IN THE NEWS

Statins branch out

Statins — better known for their use in cutting cholesterol levels — might also significantly decrease the risk of developing some cancers, according to the results of two studies presented at the 40th annual meeting of the American Society of Clinical Oncology.

"We were interested in the relationship between statin use and prostate cancer because recent research has demonstrated that in a number of tumour types, statins also induce cancer cell death and growth arrest", said Jackilen Shannon, lead researcher for one of the studies (*www.cnn.com*, 7 June 2004). Her team surveyed the records of 430 men who had undergone prostate biopsies and found that the risk of developing prostate cancer was 58% lower for those who had taken statins.

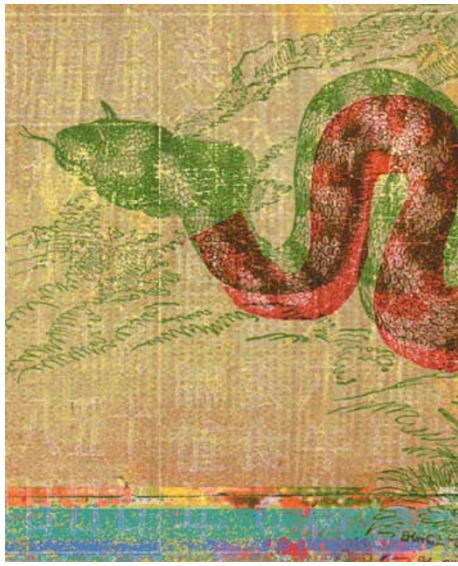
In a second study, 3,342 Israelis were asked about their past use of statins to look for potential effects in preventing colorectal cancer. In those who had taken the drugs for 5 years or more, the chance of developing the disease was cut by 51%. Stephen Gruber, who led the study, thinks that all statins might have similar effects: "Simvastatin and pravastatin are the most commonly used statins in Israel and there was no difference between these two drugs. So this appears to be a class effect" (*www.medscape.com*, 9 June 2004).

However, as Gruber and other experts in the field point out, further studies are needed before statins can be prescribed for cancer prevention. "To say to an otherwise healthy person to go start taking statins right now would be imprudent", commented Monica Morrow of Chicago's Northwestern Memorial Hospital (*New York Times*, 6 June 2004).

Louisa Flintoft

CANCER STEM CELLS

Self-renewal



Evidence that cancer is a stem-cell disease comes mainly from studies of acute myeloid leukaemia (AML) in humans. Most leukaemic cells do not proliferate and the leukaemia must be sustained by rare, self-renewing leukaemic stem cells (LSCs), which, instead of becoming more specialized, retain the ability to divide. John Dick and colleagues have now further characterized LSCs and the LSC hierarchy.

Previous experiments in a non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mouse model showed that normal human stem cells (HSCs) and the cells capable of initiating AML in these mice — SCID leukaemia-initiating cells (SL-ICs) — have many of the same cell differentiation markers. Isolated SL-ICs derived from patients with AML can generate AML grafts in mice that resemble the original patient's disease. The authors hypothesized that LSCs originated from the HSC pool, rather than from a committed clonogenic progenitor pool as previously thought.

Normal HSCs vary in their repopulation capacity — they yield both short- and long-term repopulating cells — so Dick and colleagues investigated whether the LSC pool is similarly complex. Using lentivirus-vector-mediated clonal tracking of patient samples engrafted to NOD/SCID mice, they found that the tracked SL-ICs could be divided into clones that occurred transiently during the engraftment process (short-term SL-ICs) and those that contributed stably throughout the experiment (long-term SL-ICs).

So, what underlies the functional heterogeneity of SL-ICs? It has been suggested that SL-ICs have increased self-renewal capacity compared with normal HSCs. To study this further, the authors used a serial transplantation technique — they injected bone marrow from an engrafted NOD/SCID mouse into two secondary recipient mice and then injected bone marrow from one of the secondary mice into two tertiary mice. SL-ICs were efficiently transduced from mouse to mouse. Some clones from primary mice were present in one or both of the secondary recipients, proving that long-term SL-ICs must have undergone self-renewal in the primary mouse. Of the 169 clones that were unique to the primary mouse, many were not found

TUMOUR SUPPRESSORS

Happy couple

Whereas p53 is a well-studied tumour suppressor that is inactivated in a large percentage of tumours, less is known about its structural and functional homologue p73 — especially as there have been no loss-of-function mutations in this protein associated with cancer. Pier Paolo Pandolfi and colleagues report that the interaction between p73 and the promyelocytic leukaemia (PML) gene product might be an important aspect of tumour suppression.

Like p53, p73 is a transcriptional activator that regulates expression of genes that control cell death, growth arrest and differentiation. Whereas p53 stability is regulated by MDM2-mediated ubiquitylation, the mechanisms that regulate the steady-state levels of p73 are unknown. In studying this molecule, Pandolfi's group found that in human lung carcinoma cells, p73 is also degraded through the ubiquitin–proteasome pathway. Unlike p53, however, p73 phosphorylation by the mitogen-activated protein kinase p38 protects it from degradation. How does this work? Phosphorylation by p38 allowed p73 to interact with the tumour suppressor PML and to co-localize to nuclear bodies, which promoted the stability of p73. The acetyltransferase p300 also co-localizes with PML in nuclear bodies, and Pandolfi's group showed that acetylation by p300 protected p73 from ubiquitylation and degradation. So, PML seems to be an important stabilizer of p73.

What effect does PML-mediated stabilization of p73 have on cells? The authors showed that overexpression of PML increased the ability of p73 to transactivate its gene targets, including *BAX* and *CDKN1A* (which encodes WAF1, also known as p21), and to induce apoptosis. During the pathogenesis of acute promyelocytic leukaemia (APL), a reciprocal translocation causes fusion between *PML* and the retinoic-acid receptor-α (*RARα*) gene, resulting in a dominant-