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