IN THE NEWS

Second-hand smoke

Children who are exposed to second-hand smoke are more likely than other kids to develop lung cancer later in life, according to a European study of more than 60,000 people who had never smoked.

For those who reported having been in a smoky environment for many hours daily, the risk tripled, but even exposure once a week had significant consequences. The work, published in the *British Medical Journal*, also found that ex-smokers are affected more by passive smoking than non-smokers.

"Passive smoking clearly increases the risk of lung cancer," says Paolo Vineis, author of the research and an epidemiologist at Imperial College London. "People should not smoke in the presence of their children." (www.reuters.co.uk, 28 January 2005)

"This study raises a terrifying spectre for smoking parents", said Robert West of Cancer Research UK. "Exposing their children to cigarette smoke not only damages the child's airways at the time, but may lead to development of lung cancer in later life." (*The Guardian*, UK, 28 January 2005)

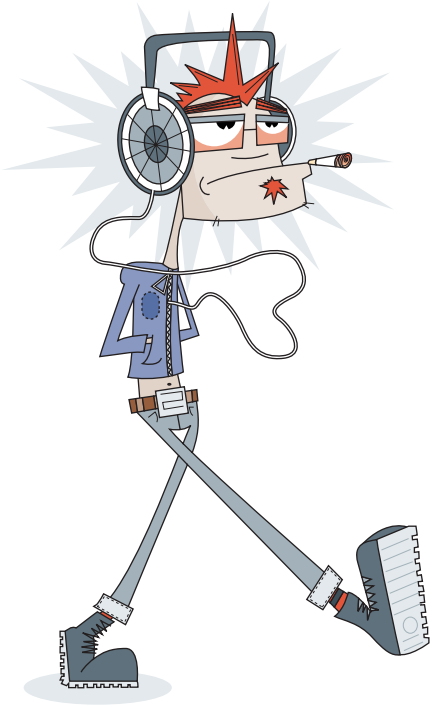
Vineis is unsure whether children are more vulnerable to the effects of smoke, or whether their longer-term exposure increases their risk. However, he points to evidence indicating that young animals are more susceptible to carcinogens (www.abc.net.au/am/content/2005/s1291698.htm, 29 January 2005).

Simon Clark, of the UK smoker's lobby group Forest, says the effects of passive smoking are difficult to measure, most studies being based on "…imprecise recall and anecdotal evidence". He suggests the work is "…a further attempt to demonise smokers for their habit" (http://news.bbc.co.uk/, 28 January 2005).

Helen Dell

EPIGENETICS

A silenced suppressor



Although epigenetic alterations are known to contribute to tumorigenesis, the influence of these alterations on the progression of cancer are particularly hard to study. Can mouse models be used to identify epigenic changes, and are such models relevant to human tumours? A group co-led by Christoph Plass and Michael Caligiuri has developed a model of acute leukaemic transformation that they have used to measure the changes in CpG methylation that occur during the progression of leukaemia. In doing this, they have also uncovered a new, putative tumour suppressor that is epigenetically silenced in human and mouse tumours.

In their mouse model, which overexpresses interleukin-15 (IL-15), 30% of the mice develop acute lymphoblastic leukaemia, and this is always preceeded by benign polyclonal lymphocyte expansion. The researchers followed the changes in DNA-methylation patterns across the genome during the progression of leukaemia using restriction landmark genome scanning (RLGS). This method takes advantage of methylation-sensitive restriction enzymes to compare genomic methylation levels between normal and cancer cell genomes, and to identify methylated sites.

The researchers showed that the genomes of mice with acute leukaemic transformation had substantially higher levels of methylation than mice with benign polyclonal lymphocyte expansion or normal mice. Remarkably, they also found that the sites of increased methylation did not occur at random, but followed consistent patterns. Furthermore, the pattern of methylation observed was similar to the pattern described for corresponding human malignancies.

The researchers went on to clone the RLGS fragments that had increased levels of methylation and

INFLAMMATION

Well connected

The link between inflammation and cancer is well established and a connection between chromatin remodelling and cancer is evident, but, at first glance, a link between all three pathways seems surprising. This is, however, the relationship that has been unearthed by Oleksi Petrenko and Ute Moll through their studies on the pro-inflammatory protein macrophage migration inhibitory factor (MIF).

MIF activates both macrophages and T cells during an inflammatory response and has been previously shown to affect the E2F family of transcription factors. MIF-knockout cells have a reduced capacity to proliferate and to undergo oncogenic transformation, characteristics that are E2F dependent, but the nature of the molecular interaction between MIF and the E2Fs has been unclear.

The capacity of the E2F proteins to activate or repress gene expression is regulated by members of the retinoblastoma (RB) protein family. In concert with the E2Fs, RB can repress gene transcription and suppress entry into S phase by binding to specific gene promoters. Release of the E2Fs from RB family members enables E2F-dependent gene transcription. Importantly though, RB complexes can also regulate chromatin conformation and DNA replication by interacting with components of the DNA-replication complex. Petrenko and Moll used a series of gene expression and deletion experiments to establish that mouse embryonic fibroblasts deficient in MIF expression are not compromised in their capacity to proliferate due to defects in E2F-mediated gene transcription. Instead, these fibroblasts are hampered by the inability of E2F4 to repress the capacity of RB to recruit histone deacetylases that close up the chromatin structure, and by the reduced capacity of E2F4 to promote the recruitment of histone acetyl transferases that open up the DNA and enable DNA replication in the absence of MIF expression.

These findings indicate that chronic inflammation leading to increased MIF expression will antagonize RB-mediated repression of E2F-responsive genes. This might increase the capacity for active E2Fs to initiate DNA replication, enhancing proliferation and tumorigenesis. The *in vivo* role of MIF is now being investigated by the authors.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPER Petrenko, O. & Moll, U. M. Macrophage migration inhibitory factor MIF interferes with the Rb–E2F pathway. *Mol. Cell* **17**, 225–236 (2005)

FURTHER READING Dranoff, G. Cytokines in cancer pathogenesis and cancer therapy. *Nature Rev. Cancer* **4**, 11–22 (2004)

WEB SITE

Ute Moll's lab: http://www.path.sunysb.edu/faculty/umoll/default.htm