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INTEGRIN CELL BIOLOGY

Group Leader
Jim Norman

Associate Scientist
Cassie Clarke

Research Scientists
Sergi Marco-Martin
Madeleine Moore
Grant McGregor
Sarah Palmer[1]
Luis Pardo

Associate Clinical Scientist
Iain MacPherson

Scientific Officer
Louise Mitchell

Clinical Research Fellow
Dominik Kössinger

Graduate Students
Michalis Gounis
David Novo
Nicholas Rabas
David Novo

[1]West of Scotland Women's Bowling Association Fellow

One of the main challenges that we face 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 metastases. We anticipate that a deeper understanding of the mechanisms underlying metastatic niche priming will enable us to predict patterns of metastasis and the likelihood of disease recurrence and will reveal therapeutic vulnerabilities.

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

1. To establish how metabolites released by primary tumours influence invasiveness and the priming of metastatic niches; and

2. To determine the mechanisms through which mutant p53s generate metastatic niches

By addressing these aims, we will identify circulating biomarkers that can predict recurrence, and discover how tumour metabolism influences cellular processes (such as cell migration and endosomal trafficking) which drive invasion, metastasis, and awakening of dormant disseminated tumour cells.

How do metabolites released by primary tumours influence invasiveness and the priming of metastatic niches?

Using a comprehensive metabolomic screen, we have found that the landscape of serum metabolites is markedly different in women with metastatic breast cancer by comparison with healthy volunteers (Fig. 1a). We have found that we are able to recapitulate these changes in the serum metabolome using genetically engineered mouse models of mammary carcinoma (Fig. 1b). Importantly, levels of glutamate in the serum reflect tumour burden and acquisition of primary tumour invasiveness (Fig. 1b), and plasma aspartate and γ-amino butyric acid (GABA) concentrations increase as frank metastases form in the lung. Preliminary evidence indicates that glutamate and aspartate release from tumour cells is mediated by alterations in the expression of metabolite transporters of the SLC family, and that these alterations are triggered by the response of tumour cells to metabolic stresses. We are investigating how extracellular levels of glutamate, GABA and aspartate drive invasiveness and metastatic niche priming by activating plasma membrane receptors for these metabolites (i.e. the mGluR, NMDA and GABAR families) on fibroblastic and other cell types to influence extracellular matrix (ECM) deposition in metastatic target organs. Furthermore, we are interested in how these metabolites modulate the immune landscape of tumours and metastatic target organs.

What are the mechanisms through which the expression of mutant p53s and other pro-metastatic oncogenes generate metastatic niches?

We have found that key membrane trafficking events evoked by gain-of-function p53 mutations in primary tumours may be transferred via exosome-mediated mechanisms to cells in other organs. Indeed, exosomes from mutant p53–expressing pancreatic adenocarcinoma (PDAC) (but not in PDAC with p53 loss) can influence integrin trafficking in lung fibroblasts to alter the deposition of ECM proteins such as collagen VI in the lung (Fig. 2). This altered microenvironment provides migratory cues which lead to priming of the lung as a metastatic niche, thus providing a mechanistic rational for why mutant p53¬–expressing PDAC are more metastatic than their p53 null counterparts. We are investigating how pancreatic and colon adenocarcinoma can foster certain ECM microenvironments in metastatic target organs, and how this can promote recruitment of circulating tumour cells and components of the innate and acquired immune systems to break dormancy and drive metastasis. We are using a range of non-invasive ECM imaging available at the Institute to assess the priming of metastatic organs, and to explore pharmacological approaches to reducing metastatic niche formation to oppose cancer recurrence following surgery.

Publications listed on page 90

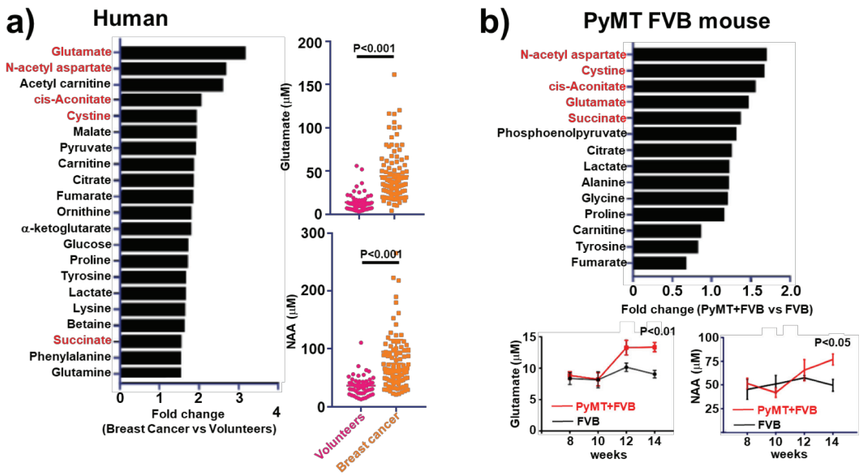

Figure 1
Circulating metabolites in mammary carcinoma in human and mouse.
Circulating metabolites which are significantly different between breast cancer patients and healthy volunteers (a) and MMTV-PyMT and non-tumour bearing FVB control mice (b). Metabolites which are common to human and mouse are highlighted in red. The graphs in (b) indicate that glutamate and N-acetyl aspartate (NAA) levels are significantly elevated in the serum of MMTV-PyMT mice as 12-14 weeks of age. Volunteers, n=35; breast cancer patients, n=120. Non-tumour bearing and MMTV-PyMT mice, n=30.

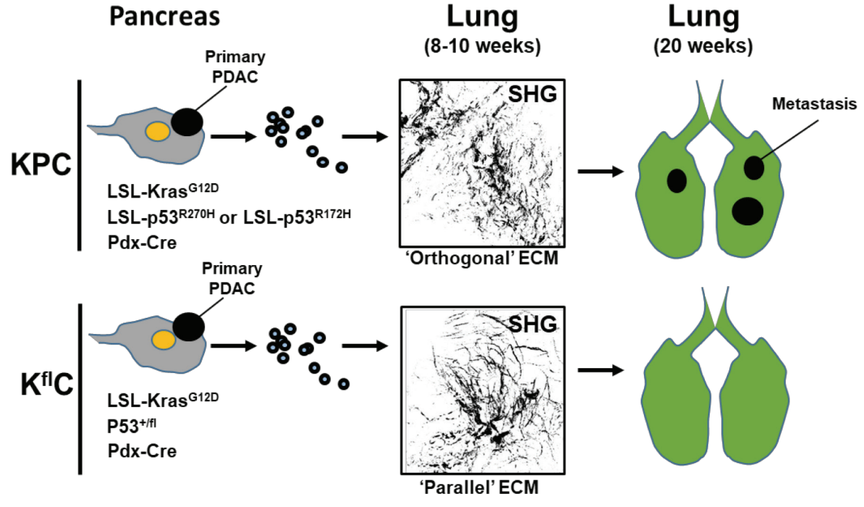

Figure 2
KPC and KflC models of PDAC to study metastatic niche priming.
The KPC model of pancreatic ductal adenocarcinoma (PDAC) is driven by autochthonous expression of mutant KRas and mutant p53 (either p53^{R70H} or p53^{R172H}) in the pancreatic epithelium. The KflC model of PDAC is driven by mutant KRas in combination with a floxed allele of p53. Both models promote primary tumour growth with similar penetrance and speed. However, KPC, but not K^{fl}C, form metastases which are detectable at 20 weeks of age. Second harmonic generation (SHG) analysis indicates that KPC, but not KflC, mice display alterations to the extracellular matrix (ECM) of the lung at 8-10 weeks of age – prior to the establishment of detectable metastases. The lung ECM of KPC mice is different from that of K^{fl}C mice in a number of quantifiable ways, such as a more orthogonal filament organisation.