IN THE NEWS

Stress is good for you? Women who experience increased levels of stress are less likely to develop breast cancer, according to a study by Danish scientists (Nielsen, N. R. *et al.*, *Br. Med. J.* 9 September 2005 (doi: 10.1136/bmj.38547.638183.06)).

Stress can reduce oestrogen production and oestrogen is a known risk factor in breast cancer. Therefore, the authors followed the incidence of breast cancer in the 6,689 women of the Copenhagen City Heart Study who had assessed their own stress levels between 1981 and 1983. They found that 251 women developed breast cancer, and that those who had put themselves in the higher stress category were 40% less at risk.

However, caution has been advised from all quarters. "Even though we find a lower risk of breast cancer among stressed women, let me just emphasize that stress cannot be considered a healthy response", said lead researcher Naja Rod Nielsen of the National Institute of Public Health in Copenhagen (http://www.forbes.com, 9 September 2005).

Previously, stress had been thought to increase the risk of breast cancer. Emma Pennery from Breast Cancer Care, UK, said "We know from talking to women with breast cancer that some of them believe stress to be a contributory factor. This new study is therefore very interesting" (http://news.bbc.co.uk, 9 September 2005).

Summing up, Sarah Rawlings, of Breakthrough Breast Cancer, UK, reminded people that "…maintaining a healthy, balanced lifestyle is important — we know that high stress levels can lead to unhealthy behaviour, which may alter your risk of breast cancer and other diseases" (http://www.guardian.co.uk, 9 September 2005).

Patrick Goymer

METASTASIS

A plausible candidate

Cancer mortality is most often the result of metastasis rather than the primary tumour. Previous studies from Kent Hunter's group demonstrated that the genetic background of the host can influence metastatic efficiency. Now, Hunter and colleagues have identified a candidate gene, *Sipa1*, with an amino-acid polymorphism that influences this process.

The authors previously used a mouse model of breast cancer to investigate the effect of constitutional genetic polymorphism on metastasis. They expressed the polyoma middle-T transgene in various strains of inbred mice and through quantitative trait genetic mapping showed the presence of a putative metastasis efficiency locus (*Mtes1*) on mouse chromosome 19. This chromosome region, which is orthologous to human 11q12–13, harbours a known metastasis suppressor gene *Brms1*. However, this gene has no obvious polymorphisms that influence metastasis and so was discounted from this study.

To identify other potential candidates the authors used a multiple cross-mapping strategy that uses the shared haplotypes in different inbred strains of mice to reduce the number of candidate genes. This reduced the number of potential genes from 500 to 23, which were then prioritized based on their known molecular function. After analysing and discounting several of the genes, the authors found that *Sipa1* had a polymorphism that results in an alanine (as found in the DBA mouse strain) to threonine (as found in the FVB mouse strain) substitution in a protein–protein interaction domain known as a PDZ domain. *Sipa1* is a mitogen-inducible gene that encodes a GTPase activating protein (GAP) that negatively regulates RAP1 and RAP2 GTPases. Human SIPA1 has recently been found to interact with the water channel aquaporin 2 (AQP2), by its PDZ domain, so the authors used AQP2 to see if the alanine to threonine substitution affected this interaction. They found that it did — the FVB allele bound AQP2 less effectively.

What does this mean biologically? Transient transfection assays demonstrated that the FVB allele is less efficient than the DBA allele at reducing the activity of GTP RAP1. AQP2 inhibits this and does so more effectively with the DBA allele. So, cells expressing the FVB allele will have reduced levels of Rap–GTP activity. Reducing the expression of *Sipa1* in cells *in vitro* indicates that SIPA1 modulates the adhesive properties of cells, consistent with its effect on RAP1, which is known

SIGNALLING

Turning off the tap

The mitogen-activated protein kinase (MAPK) signalling pathway activates many important cell processes, such as proliferation, but how are these signals ever turned off? Madhu Macrae *et al.* report that downstream gene targets of the pathway, such as the gene encoding the ephrin receptor A2 (EPHA2), mediate a negative feedback loop that is lost in cancer cells.

In a search for MAPK pathway gene targets, Macrae *et al.* observed that expression of the receptor tyrosine kinase EPHA2 was upregulated fivefold when MAPK signalling was activated. Interestingly, they also found that once EPHA2 is transported to the cell surface, it binds to its ligand, ephrin-A1, and MAPK signalling is downregulated. This seems to be a negative feedback loop that controls MAPK signalling and cell proliferation.

Previous studies had shown that the EPHA2 receptor tyrosine

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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.

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