INTEGRIN CELL BIOLOGY

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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 are, therefore, focussed on understanding how primary tumours are able to prime organs for metastasis, how this priming may be assessed and how the metastatic niche may be targeted therapeutically. We have recently discovered that certain oncogenes influence the release of metabolites and other factors, such as exosomes, which lead to metastatic niche priming. In particular, we have elucidated how tumour metabolites and exosomes drive alterations to endosomal trafficking in lung fibroblasts to change the deposition of collagens and other extracellular matrix proteins in this metastatic target organ. We are currently determining how to use non-invasive imaging approaches to assess the extracellular matrix of primed metastatic organs, and we are exploring pharmacological approaches to reducing metastatic niche formation to oppose cancer recurrence following surgery.

Expression of mutant p53s and other pro-metastatic oncogenes generates 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 adenocarcinoma in the pancreas can influence integrin trafficking in lung fibroblasts to alter the deposition of extracellular matrix (ECM) proteins, such as collagen VI, in the lung. This altered microenvironment provides migratory cues which lead to priming of the lung as a metastatic niche. 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. Finally, we are determining how to use non-invasive ECM imaging to assess the priming of metastatic organs, and to explore pharmacological approaches to reducing metastatic niche formation to oppose cancer recurrence following surgery.

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 alters markedly during the progression of mammary tumours in mice. Levels of glutamate in the serum reflect tumour burden and acquisition of primary tumour invasiveness, and plasma aspartate and γ-amino butyric acid (GABA) concentrations increase as metastases form in the lung. Our 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 ECM deposition in metastatic target organs. Furthermore, we are determining how these metabolites modulate the immune landscape of tumours and metastatic target organs.

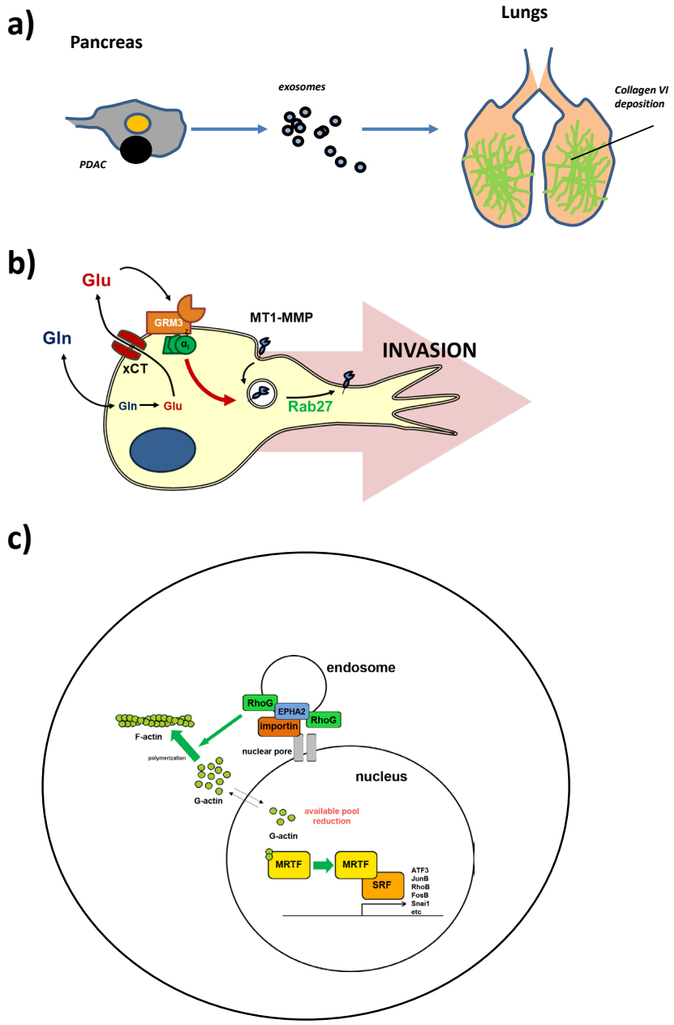

Figure 1
(a) Exosomes from mutant p53–expressing pancreatic adenocarcinoma tumours influence extracellular matrix deposition during lung remodelling.
(b) Glutamate secretion from mammary carcinoma promotes invasion by activation of the GRM3 metabotropic glutamate receptor.
(c) EphA2 mediates the nuclear capture of endosomes to promote local actin polymerisation to activate SRF-dependent transcription.

'Nuclear capture' of endosomes activates transcriptional programmes to favour metastasis

By designing a novel screen to identify receptors that are transported from the cell surface to the nuclear membrane, we have discovered a mechanism whereby endosomes are 'captured' at the nuclear surface by interaction of a nuclear localisation sequence in the cytodomain of the receptor tyrosine kinase EphA2 with the nuclear import machinery. This process promotes juxta-nuclear actin polymerisation, leading to activation of MRTF/SRF transcription factors and generation of a transcriptional programme favouring dissemination and metastasis of pancreatic cancer. Antisense oligonucleotide (ASO) drugs are being developed to target mutated oncogene products, such as KRas, and these are now entering clinical trials. We are currently investigating whether the 'nuclear-capture' of endosomes mediates delivery of ASOs to the nucleus where they act to oppose proliferation of cancer cells. As nuclear-capture mechanisms are most active in cancer cells engaged in disseminations, we are investigating how this pathway may be exploited to target the delivery of ASOs to cancer cells that are actively metastasising.

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