Determining how certain mutations can drive carcinoma growth and progression, and how tumour cells with particular mutational landscapes may be targeted therapeutically, is of key importance. However, it is now clear that a tumour’s ability to engender alterations to the extracellular matrix, both locally and within organs which are distant from the primary tumour, influences its growth and metastatic spread. We are, therefore, focusing on describing the molecular and cellular mechanisms through which tumours influence extracellular matrix organisation. We are investigating how some of the mutations and metabolic alterations which occur in cancers lead to the release of factors (exosomes and metabolites) which influence extracellular matrix deposition. Furthermore, we are studying the molecular details of how a cell’s protein synthesis machinery may be reprogrammed to promote synthesis of extracellular matrix proteins which favour tumour initiation, growth and metastasis.

Our laboratory is dedicated to furthering our understanding of how primary tumours influence the extracellular microenvironment of primary tumours and of metastatic target organs by addressing two interlinked research aims:  

1. To establish how the metabolic re-wiring, which occurs in primary tumours to enable them to grow, influences metastasis. We are particularly interested in how tumours’ influence metabolic levels in the circulation and how these changes promote metastatic seeding.  

2. To investigate how exosomes and other extracellular vesicles released by primary tumours influence the surrounding microenvironment, and that of other organs, to favour invasive spread of tumour cells and metastasis.  

By addressing these aims, we will be able to determine how factors released by primary tumours can prime metastatic niches and thus influence the likelihood of disease recurrence following excision of primary tumours. This will facilitate the prediction of metastasis, and the stratification of therapies aimed at preventing post-surgical recurrence.

Metastasis & exosomes: Understanding the role of uracil in priming metastatic niches and influencing invasive cell behaviour

In collaboration with Karen Blyth, Owen Sansom and David Sumpton

To characterise the metabolic landscape of metastasis, we profiled non-polar metabolites in the serum of mice with varying levels of metastatic disease. Initially, we deployed the MMTV-PyMT mouse model of metastatic mammary cancer. We collected serum from a cohort of mice with mammary cancer, and then looked for specific metabolites which tracked with the number of metastases in the lungs. (Figure 1A). This indicated that there are 35 circulating metabolites which correlate with metastasis, and notable amongst these is the pyrimidine uracil (Figure 1B). We also used genetically engineered mouse models of pancreatic adenocarcinoma (PDAC), comparing a model which metastasises efficiently to the liver and lung (mutant p53– driven KPC tumours), with a model which progresses without liver or lung involvement (Figure 1C). In both cases, we found uracil significantly increased in the serum of mice with metastases, and notably this increase in uracil occurred in a concentration-dependent manner, which is consistent with the idea that increasing serum uracil levels correlate with the amount of metastatic disease.

The circulating serum uracil concentration could influence the tumour microenvironment in a way which favours the subsequent migration and infiltration of these GBM cells. We have found that mutant p53–expressing GBM release exosomes which influence the brain microenvironment in a way which favours the subsequent migration and infiltration of these GBM cells. We have characterised a mechanism through which expression of the mutant p53 oncogene in GBM cells influences the sorting of a sialomucin – podocalyxin – into exosomes. These podocalyxin-containing exosomes then instruct the principal non-neuronal cells of the brain, the astrocytes, to deposit ECM which is highly enriched in hyaluronic acid. This hyaluronic acid–rich ECM then supports GBM cell invasion and migration. Thus, mutant p53+, by influencing the podocalyxin content of exosomes, allow GBM cells to pave the way for their own invasive migration through the brain. We are currently investigating how strategies for reducing hyaluronic acid content of the brain ECM may reduce GBM spread and render these tumours more amenable to therapy.

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