In recent years tumour immunotherapy has led to dramatic patient benefit in a variety of cancers previously refractory to treatment. Despite these successes, only a minority of patients currently benefit from immunotherapy and more work is needed to expand their applicability. Using cutting-edge microscopy and flow cytometry, we are studying the dysfunctional initiation of anti-tumour immune responses in the lymph node. This understanding will inform future work seeking to augment anti-tumour immune responses and to increase the number of patients who can benefit from existing immunotherapies.

Our research primarily focuses on the role of dendritic cells (DC) and the initiation of anti-tumour immunity (Figure 1). DC precursors develop in the bone marrow and traffic to the tumour where they sample tumour antigens before migrating to the tumour-draining lymph node and activating anti-tumour T-cells. We have previously shown that T-cells are suboptimally activated in the tumour-draining lymph node and that improving DC functionality, and consequently T-cell activation, improves responses to immunotherapy. To understand how the tumour leads to sub-optimal immune activation, we are seeking to elucidate the mechanisms involved at each stage of the DC lifecycle.

DC recruitment to the tumour

Previous work has shown that patients with higher numbers of DC infiltrating their tumours have better outcomes and responses to immunotherapy; however, it is unknown what controls their recruitment and number within the tumour microenvironment. We aim to identify which signals attract DC precursors to migrate into the tumour. We have identified trafficking receptors on precursor DC and are generating an assay to screen receptors individually and in combination to identify those required for DC entry to both tumours and sites of infection. We will then determine which cells are producing the signals drawing in the DC precursors both during viral infection, where immune responses are robust, and in the tumour, where the response is sub-optimal. We will finally seek to understand what induces expression of these signals and attempt to increase DC recruitment to the tumour in order to improve both initial priming in the lymph node and to augment repriming at the tumour site.

Antigen traffic to the lymph node

Beyond the number of DC at the tumour site, how DC carry tumour material to the lymph node, and how they distribute it, is also key to understanding how anti-tumour immune responses are generated. We have shown that the same protein, when expressed within a tumour cell, is handled differently than when expressed in normal tissue. Indeed, during normal development DC restrict these proteins and do not transfer them to other DC subsets resident in the lymph node (Figure 2). During tumour development, however, this protein is handed off to lymph node resident cells and we have shown that these stimulate T-cell proliferation sub-optimally (Figure 2). We have identified a subset of DC which are responsible for the transport and transfer of antigen to the lymph node (Figure 2). During tumour development, however; this protein is handled off to lymph node resident cells and we have shown that these stimulate T cell proliferation sub-optimally (Figure 2). 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