CARCINOGENESIS

Missing mismatch repair

Miroslav Radman and Robert Wagner

TWO decades of research with bacterial systems have revealed a highly sophisticated enzymatic DNA-editing system that controls the precision of DNA replication and recombination through the detection of unpaired and mispaired bases in DNA (see ref. 1 for review). Predictions that a malfunction of this repair system in humans should accelerate carcinogenesis have now proved to be correct — papers in *Cell*[2–4] describe the discovery of a gene that is apparently involved in mismatch repair and which, when mutant, predisposes its bearer to several common cancers.

Mutations in this gene, called *HNPCC* (for hereditary non-polyposis colon cancer) or human *MSH2* (for *MutS* homologue 2), occur in about 0.5 per cent of the population and apparently increase dramatically the risk of colon, ovarian, uterine and kidney cancers. The gene shares considerable homology with the bacterial *mutS* and yeast *MSH2* genes, which are both involved in the earliest stages of mismatch repair. Indeed, previous work with bacteria and yeast made the search for the human *MSH2* gene serendipitously straightforward; one group[2] isolated it by using primers in the polymerase chain reaction that had been employed in the identification of *mutS* homologues in yeast.

The idea that HNPCC might be caused by defective mismatch repair came from findings that HNPCC tumour cells show a characteristic size instability in simple sequence repeats (the 'accordion effect')[2,3]. These sequence blocks, most often di- or trinucleotide repeats, are notoriously 'slippery' for the DNA replication machinery such that unpaired bases are occasionally left in the parental or newly synthesized strand. These small deletions or insertions are normally rectified by the mismatch repair system. Although the origin of simple sequence repeat blocks has yet to be explained, it may be that they are 'scars' left from the repair of broken chromosomes when recombinational repair could not operate. Repair may have involved the addition of such sequences to the broken ends of chromosomes, followed by annealing to rejoin the fragments.

Perhaps the strongest evidence that the mutation responsible for HNPCC affects mismatch repair comes from the finding that extracts of HNPCC tumour cells are deficient in such repair *in vitro*[4]. However, mismatch repair levels in HNPCC germ-line cells heterozygous for a mutation in the human *MSH2* gene were indistinguishable from those in normal cells. The authors propose that some regulatory event may inactivate the functional human *MSH2* gene in tumour cells[2,3], but it seems as likely that a second mutation may inactivate the functional copy of the gene. A second *MSH2* mutation was found in one HNPCC tumour (the system used may not have allowed detection of every *MSH2* mutation). Such mutational inactivation may, in fact, be an obligate step in HNPCC tumorigenesis.

The predisposition to cancer associated with the HNPCC syndrome may be the result of a greatly increased frequency of specific oncogenic mutations caused by a generalized mutator effect in homozygous *MSH2* mutant cells. But the apparent absence of homozygous *MSH2* mutations in the germ-line cells of HNPCC patients may indicate that such homozygosity, and the attendant high level of mutation, is lethal. If so, survival of somatic cells homozygous for *MSH2* mutations may require some specific oncogenic alteration. This would explain the tissue specificity of HNPCC tumours, because not every oncogenic alteration may allow cell survival. Perhaps the relatively good prognosis for patients with HNPCC colon tumours (and sporadic tumours with an HNPCC phenotype) reflects the relatively low fitness of such tumour cells resulting from the mutator phenotype. The deleterious effect of such a potent mutator may also result in the strong selection for *MSH2* revertants or suppressors during the later stages of tumour progression, or during the establishment of tumour cell lines, so that the extent of mismatch repair deficiency in human carcinogenesis may be underestimated.

HNPCC tumours seem to be chromosomally more stable than other types of tumours, although bacterial *mutS* mutants exhibit considerable chromosomal instability as a result of recombination between diverged repeats. But bacteria appear to have only one MutS function, whereas in eukaryotes *MSH* has different roles, so *MSH2* may be primarily a replication editor and *MSH3* a recombination editor. Perhaps some common cancers and cancer-prone syndromes with hyper-recombination phenotypes involve *MSH3* mutations. □

Miroslav Radman and Robert Wagner are in the Laboratory of Mutagenesis, Institute Jacques Monod, CNRS/University Paris 7, 2 Place Jussieu, Tour 43, 75251 Paris Cedex 05, France.

1. Radman, M. & Wagner, R. *Chromosoma* **102**, 369–373 (1993).
2. Fishel, R. *et al. Cell* **75**, 1027–1038 (1993).
3. Leach, F. S. *et al. Cell* **75**, 1215–1225 (1993).
4. Parsons, R. *et al. Cell* **75**, 1227–1236 (1993).

DAEDALUS

Geolubrication

WHEREVER two continental plates are moving against each other, earthquakes are a major worry. The plate edges bind together, so that stress slowly builds up at their interface. When the stressed joint finally fails, the two edges suddenly shear past each other, releasing enough energy to devastate the land above. The edges then bind together once more and the process starts again, in the most dramatic example of stick–slip friction known to science.

So Daedalus wants to lubricate the interface. The plate edges would then glide smoothly past each other, dissipating their energy slowly and undramatically. Lubricating oil would be useless at the temperatures and pressures around 100 km down, where the plates clash. A meltable solid such as glass or salt would be a better high-pressure lubricant for the hot rocks. But even the best drilling methods can hardly penetrate 10 km into the Earth. How to get the lubricant down there?

Daedalus's bold plan is to lubricate the fault lines of the Earth with high-level radioactive waste, and to let it melt its way down to the fault. All over the world, large amounts of high-level waste are sitting in water-cooled tanks, awaiting the day when it is cool enough to bury. Bury the waste now, says Daedalus, and bury it in boreholes immediately above the more threatening of the seismogenic faults of the world. Many nuclear power plants have been thoughtfully sited in these earthquake zones already, simplifying the transport problems. Once in place at the bottom of a borehole, the waste will heat up the surrounding rock, and melt its way downwards. Ultimately it will reach the fault, where it will raise the local temperature by hundreds of degrees. The shear strength of rock drops dramatically with temperature, so the waste will create a local weak spot in the stressed fault. A line of boreholes would create many such weak spots. Instead of generating huge and damaging earthquakes at long intervals, the fault would grumble its way through many small, harmless slips, as each weak spot relaxed its own local stress.

Environmentalists should welcome the scheme. At one stroke it gets rid of a dangerous material and reduces the threat of earthquakes. But timing would be tricky. Lubricating a highly stressed fault would simply precipitate an earthquake. You would have to wait until an earthquake had just occurred, and then lubricate the momentarily relaxed fault. Stress would no longer build up in it, and the lethal succession of earthquakes would cease.

David Jones