Knock-out of PSD4 (EFA6B) promotes collective invasion of human mammary cells: implication in breast cancer

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Metastases are responsible for most of cancer mortality. Cancer is caused by somatic mutations in oncogenes or tumor suppressor genes, however additional mutations provide selective advantages to the tumor cells to develop metastatic cancers. The identification of such mutations is therefore of paramount importance. EFA6B (Exchange Factor for Arf6, B) expression is reduced in aggressive breast cancer. To establish the pro-tumoral impact of the loss of EFA6B we have invalidated its gene in normal human mammary cells and found that it is sufficient to promote collective invasion in collagen. This is accompanied by an epithelial-to-mesenchymal transition, alteration of the matrisome, changes in the integrin repertoire and increased cell contractility. The knock-out cells form integrin β1-based and MMP14-enriched invadopodia responsible for the matrix degradation, which depends on the activation of Cdc42 and two of its effector pathways: Cdc42-MRCK-pMLC and Cdc42-N-WASP-Arp2/3 that control cell contractility and invadopodia formation, respectively. Furthermore, the expression of EFA6B is decreased in invasive compared to intraductal tumors isolated from patients. Our results demonstrate a novel negative regulatory pathway of tumor invasion, which is regulated by EFA6B, and open up new therapeutic perspectives for breast cancer.
Macrophages: bad actors in cancer

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The majority of deaths caused by cancer are due to metastasis. This fact indicates that metastatic tumours are resistant to available therapies. Tumors consist not only of malignant cells but also a wide-range of non-mutated normal cells including those of the immune system. Among these immune cells, macrophages are particularly abundant in a wide range of tumors. Our studies focussing on breast cancer have indicated that these tumour-associated macrophages (TAMs) promote tumor progression to malignancy in mouse models.1 Recently we have identified a sub-population of macrophages (MAMS) that help metastatic cells seed at distant sites and prosper. Lineage tracking indicates that these metastasis-associated macrophages (MAMs) derive from the Ly6Chi population of monocytes recruited by the tumour cell produced chemokine CCL2. These monocytes differentiate through a precursors stage to a mature MAM that is immunosuppressive towards cytotoxic T cells.2 We have defined signalling pathway involving chemokines and growth factors that propagate MAMS and that are required for their metastasis promoting activities.1

The pro-tumoral activities of TAMs and MAMs suggest that pharmaceutical intervention in any of these signalling steps might become part of a therapeutic strategy that will improve survival of patients with metastatic disease.3 To address this we have also profiled human TAMs in breast cancer and defined signalling pathways that might be targeted in this endeavour.4 These data will be discussed during the presentation.

A hole lot better:
the dural puncture epidural technique

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Neuraxial techniques provide the closest representation of an ideal labor analgesia technique, which would have quick onset, predictable quality, adjustable depth duration, and minimal maternal and fetal side effects.

The CSE technique, when compared to a conventional epidural technique, harnesses the ability to confirm placement, produce analgesia of fast onset and high quality, and result in shorter labor duration, yet is associated with an increase the incidence of fetal bradycardia and an inability to adequately test the epidural catheter.

The dural puncture epidural (DPE) technique, in which a dural puncture is performed but labor analgesia medications are placed only in the epidural space, was developed as an alternative. When compared to a traditional epidural technique, the DPE technique provided faster onset, greater sacral coverage, and less unilateral block with no differences in motor blockade, highest sensory blockade or post-dural puncture headache. When compared to the CSE technique, the DPE offers less fetal bradycardia, less uterine hypertonus, less provider work load, and the ability to test the epidural catheter.

Host-microbiota interactions in health and disease

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The intestinal tract of mammals is colonized by a large number of microorganisms including trillions of bacteria that are referred to collectively as the gut microbiota. These indigenous microorganisms have co-evolved with the host in a symbiotic relationship. In addition to metabolic benefits, symbiotic bacteria provide the host with several functions that promote immune homeostasis and protection against pathogen colonization. Our laboratory is using Citrobacter rodentium, a mouse pathogen that models human infections by enteropathogenic E. coli, to understand the mechanisms by which the microbiota promote clearance of the pathogen in the gut. Bacterial symbions can also promote disease including inflammatory disorders such as Crohn's disease in genetically susceptible individuals. We will show recent results that demonstrate that particular symbiotic bacteria can accumulate in the intestine and trigger Crohn's disease-like colitis in mice with mutations relevant to the development of inflammatory bowel disease in humans.
Mechanisms of promotion of metastasis by lymphatic endothelium

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Tumor-induced lymphangiogenesis promotes cancer metastasis to lymph nodes and likely beyond. Tumor draining lymphatic vessels and the expanded lymphatic vessels in tumor-draining lymph nodes provide a (pre-) metastatic niche for cancer stem cells, as evidenced by the occurrence of in-transit metastases and persistence of cancer cells in lymph node sinuses, mediated by specific chemokines. Using near-infrared in vivo imaging, we found enhanced flow in tumor-draining lymphatic vessels, as well as re-routing of lymphatic tumor drainage after sentinel lymph node metastasis. Evaluation of tumor-draining lymph nodes by light-sheet microscopy in 3D at single cell resolution revealed that proliferation and sprouting of lymph node lymphatics precedes tumor metastasis, and transcriptional profiling of tumor-activated lymphatic vessels identified upregulation of factors involved in the control of the immune response such as PD-L1. Indeed, lymphatic endothelium-expressed PD-L1 was found to dampen anti-tumor immune responses. Our recent data reveal that lymphangiogenesis also occurs in distant organ metastases in human and experimental mouse cancers, and studies in a genetic mouse model for increased lymphatic vessel density in the lung revealed that increased lymphatic density in peripheral organs promotes further cancer spread. Importantly, lymphangiogenesis in lung metastases of human cutaneous melanomas is correlated with lung-draining lymph node metastasis and with reduced overall survival. These findings reveal an unanticipated role of lymphatic vessels in facilitating systemic cancer metastasis.