to affect cell–cell interactions. But does *Sipa1* influence metastasis? A series of experiments in mouse models showed that RNA inhibition of *Sipa1* decreased the numbers of pulmonary metastases from a highly metastatic mammary tumour cell line. Conversely, overexpression of the FVB allele increased the numbers of pulmonary metastases. Analysis of human tumours also demonstrated that overexpression of *SIPA1* is associated with metastatic progression.

These results demonstrate that *Sipa1*, as determined by its overall protein concentration and/or its availability to inactivate RAP1, modulates metastatic progression. The data also predict that homozygotes for the DBA allele would have reduced metastatic capacity because, in the primary tumour, cells are more likely to closely interact with one another. Additional studies are required to verify this and to investigate another potential gene close to *Sipa1* that might also contribute to the *Mtes1* locus.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPER Park, Y. G. *et al*. *Sipa1* is a candidate for the metastasis efficiency modifier locus *Mtes1*. *Nature Genet*. 4 September 2005 (doi: 10.1038/ng1635)

kinase is commonly overexpressed in human cancers, including 40% of breast cancers. So, how can cancer cells express high levels of EPHA2 and maintain signalling along the MAPK pathway? A survey of EPHA2 and its ligand in a panel of 28 breast cancer cell lines revealed that cells that overexpress EPHA2 do not express ephrin-A1 — expression of the receptor and its ligand is mutually exclusive. This is because in addition to upregulating the expression of *EPH2A*, another outcome of MAPK signalling is downregulation of the ephrin-A1 gene *EFNA1*.

The authors propose that in normal tissue architecture, one cell type downregulates MAPK signalling and is therefore able to express ephrin-A1, whereas neighbouring cells activate the MAPK signalling pathway and express only the receptor. This interaction between ligand and receptor on adjoining cell types keeps cell proliferation in check. When this structure is lost, such as during tumour formation, EPHA2-expressing cells no longer interact with ephrin-A1 produced by neighbouring cells, resulting in uncontrolled MAPK signalling and proliferation.

In support of this model, the authors showed that ERBB transformation, which is mediated by the MAPK signalling pathway, is suppressed by ephrin-A1 expression in cultured cells. The authors suggest that maintaining normal interactions between ephrin ligands and receptors is an important mechanism of tissue homeostasis that is disrupted during the development of breast and other cancers.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Macrae, M. *et al*. A conditional feedback loop regulates Ras activity through EphA2. *Cancer Cell* **8**, 111–118 (2005)

IN BRIEF

VACCINES

T cell-mediated suppression of angiogenesis results in tumor protective immunity.

Zhou, H. *et al*. *Blood* **106**, 2026–2032 (2005)

Tumour growth can be inhibited by anti-angiogenic intervention. The authors had previously shown that vaccination with a complete copy of the murine growth factor receptor gene *Flk1* triggered the production of antibodies against proliferating endothelial cells in the tumour vasculature. Now they show that the use of an engineered minigene containing only one cytotoxic epitope of *Flk1*, delivered to mice in a *Salmonella*-based vector, results in an antibody that prevents angiogenesis and protects against various tumours, but does not cross react with healthy tissue.

CANCER GENETICS

Dido gene expression alterations are implicated in the induction of hematological myeloid neoplasms.

Fütterer, A. *et al*. *J. Clin. Invest.* **115**, 2351–2362 (2005)

Myelodysplastic/myeloproliferative diseases (MDS/MPDs) are a heterogeneous group of myeloid neoplasms that are associated with deletions on chromosome 20q. The authors map the death inducer-obliterator (*DIDO*) gene to this location and show that all patients with MDS/MPDs have *DIDO*-expression abnormalities. Furthermore, targeting *Dido* in mice caused a disease with symptoms similar to those of MDS/MPDs. These results indicate that *DIDO* might be a tumour suppressor gene for MDS/MPDs.

TUMORIGENESIS

Genetic ablation of cyclin D1 abrogates genesis of rhabdoid tumors resulting from *Ini1* loss

Tsikitis, M. *et al*. *Proc. Natl Acad. Sci. USA* **102**, 12129–12134 (2005)

Rhabdoid tumours are aggressive paediatric malignancies that arise because of the loss of the tumour suppressor gene *INI1*. *INI1* represses cyclin D1 (*CCND1*) gene expression, and the authors found that *Ini1*$^{+/-}$mice develop rhabdoid tumours that have defective *INI1* expression but express *CCND1*. *CCND1* de-repression is therefore important for rhabdoid tumorigenesis.

TELOMERES

XPF nuclease-dependent telomere loss and increased DNA damage in mice overexpressing TRF2 result in premature aging and cancer.

Muñoz, P. *et al*. *Nature Genet*. 4 September 2005 (doi: 10.1038/ng1633)

TRF2, a protein that functions to protect telomeric ends of DNA, paradoxically induces increased rates of skin cancer when overexpressed in mouse skin. The authors show that TRF2 interacts with the ultraviolet light-induced DNA repair nuclease XPF and activates XPF function at telomeres. This leads to disruption of the telomere structure and shortening of the telomeres. In addition, TRF2 is also overexpressed in human tumours, indicating that it can be oncogenic in man.