IN THE NEWS

Caffeine — a new cancer cure?

"Chocolate, cola and coffee could form the basis of new anticancer drugs, scientists believe" (*BBC News*).

Peter Shepherd and colleagues say that the active ingredients in these, caffeine and theophylline, might be effective in fighting cancer because they target phosphatidylinositol 3-kinase (PI3K), a signalling molecule that regulates cell motility and survival. Many pharmaceutical companies are in the process of developing agents that target PI3K as cancer therapeutics.

Researchers expressed the p110δ subunit of PI3K in insect cells, and showed that its lipid-kinase activity could be inhibited by both caffeine and theophylline.

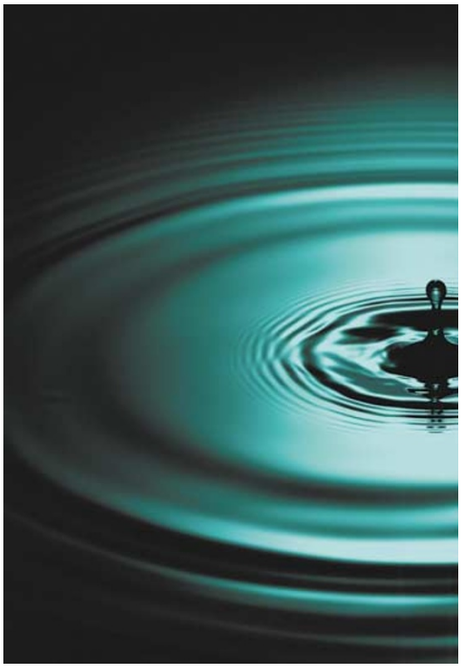
But before you rush off to buy more chocolate, be warned that the study involved "high concentrations of caffeine that would be unhealthy for human use. Caffeine has well-known side effects that make it inappropriate for drug use" (*The Guardian*).

The next step will therefore be to develop compounds that mimic the structure of caffeine without the negative effects.

Emma Greenwood

DNA REPAIR

Small cause, large effect



The Mre11 complex is a multisubunit nuclease that contains three components — Mre11, Rad50 and Nbs1 (known as Xrs2 in yeast). It acts as a sensor of double-stranded DNA breaks, but also has roles in checkpoint signalling and DNA replication. Research into the individual components has been hampered by the fact that null mutants are not viable, but John Petrini and colleagues now present their studies of a functionally impaired *Rad50* mutant. And the results underline the importance of the Mre11 complex in the homeostasis of proliferative tissues.

Reporting in *Genes and Development*, Petrini and co-workers describe the generation of a group of hypomorphic *Rad50* mutants, one of which — $Rad50^{K22M}$ — was used to derive so-called $Rad50^{S/S}$-mutant mice. $Rad50^{S/S}$ mouse-embryo fibroblasts contained wild-type levels of Mre11, Nbs1 and $Rad50^{K22M}$, and these components could assemble functional complexes. However, the $Rad50^{S/S}$ mice showed partial embryonic lethality, and those that survived were only 60% of the weight of their wild-type littermates. By 4–8 weeks of age, the mice showed signs of anaemia, and most of them died by 4 months. Of those that survived up to 7 months, 20% died from a variety of tumours.

As the premature death was associated with severe anaemia, the authors first looked more closely at haematopoietic cells in the $Rad50^{S/S}$ mice. At 2 weeks, there was no difference between wild-type and $Rad50^{S/S}$ mice, but by 4 weeks of age, lymphocytes, macrophages, red blood cells and platelets were severely depleted in the mutant mice. Further experiments indicated that the progressive depletion was due to the failure of haematopoietic stem cells. Moreover, a similar depletion of cells was observed in the spermatogenic lineages of $Rad50^{S/S}$ mice.

Given the age-dependent cellular depletion in the bone marrow and testes, and the fact that those mice that survived longest developed tumours, Petrini and co-workers wondered whether the $Rad50^{K22M}$ mutation might cause genotoxic stress. If this were the case, mutation in the gene that encodes p53 — which is involved in the response to genotoxic stress —

DRUG METABOLISM

Not so innocent

St. John's wort has been used as a medicinal plant for centuries and it has been widely assumed that, as a herbal preparation, it is harmless. However, in 2000, a seminal paper in *The Lancet* showed that the herb lowers plasma concentrations of indinavir, a protease inhibitor that is used to treat patients with HIV. Now, Mathijssen and colleagues, reporting in the 21 August issue of the *Journal of the National Cancer Institute*, show that it also interacts with a drug that is used to treat cancer, mitigating its effects in a similar way.

St. John's wort is thought to alleviate mild to moderate depression and is used widely among cancer patients. However, it is now recognized that the herbal medicine induces drug detoxification pathways — the cytochrome P450 enzyme system and the P-glycoprotein drug transporter — and so interferes with the metabolism of classes of drugs that are substrates for these pathways.

Mathijssen *et al.* conducted a small randomized study of five cancer patients, treating them with irinotecan with or without St. John's wort. Irinotecan is, in part, eliminated by routes that are mediated by an isoform of P450, CYP3A4. The authors report that plasma levels of the active metabolite, SN-38, were decreased by 42% after co-treatment with St. John's wort and that myelosuppression was also greatly reduced — about 60% with irinotecan alone, but less than 8% with the combination. As irinotecan has a narrow therapeutic index, decreased plasma concentrations might be expected to lead to loss of antitumour activity.

The authors conclude that irinotecan and St. John's wort should not be given in combination. They hypothesize that these results are probably representative of other anticancer drugs that are at least partial substrates for CYP3A4, such as etoposide, tamoxifen and paclitaxel. The understanding of drug metabolism and mechanism of action of herbal preparations, and their interactions, are therefore highlighted as key areas of cancer research.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPER Mathijssen, R. H. J. *et al.* Effects of St. John's wort on irinotecan metabolism. *J. Natl Cancer Inst.* **94**, 1247–1249 (2002)