

Migration, Invasion and Metastasis

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There remain few treatments or prevention measures for metastatic cancer and currently most cancer related deaths result from metastatic disease. Understanding the basic science of actin cytoskeleton regulation is crucial to determining how tumour cells invade and migrate to distant sites in the body. We therefore aim to understand the fundamental control and mechanisms of actin assembly in various normal and cancer cells with the hope of thus defining the molecular mechanisms that control cell movement. These studies also impact on our understanding of normal human development, the immune system and blood cell function.

Role of actin nucleating proteins

The Arp2/3 complex is the major inducer of actin filaments in response to extracellular signals. The Wiskott-Aldrich syndrome protein (WASP) family proteins transmit signals to trigger actin assembly (Fig. 1: Scar/WAVE, N-WASP, WASH, NHS-1A, WHAMM and JMY). Scar/WAVE proteins are part of a large complex that regulates Scar/WAVE localisation, activity and stability. This year, Hao Ran Tang showed together with Alison Hardcastle in London that the Nance-Horan Syndrome Protein (NHS-1A) is homologous to Scar/WAVE and interacts with the same complex of proteins. It also interacts with Scribble/Dlg proteins and thus may be an important regulator of cell polarity and a tumour suppressor. Richard Stevenson will further examine the role of NHS-1A in motility, polarity and tumorigenesis. N-WASP and WASP are regulated differently but also participate in protein complexes. All WASP family proteins appear to be regulated by phosphorylation and interaction with small GTPases. In the past few years, new WASP family members have been discovered that play an important role in intracellular membrane trafficking. These include WASH, JMY and WHAMM. Tobias Zech and Simon Calaminus have discovered a role for WASH in trafficking of integrins in invasive carcinoma cells in collaboration with Jim Norman's group. Yafeng Ma is also characterising

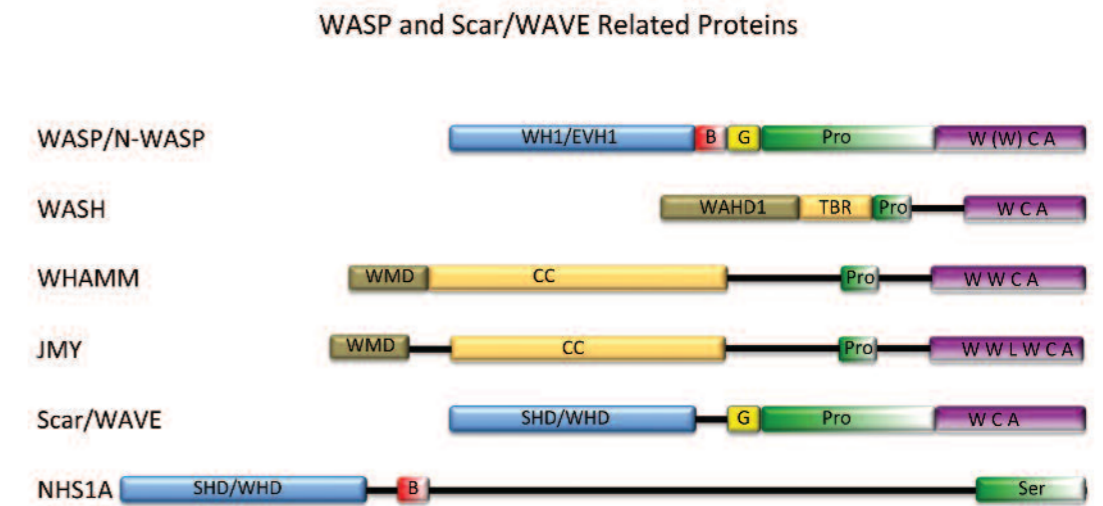
JMY, which seems to have a role in Golgi and endoplasmic reticulum architecture. Networks of actin generated by the Arp2/3 complex are important at multiple sites within the cell in regulating membrane trafficking as well as actin-based protrusion. It is emerging that N-WASP and Scar/WAVE have different roles in cells and Xinzi Yu has found that N-WASP has an important role in cancer cell invasion (Fig.2). We aim to test this in vivo in collaboration with Scott Snapper in Boston.

Fascin as a potential therapeutic target

Fascin is an actin-bundling protein implicated in filopodia assembly and migration. Over 50 studies correlate upregulation of its expression with worse grade, stage and/or metastatic status of epithelial cancers. Ang Li has found that fascin is an important component of invasive protrusions and matrix-remodelling filopodia in cancer cells in a three-dimensional, reconstituted extracellular matrix. Cancer cells depleted of fascin lacked filopod protrusions and showed diminished invasion into three-dimensional Matrigel-collagen matrix. We are interested in the potential of fascin as a drug target against invasion and metastasis. We (Yafeng Ma, Ang Li, Richard Stevenson) are currently collaborating with Martin Drysdale as well as MRC Technology and Cancer Research Technology to identify compounds that target fascin and cancer

Figure 1

Domain structure of selected WASP and Scar/WAVE related proteins: WH1/EVH1 WASP-homology 1; Ena/WASP homology 1; B basic; G GTPase binding; Pro proline rich; WCA denotes the region of the protein that interacts with and activates the Arp2/3 complex with W being WASP homology 2, C being connecting helix and A being acidic; WAHD1 WASH homology 1; TBR tubulin binding region; WMD WHAMM homology domain; SHD/WHD Scar WAVE homology domain; Ser serine rich.



invasion. Heather Spence is performing siRNA screens together with Lynn McGarry to identify additional targets for invasion and metastasis.

Control of actin-based motility in melanoblasts

Small GTPases of the Rho family regulate cell migration and actin dynamics downstream of membrane receptors. Rac proteins trigger lamellipodia protrusions as well as membrane trafficking, while Rho proteins control contractility and cell adhesion. We have collaborated with Victor Tybulewicz in London, Lionel Larue in Orsay, Ian Jackson in Edinburgh and Owen Sansom to study the role of Rac1 in the migration of melanoblasts, the precursor cells to pigment-producing melanocytes. Together, we (with Ang Li) combined model systems to study how melanoblasts move during embryogenesis and to determine the importance of the small GTPase Rac1 in their motility. Ang Li found that Rac1 is important for melanoblast migration and proliferation, and we aim to determine its importance in melanoma development, progression and metastasis.

Wnt signalling in megakaryocytes

We have begun a collaboration with Tessa Holyoake at the Paul O' Gorman Leukaemia Research Centre, Steve Watson in Birmingham and Owen Sansom to understand the role of Wnt signalling in megakaryocytes, which are the precursor cells to blood platelets. Platelets are small disc-shaped enucleated cell fragments that circulate in the blood and rapidly aggregate into a thrombus when an injury occurs in the vasculature. We found that dramatic changes occurred when we aberrantly activated Wnt signalling in megakaryocytic precursor cells. Intriguingly, we find parallels with human myeloproliferative disorders, suggesting an important and previously unknown role of megakaryocytes in the establishment and maintenance of bone marrow homeostasis. Simon Calaminus presented this work in a talk at the American Society for Haematology meeting in December.

Publications listed on page 80

Figure 2

A CHL-1 melanoma cell invading into Matrigel, with N-WASP in green, cortactin in red and actin filaments in blue. (Xinzi Yu)

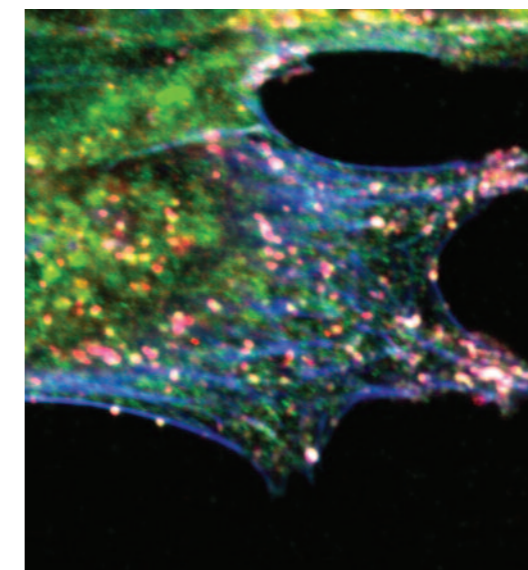


Figure 2

Figure 3

A melanoblast (grey) navigating between keratinocytes in the skin. Actin filaments are red, tubulin is green and nuclei are blue. (Ang Li)

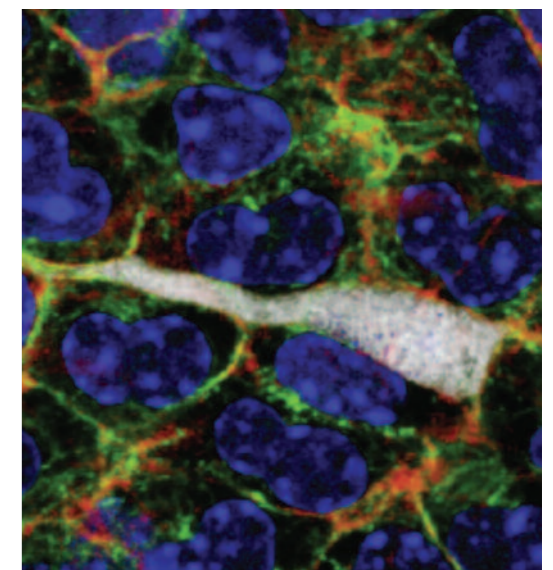


Figure 3