MIGRATION, INVASION AND METASTASIS

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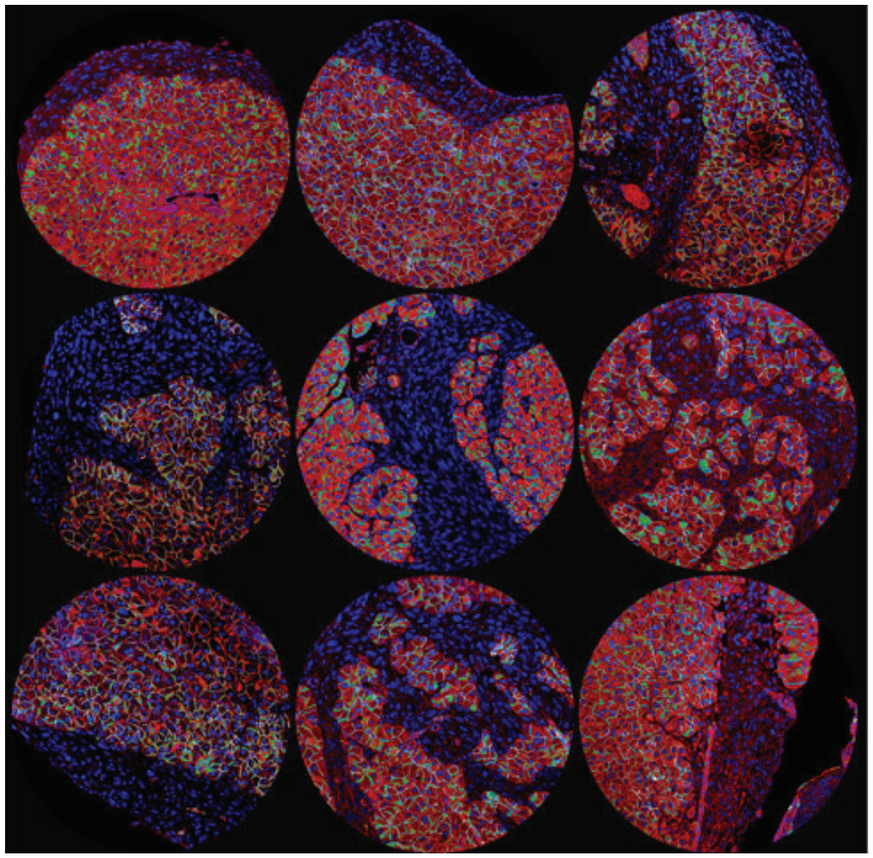
Cancer metastasis and recurrence after treatment still account for the vast majority of cancer deaths and new strategies are urgently needed in these areas. Reasons why metastasis is difficult to target include difficulty of detecting or eradicating disseminated tumour cells, lack of understanding of the mechanisms of spread and heterogeneity of tumours. Our group aims to improve understanding of the mechanisms of cancer metastasis with the goal of identifying new strategies to improve outcomes for patients with metastatic cancer. We study mechanisms of cell migration control, Rho-family GTPase signalling and mechanosensing by tumour cells. We are also interested in crosstalk between mechanosensing and metabolism. Our focus is mainly on pancreatic cancer and melanoma, but our basic science is relevant to multiple cancer types and to normal developmental migration.

The actin-nucleating protein N-WASP is implicated in cancer cell invasion and metastasis due to its ability to trigger actin assembly and link with signalling pathways via Rho GTPases that control both actin-based motility and vesicle trafficking. This year, clinical research fellow Dr Hayley Morris discovered that N-WASP is also important for maintenance of normal tissue homeostasis in the intestine and colon and can act as a suppressor of tumourigenesis in an APC-driven model of colorectal cancer. Additionally, postdoc Dr Amelie Juin implicated N-WASP in a chemotactic signalling loop regulating invasion and metastasis of pancreatic ductal adenocarcinoma (manuscript under review). Loss of N-WASP in a KRas- and mutant p53– driven model of pancreatic ductal adenocarcinoma (PDAC) led to reduced metastatic spread to distant sites such as the liver and peritoneal cavity. N-WASP is thus a promising but complex target, due to its strong role in invasion and metastasis, combined with its contrasting requirement for maintaining normal tissue homeostasis in the early stages of cancer progression. Amelie and scientific officer Heather Spence are also investigating the role of the sorting and trafficking protein strumpellin in cancer metastasis in both prostate cancer (with Rachana Patel and Hing Leung) and PDAC.

Rac1 is well known to be important in Ras-mediated transformation of cancer cells and is one of the more commonly mutated genes in sun-exposed melanomas. Rac1 regulates actin dynamics via a direct interaction with the Scar/WAVE complex, which generates new actin filaments at the leading edges of cells. In a collaborative effort with Robert Insall's group, we discovered a new regulator of actin dynamics, CYRI (in humans, CYRI-A and CYRI-B), encoded by the *FAM49* gene. CYRI is a Rac1-interacting protein that negatively regulates Rac1 signalling to activate the Scar/WAVE Complex. CYRI is well conserved in evolution and represents an example of a 'local inhibitor' of actin-based protrusions. Postdoc Jamie Whitelaw and PhD student Anh Le are further investigating the role of the Scar/WAVE complex and CYRI-A/B in the control of actin dynamics. PhD student Savvas Nikolaou has found CYRI-B to be particularly highly expressed in PDAC and is investigating a possible role in regulation of Rac1 activity during PDAC progression. Postdoc Karthic Swaminathan is investigating how the Scar/WAVE complex controls melanocyte migration and melanoma progression. Another downstream target of Rac1 is the actin bundling protein fascin-1, which we continue to collaborate on with the Institute's Drug Discovery Unit and also with David France and Sarah Memarzedah in the Department of Chemistry at the University of Glasgow to make a fascin-targeting degradation reagent using the PROTAC ubiquitin targeting method.

Figure 1
Tissue sections from pancreatic cancer metastatic nodules showing DNA/nucleus in blue and E-cadherin cell junctions in green.

Photo Credit: Dr Amelie Juin



Pancreatic tumours are particularly stiff due to accumulation of collagen-containing stroma. They are also nutrient- and oxygen-depleted, potentially leading to high selective pressure for metabolic plasticity to overcome the hostile environmental challenges. Actin dynamics for cell migration require ATP turnover, and tumour cells have particularly high metabolic demands due to uncontrolled proliferation and poor nutrient access. We are investigating how the stiff environment of the tumour changes pancreatic cancer cell metabolism and how metabolic pathways are coupled with cell migration and the actin cytoskeleton. Postdoc Nikki Paul is on an MRC-funded project to screen for metabolic regulators that regulate the cytoskeleton and motility properties of PDAC cells. Student Vassilis Papalazarou is funded by the Cancer Research UK Glasgow Centre as a collaboration with the Bioengineering group of Manuel Salmeron-Sanchez (University of Glasgow) to study how mechanosensing couples with metabolism in PDAC cells. We also collaborate with Oliver Maddocks (University of Glasgow) to perform metabolomics on PDAC cells. Our studies are revealing how cancer cells can still remain exquisitely mechanosensitive and enter into states of relative dormancy or active growth depending on mechanical cues. Cancer dormancy accounts for many types of relapse of disease after treatment and we urgently need more information about the dormant state of cancer in order to develop new treatments against recurrence.

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