IMMUNE PRIMING AND TUMOUR MICROENVIRONMENT

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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 tissue microenvironment is dictated and how this influences 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.

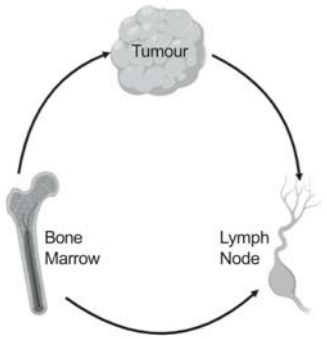

Figure 1. The DC lifecycle
DC precursors develop in the bone marrow and migrate to the tumour and the lymph node. Once within the tumour, they sample proteins from the microenvironment and then mature and migrate to the lymph node. There are the DC which migrated straight to the lymph node and those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

Immune history and impacts on tumours

We have shown that there are long term changes in tissues after infections and have recently shown that these alter tumour development within the tissue. Using a model of influenza we have shown that several models of cancer within the lung are more aggressive if they occur after the resolution of a previous lung infection. Indeed, this was also the case after a more simple inflammatory response. This does not appear to be due to a history of inflammation as preventing this with paracetamol did not reverse this impact and so we are currently investigating which changes in the lung are responsible for this pro-tumorigenic environment.

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 have identified trafficking receptors on precursor DCs and have generated an assay to screen receptors individually and in combination to identify those required for DC entry to both tumours and sites of infection. We are now unpicking which signals draw DC into different tissues and will next determine which cells are producing these signals 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.

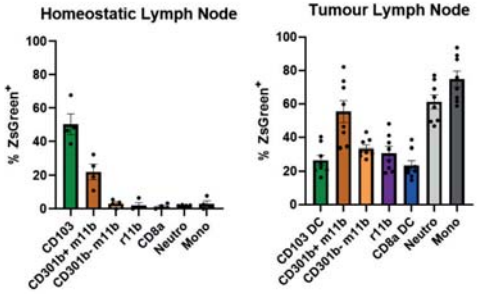

Figure 2. Tumour antigen is handled uniquely
ZsGreen expressed within the lung is carried to the lymph node by migratory DC, but the protein remains restricted to the migratory DC. When the same protein is expressed in a tumour, the protein is carried to the lymph node by migratory DC in a similar fashion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

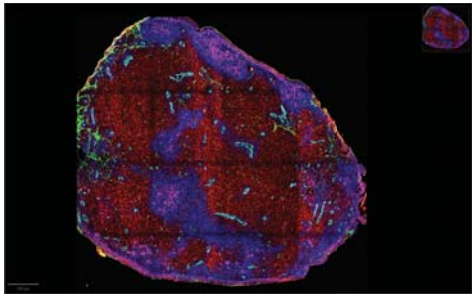

Figure 3. Lymph node organisation
A whole cleared lymph node stained for T cell, B cell and DC markers shows the organisation of a lung tumour-draining lymph node.

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 or viral infection, however, this protein is handed off to lymph node resident cells and we have shown that their activation mimics that of DC activated in the tissue (Figure 2). We have shown that this is due to co-transfer of this antigen alongside contextual cues communicating the nature of the challenge. This means that tumour derived dysfunction spreads to the lymph node leading to poor activation. We are now investigating how this transfer occurs and have seen that transfer relies on signals through specific costimulatory molecules in both cancer and in influenza infection. This implies that transfer relies on structures called tunnelling nanotubes which would allow transfer of co-packaged antigen and contextual information.

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 have seen that in the cancer setting DC are only partially activated and this leads to them remaining excluded from regions where they normally fully activate T cells. Addition of inflammatory signals can drive relocalisation of these DC and improve the anti-tumour immune response. We now are investigating how this relates to human cancer by interrogating human lymph nodes.

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