

IMMUNE PRIMING AND THE TUMOUR MICROENVIRONMENT



Group Leader
Ed Roberts

Research Scientists
Sarwah Al-Khalidi
Chiara Pirillo

Scientific Officer
Alberto Bravo Blas

Graduate Students
Ryan Devlin
Youhani Samarakoon
Amy Shergold

In recent years immune checkpoint blockade has led to dramatic patient benefit in a variety of cancers previously refractory to treatment. These therapies function by re-invigorating existing anti-tumour immune responses which have been rendered ineffective but only show efficacy in a subset of patients. By comparing robust immune responses against viral challenges with those raised against tumours we are unpicking how the tumour microenvironment coordinates its immune composition and how it communicates with the lymph node to induce sub-optimal T-cell responses. Using these insights, we hope to define approaches to improve anti-tumour immune responses to expand the number of patients who can benefit from these therapies.

Our research primarily focuses on the role of dendritic cells (DC) and the initiation of anti-tumour immunity (Figure 1). DC progenitors 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 sub-optimally 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 DCs 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 DCs 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 DCs at the tumour site, how DCs 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 DCs 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 DCs which are responsible for the transport and transfer of antigen to the lymph node and are now seeking to understand how this process is controlled. Furthermore, by studying this process in a viral setting we have determined a key communication channel between tissues and their lymph nodes which inform the behaviour of lymph node resident cells. In the tumour setting this process is

co-opted and leads to the transfer of DC dysfunction from the tumour to the lymph node.

DC functionality within the lymph node

Finally, once the antigen has been trafficked to the lymph node, in order to drive effective anti-tumour immune responses, the lymph node must be highly organised, facilitating numerous specific cell-cell interactions. During tumour development the draining lymph node has been shown to be disorganised, and it has been proposed that several of these critical cell-cell interactions are disrupted. We have, however, demonstrated that the tumour-draining lymph node is capable of supporting robust immune responses, suggesting the problem is with the tumour-derived DC rather than with the node as

a whole. In order to study how these cells interact differentially in the tumour setting, we have developed a protocol allowing us to stain the entire lymph node and to identify the location of critical cellular subsets within the 3D environment of the lymph node (Figure 3). We have also developed complementary approaches to allow identification of even more cell types within the lymph node microenvironment and are now building systems to allow robust analysis of tissue organisation. We aim to use these approaches to identify organisational defects which occur in the context of tumour development which affect the quality of the anti-tumour immune response.

Publications listed on page 109

Figure 1
The DC lifecycle
DC precursors develop in the bone marrow and migrate to the tumour and the lymph node. Once within the tumour they sample proteins from the microenvironment and then mature and migrate to the lymph node. There the DC which migrated straight to the lymph node and those which migrated from the tumour coordinate to drive anti-tumour T cell priming.

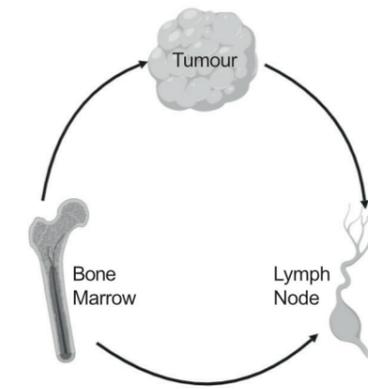


Figure 2
Tumour antigen is handled uniquely
ZsGreen expressed within the lung is carried to the lymph node by migratory DC, but the protein remains restricted to the migratory DC. When the same protein is expressed in a tumour, the protein is carried to the lymph node by migratory DC in a similar fashion but is transferred to other lymph node resident populations.

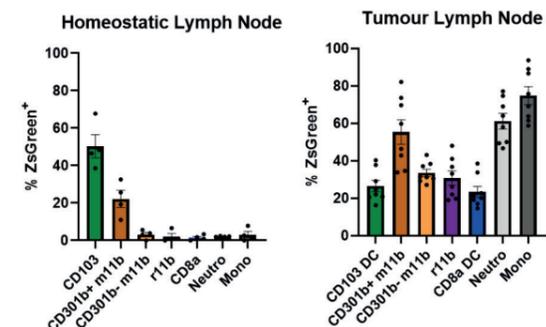


Figure 3
Lymph node organisation
A whole cleared lymph node stained for T cell, B cell and DC markers shows the organisation of a lung tumour-draining lymph node.

