IN THE NEWS

Puberty — a cancer risk?

Women who are genetically predisposed to breast cancer often have a family history of the disease, although little is known about the factors that actually initiate tumour development. Now, an epidemiological study of female twins — published in *The New England Journal of Medicine* (5 June 2003) — indicates that puberty might trigger breast cancer in women who are genetically susceptible to this disease.

Ann S. Hamilton and her co-author Thomas M. Mack examined 1,811 pairs of twins — one or both of whom had breast cancer — and looked for associations with age at puberty, menopause and pregnancy. If both twins had breast cancer — assumed to be the hereditary form — they found that the first twin to reach puberty was five times more likely to have developed breast cancer earlier. But for twins with non-hereditary breast cancer — affecting only one twin — the age of puberty onset did not affect risk. So, Hamilton proposes that "…within the general population, there exists a subset of women who may be at increased risk of developing breast cancer from exposure to hormones at the time of puberty" (*Reuters Health*, 5 June 2003).

According to Hamilton, "We still have a lot to learn about breast cancer and the genetic factors that have been identified so far do not account for all the cases of breast cancer thought to be associated with genetic susceptibility" (*Reuters Health*). "This [study] provides some more clues about a different approach in looking for genetic factors" (*New York Times*, 5 June 2003).

Emma Croager

THERAPEUTICS

Cellular powercut

Mitochondria not only provide cells with energy through respiration, they also determine whether they live or die. Specific stimuli can cause the mitochondrial permeability transition pore (MPTP), which spans the mitochondrial inner and outer membrane, to open. This, in turn, leads to release of cytochrome *c* and apoptosis-inducing factor, caspase activation and apoptosis. Now, Philip Hogg and colleagues have investigated whether targeting the MPTP could be a useful strategy for treating cancer.

The trivalent arsenical PAO has previously been found to activate the MPTP by binding to the adenine nucleotide translocator (ANT) component, but is lipophilic and hence toxic to all cultured cells. The authors therefore made a hydrophilic derivative of it — GSAO — and investigated its effects. GSAO was able to trigger swelling of isolated mitochondria, which is characteristic of MPTP opening, and was also found to bind to ANT. It also rapidly localized to mitochondria in both bovine (BAE) and human endothelial cells.

But how does GSAO actually affect these cells? Because calcium is required for GSAO's effect on ANT function, and cell growth is associated with increased mitochondrial calcium, it was possible that only proliferating cells would be sensitive to GSAO, and this was found to be correct. When BAE cells were incubated with GSAO, proliferating, but not quiescent, cells were affected. At low concentrations of GSAO, proliferation was arrested, whereas cell death occurred as GSAO levels increased. The concomitant decrease in cellular levels of ATP and mitochondrial potential, and increase in activated caspase-3 and -7, indicated that apoptosis was induced.

Sub-apoptotic concentrations of GSAO affected respiration, with an increase in the reactive oxygen species superoxide anion. Again, these effects were only found in proliferating cells and could contribute to the cell-cycle arrest, disruption of mitochondrial integrity and apoptosis. Perhaps surprisingly, much higher concentrations of GSAO were needed for a similar effect on tumour cells, compared with endothelial cells, but this doesn't mean that they can't be used in cancer therapy because endothelial cells provide the tumour blood supply. The chick chorioallantoic membrane assay was used to show that GSAO could inhibit angiogenesis, but could it inhibit tumour angiogenesis, and hence tumour growth in mice?

GSAO was administered by subcutaneous injection to either immunocompromised mice or immunocompetent mice with, respectively, human or mouse primary tumours. Tumour growth was inhibited in these mice by up to 90%, and this corresponded with a decrease in blood-vessel density. Although the proliferative rate of the tumour cells was unchecked, the loss of the blood supply caused an increase in apoptosis, which resulted in no net gain in tumour size.

So, although arsenic-derived therapies have been used in medicine since Hippocrates used it to treat ulcers, we still have things to learn about their use in cancer therapy.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Don, A. S. *et al.* A peptide trivalent arsenical inhibits tumor angiogenesis by perturbing mitochondrial function in angiogenic endothelial cells. *Cancer Cell* **3**, 497–509 (2003)

FURTHER READING Zhu, J. *et al.* How acute promyelocytic leukaemia revived arsenic. *Nature Rev. Cancer* **2**, 705–713 (2002)

WEB SITE

Philip Hogg's lab:
http://notes.med.unsw.edu.au/resinterests.nsf/sw/9100604