TUMOUR-STROMA INTERACTIONS

The causes of crime

Are criminals inherently bad, or are they influenced by living in areas where crime is rife? Yuan Zhu and colleagues have solved the causes of crime for hereditary type 1 neurofibromatosis (NF1): it's the environment that brings out the criminal tendencies of budding neurofibroma cells.

In people with hereditary-cancer-predisposition syndromes, every cell in the body starts off as heterozygous for a tumour suppressor, and cancer is thought to arise as a result of loss of heterozygosity in a single cell. But do the surrounding heterozygous cells influence tumour formation? To find out, the authors used Cre-Lox technology to generate mice that were heterozygous for the *Nf1* tumour suppressor in every cell in the body, but in which Cre-mediated recombination occurred specifically in Schwann cells to generate only a few *Nf1*^{-/-} cells. These mice all developed plexiform neurofibromas — a tumour type that is characteristic of people with NF1 but never occurs sporadically.

One striking feature of the tumours was extensive infiltration of mast cells; does their *Nf1* status also affect tumorigenesis? The authors answered this question by constructing mice that were wild type for *Nf1* in all cell types except the Cre-targeted Schwann cells, which were a mixture of *Nf1*^{+/-} and *Nf1*^{-/-}, depending on whether Cre-mediated recombination had occurred. Remarkably, these mice didn't develop frank tumours, and the small hyperplasias that occurred had no mast-cell infiltration.

So the proximity of *Nf1*^{+/-} cells — possibly mast cells — determines whether *Nf1*^{-/-} Schwann cells develop into tumours. Current therapy for hereditary neurofibromatosis is tough on crime, but this study indicates that therapies that are tough on the causes of crime — for example, drugs that block mast-cell infiltration or cytokine production — might be far more promising. And perhaps other hereditary cancer syndromes will prove to be subject to similar influences.

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References and links

ORIGINAL RESEARCH PAPER Zhu, Y. *et al.* Neurofibromas in NF1: Schwann cell origin and role of tumor environment. *Science* **296**, 920–922 (2002)

CHEMOPREVENTION

Long-distance relationship

Epidemiological studies have consistently associated a high-fat diet with colorectal cancer. A diet that is rich in vitamin D, on the other hand, supposedly has protective effects against this disease. A new study makes a surprising connection between these eating habits.

High-fat diets cause the liver to excrete increased amounts of bile acids. One of these

— lithocholic acid (LCA) — is poorly reabsorbed into the circulation. At high enough concentrations, LCA can induce DNA damage and initiate carcinogenesis. Faecal samples of colorectal cancer patients have a higher concentration of LCA, compared with other bile acids, and LCA injection has been shown to promote colon cancer in animals.

Vitamin D, on the other hand, inhibits colon carcinogenesis induced by either high-fat diets or by LCA treatment. But is there a relationship between Vitamin D and LCA activity? The liver and intestine are cleared of LCA by the catabolic effects of CYP3A, a cytochrome P450 enzyme. CYP3A transcription is regulated by vitamin D, so could this detoxification enzyme be the missing link?

Vitamin D regulates gene expression by binding and activating the vitamin D receptor (VDR) — a ligand-dependent transcriptional activator. Makishima *et al.* found that LCA also binds VDR and activates transcription of target genes. Previous studies reported that the human CYP3A gene contains a VDR response element,

so does LCA treatment activate expression of a factor that mediates its own catabolism?

Treatment of human embryonic kidney cells with either LCA or vitamin D activated VDR-dependent transcription of CYP3A. Furthermore, treatment of mice with either LCA or vitamin D led to increased levels of CYP3A mRNA in intestinal cells. VDR therefore seems to function as a LCA sensor, inducing CYP3A expression when bile acid levels get too high.

But what goes wrong with this feedback mechanism in cancer patients? Makishima *et al.* suggest that a sustained high-fat diet might overwhelm this system, so that LCA no longer activates the VDR and CYP3A is down-regulated. Vitamin D deficiency (rickets) has also been associated with colon cancer, which might be caused by loss of CYP3A expression and LCA accumulation.

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References and links

ORIGINAL RESEARCH PAPER Makishima, M. *et al.* Vitamin D receptor as an intestinal bile acid sensor. *Science* **296**, 1313–1316 (2002)

FURTHER READING Lamprecht, S. A. & Lipkin, M. Cellular mechanisms of calcium and vitamin D in the inhibition of colorectal carcinogenesis. *Ann. NY Acad. Sci.* **952**, 73–87 (2001)

WEB SITE

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