Metastasis and recurrence remain largely untreatable aspects of many solid cancers. We are interested in discovering how cells escape from tumours and how they succeed or fail to colonise in new sites. Adhesion, migration and the balance of mechanical forces all contribute to metastasis via cell signalling and feedback. We hypothesise that understanding the molecular conversation between cancer cells and their surroundings will reveal new avenues for combating metastasis.

Solid tumours are frequently mechanically stiffer than the surrounding tissue, due to increased pressure, cell crowding, fluid accumulation and extracellular matrix (ECM) deposition. Tumour cells experience increased mechanical forces, but they show a force imbalance, thought to disrupt the normal tissue architecture and promote invasion and escape from the primary site (Figure 1). Pancreatic ductal adenocarcinoma (PDAC) presents with stiff tumours containing a fibrotic ECM and is highly metastatic. Vassilis Papalazarou, a former PhD student co-supervised by Prof. Manuel Salmeron-Sanchez in the School of Engineering and Centre for the Cellular Microenvironment, asked how mechanical stiffness of the ECM affects PDAC cells, using bioengineered matrix substrates of controlled stiffness. To our surprise, cells showed a strong link between metabolic flux and ECM stiffness, with soft matrix promoting glycolysis and stiff ECM promoting mitochondrial oxidative phosphorylation. We went on to dissect connections between mitochondrial morphology, cellular position and metabolic flux. Vassilis discovered that mitochondria are recruited into invasive pseudopodia of PDAC cells, where they provide ATP to power actin dynamics and invasion. He further found, together with Dr Oliver Maddocks, that PDAC cells also upregulated their phosphocreatine shuttle, a major ATP recycling pathway, in response to ECM stiffness. This provided a new link between mechanosensing, ATP production and ATP recycling. We are continuing to explore how the phosphocreatine shuttle is regulated by Yap/Taz signalling, which impacts on expression of the enzyme creatine kinase B (CKB), and how ATP recycling powers cell migration and invasion.

We have further revealed important functions of the major actin nucleation promoting complex, the Scar/WAVE complex, and its target, Arp2/3 complex, in migration and invasion and in metastatic niche formation. Postdoctoral researcher Jamie Whitleaw explored new connections between the actin nucleating functions of Scar/WAVE and cell-matrix adhesions. Former postdoctoral Researcher Karthic Swaminathan explored the role of the NckAP1 subunit of the Scar/WAVE complex in the melanocyte lineage of mice predisposed to melanoma driven by BrAllose1. and a loss of the tumour suppressor PTEN. These mice develop melanomas when NckAPI is present, but NckAPI deletion severely impairs melanoma development and progression, with tumours showing very slow growth and enhanced fibrosis and immune infiltration. Our study implicated NckAPI1 and the Scar/WAVE complex in cell cycle progression, likely as a key downstream target of Rac1, a key activator of the Scar/WAVE complex. We also showed that the Arp2/3 complex is crucial for migration of mouse embryo melanoblasts in the skin. Loss of the Arp3 subunit caused a failure of melanoblasts to expand in the dermis and reduced migration and mechanical stability, demonstrating the importance of Arp2/3 as a driver of migration in vivo.

The liver is a major site of metastasis of many solid cancers, and liver metastasis is a major cause of death from cancers, including PDAC. Postdoctoral researcher James Drew and PhD student Elaine Wing See Ma pioneered a new model for liver metastasis, in vitro, using human induced pluripotent stem cell (iPSC) derived mini-liver spheres. Prof. David Hay's lab at the Centre for Regenerative Medicine in Edinburgh have developed mini-liver spheres from human iPSCs to model healthy and diseased liver function. Together with Hay's group, we explored the capability of metastatic PDAC to colonise the liver spheres and to interact with the hepatocytes, stellate cells and endothelial cells present in these mini-liver spheres (Figure 2). We propose that mini liver spheres have the potential to be developed into a powerful new model for cancer metastasis in vivo that could be exploited to search for new therapies. Looking ahead, we (PhD students Sonia Rolo and Elaine Wing See Ma, and postdoctoral researcher James Drew) continue to explore the liver metastatic niche and ask how crosstalk between disseminated tumour cells and their environment controls their tendency to lie dormant or to grow into a new metastasis. We are also continuing to unravel how creatine kinase II controls ATP recycling via the phosphocreatine shuttle (Anh Le, postdoctoral researcher) to power invasive migration and link mechanosensing with metabolism.

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