One of the main challenges faced in treating cancer is the likelihood that, at the time of diagnosis, malignant cells have already left the primary tumour and spread to other organs. Thus, even following complete removal of the primary tumour, these disseminated cells can reside within ‘primed metastatic niches’ only to reappear later as metastasis. Primary tumours re-wire their metabolism in order to initiate and establish themselves, and we have found that these metabolic alterations can influence metastatic niche priming. Our research programme is dedicated to furthering our understanding of how metabolic re-wiring in the primary tumour leads to the release of factors, such as tumour metabolites and extracellular vesicles, which influence the microenvironment of other organs to prime them for metastasis. Armed with this information, we aim to target the therapeutic vulnerabilities of the metastatic microenvironment and develop strategies to oppose metastasis.

Metabolic rewiring drives release of extracellular vesicles to promote metastasis in mammary carcinoma

(i) Release of glutamate from mammary cancer cells drives invasion and metastasis by promoting release of extracellular vesicles containing mitochondrial DNA. The CRUK Beatson Institute has an ongoing programme to map cancer-associated metabolic landscapes. This has indicated that alterations to the serum metabolome presage metastatic onset. In mammary cancers, elevated circulating glutamate is a prominent feature of the metastasis-associated metabolome, and this is owing to upregulated expression of the glutamate-cysteine antiporter, xCT (SLC7A11) in metabolically-stressed cancer cells. Extracellular glutamate then activates a metabotropic glutamate receptor, mGluR3 to drive invasive behaviour by existing membrane trafficking events dependent on the Rab27 GTPase. Consistently, Rab27a knockout mice bearing autochthonous MMTV-PyMT mammary tumours display reduced metastasis to the lungs. Through exploring the cellular mechanisms responsible for this, we have found that Rab27a participates in a membrane trafficking process in which mitochondrial material (including mitochondrial DNA (mtDNA)) is packaged into extracellular vesicles (EVs). Moreover, a detailed investigation into the cellular mechanisms controlling glutamate-driven EV release indicates that the mitochondrial metabolic sensing kinase, PINK1 is responsible for the packaging of mtDNA into the EV lumen. mtDNA-containing EVs are then released from cancer cells to evoke invasive behaviour in neighbouring cells by activating a toll-like receptor, TLR9. Thus, this work has led us to discover a pathway through which metabolic rewiring in cancers can drive invasion and metastasis by releasing mtDNA-containing exosomes to influence the behaviour of other cells in the tumour microenvironment and beyond. We are currently investigating how production of these EVs may contribute to mechanisms of intercellular communication: (1) Mitochondrial damage/depletion increases levels of PINK1 to promote physical interaction of late endosomes with mitochondria. This leads to transfer of the mitochondrial chromosome into the lumen of intralumenal vesicles of late endosomes, (2) A combination of glutaminolysis and upregulation of xCT (SLC7A11) leads to increased secretion of glutamate to drive Rab27-dependent exocytosis of EVs loaded with mitochondrial DNA (mtDNA) and (3) mtDNA transported within these EVs activates a TLR9-dependent mechanism to promote pro-inflammatory endosomal trafficking of MT1-MMP in other cells.

(ii) Cells from lung micrometastases have altered glutathione levels which promote sphingomyelinase-2-dependent extracellular vesicle release

Primary tumours re-wire their metabolism to establish themselves and grow and, as we have shown above, this leads to altered invasive behaviour. We proposed that when invasive cells emanating from primary tumours arrive in metastatic target organs (such as the lung), they need to further re-wire their metabolism to adapt to the different environmental challenges posed by these locales before they can initiate metastatic outgrowth. In collaboration with Karen Blyth’s laboratory, we have isolated cells from early lung micro-metastases and compared their metabolism with that of cells from their ‘parent’ primary tumours in the mammary gland. This yielded the surprising finding that cells from lung micro-metastases have consistently reduced levels of glutaminolysis (reduced and oxidized) by comparison with cells from the primary mammary tumour and that this was associated with a marked increase in EV release. Furthermore, EV release from micro-metastatic cells is strongly dependent on the expression of sphingomyelinase-2, whereas EVs are released from primary tumour cells in a sphingomyelinase-2-independent manner. These findings indicate that alterations to redox metabolism made by cells as they establish lung metastases drives sphingomyelinase-2-dependent EV release. We are currently investigating how production of these EVs may assist in maintaining redox balance in micro-metastatic cells, and how they communicate with the immune system to help prime the metastatic niche.