IN THE NEWS

Refined tastes linked to breast cancer

Carbohydrates are the hot topic in dieting circles — the Atkins diet has consigned them to the back of the kitchen cupboard because of their purported role in weight gain. A new report in *Cancer Epidemiology Biomarkers & Prevention* (1 August 2004) now links high carbohydrate intake with breast cancer. "This study raises important questions about high carbohydrate diets", said study co-author Walter Willet (*Scientific American*, 9 August 2004). In fact, this case-control study of the dietary habits of 1,866 Mexican women found that those who acquired more than 62 percent of their calories from carbohydrates were 2.2 times more likely to develop breast cancer.

However, scientists have been quick to warn against premature conclusions: "You cannot make generalizations about 'carbohydrates', because the category contains an enormous variety of foods that have vastly different nutritional profiles and vastly different effects on the body", stated Ritva Butrum on the *American Institute for Cancer Research* web site (6 August 2004).

As the authors themselves remark, "the main carbohydrates these women ate were corn-derived, including tortillas, and soft drinks and bread" (*CNN.com*, 6 August 2004). These highly processed, 'refined' carbohydrates lack the insoluble fibre, vitamin and folate content of 'unrefined' carbohydrate sources such as vegetables and fruits. This distinction is an important one, as the study results also indicate that consumption of insoluble fibre is associated with a reduced risk of breast cancer. So, rather than instigating a blanket policy against all carbohydrates, perhaps we should simply be choosing our carbohydrate sources more carefully.

Oliver Childs

TUMORIGENESIS

Specific non-cooperation

The oncogene *RAS*, which is implicated in the initiation and progression of numerous human cancers, affects many downstream signalling pathways, one of which is inhibited by the tumour suppressor *PTEN*. Therefore, it seems logical that disruption of *PTEN* activity would synergize with activated *RAS* to promote tumour progression. However, Allan Balmain and colleagues now demonstrate a complex and sometimes mutually exclusive relationship between these pathways.

Heritable mutations of *PTEN*, which encodes a dual lipid and protein phosphatase, are evident in patients with the cancer-risk syndrome Cowden disease. These patients develop small tumour-like growths (hamartomas) in several organs including the skin. Heterozygous *Pten*^{+/-} mice also develop skin hamartomas, but unlike in patients with Cowden disease, these do not progress to squamous-cell carcinoma. To identify why *PTEN* loss promotes skin cancer development, Balmain and co-workers treated these mice with the mutagenic drug 7,12-dimethyl benz(*a*)anthracene (DMBA) and the tumour-promoting phorbol ester 12-*O*-tetradecanoylphorbol-13-acetate (TPA).

Treatment of *Pten*^{+/-} and wild-type littermates with both DMBA and TPA resulted in the *Pten*^{+/-} mice developing many more papillomas during the initial stages of treatment than their wild-type counterparts. By 44 weeks post-treatment, carcinomas were evident on all *Pten*^{+/-} animals, but on only 30% of wild-type mice. Molecular examination of the papillomas and carcinomas revealed that *Pten* loss of heterozygosity (LOH) was evident in lesions from the heterozygous mice, but not in similar lesions from the wild-type mice. So, what other mutations drive papilloma and

carcinoma formation in the wild-type mice? Activating mutations in *Hras* are common in the DMBA-initiated skin tumours and the authors found that such mutations were evident in all papillomas and carcinomas from wild-type mice. Interestingly, in *Pten*^{+/-} mice, no *Ras* mutations were evident in *Pten* LOH carcinomas, indicating that complete loss of *PTEN* abrogates the requirement for activation of the *RAS* pathway.

RAS activation or *PTEN* inhibition both result in the activation of *AKT*, leading to cell proliferation and survival. So why don't these two mutations synergize? High levels of *RAS* expression also induce, through other pathways, senescence and/or apoptosis. Accordingly, the authors propose that complete loss of *PTEN* increases proliferation, but this is balanced by *RAS* inhibition of proliferation, making it likely that tumours showing both mutations will have a more indolent phenotype. These results have important implications for the design and use of therapeutic inhibitors of the *RAS* pathway. Inhibiting *RAS* in the rare tumours that might arise through both complete loss of *PTEN* and activation of *RAS* could adversely alter the balance between apoptosis and proliferation, and, obviously, targeting *RAS* in *PTEN*-null tumours would probably have no effect. This illustrates another example where determining the phenotypic status of a tumour could be essential before treatment.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPER Mao, J.-H. et al. Mutually exclusive mutations of the *Pten* and *Ras* pathways in skin tumor progression. *Genes Dev.* **18**, 1800–1805 (2004)

FURTHER READING Downward, J. Targeting *RAS* signalling pathways in cancer therapy. *Nature Rev. Cancer* **3**, 11–22 (2003)

WEB SITE

Allan Balmain's lab: <http://cc.ucsf.edu/balmain/index.html>