for a role in tumour initiation is sparse. While BRAF mutation is a common feature of melanoma, this mutation is also found in benign nevi that rarely progress to cancer. Melanocytes harbouring mutant BRAF often senesce, highlighting that additional cell intrinsic (PTEN loss) and extrinsic (microenvironment changes) mechanisms are required to facilitate tumour initiation. While much focus has been placed on the cell intrinsic mechanisms, cell extrinsic factors, such as the role of activated dermal fibroblasts or pre-CAFs, may be critical regulators of tumour initiation. While melanoma and its pre-cancerous lesions are different in their initiation, development and clinical outcome, parallels in their microenvironment (e.g. activated fibroblasts) may exist that govern whether tumours develop.

A comprehensive analysis of the fibroblast compartment between early-stage melanoma, basal cell carcinoma, and their associated pre-cancerous lesions has yet to be conducted. This project will focus on the characterisation, classification, and functional assessment of fibroblast populations using engineered tissue models. Using these models, we will be able to track the evolution of the fibroblast compartment from pre-cancerous lesions to established tumour for each entity. We will elucidate the fibroblast/CAF populations that are essential for the initiation of each tumour type and the conditions under which these populations arise. We will use this information to assess the effects of using early fibroblast-modulating therapies to limit cancer initiation.