could be expected to lessen the severity of the observed defects. And this is just what the authors saw. For example, macrophages were increased threefold and T cells 3–20-fold in *Trp53*$^{-/-}$ *Rad50*$^{S/S}$ mice compared with *Rad50*$^{S/S}$ mice. Moreover, *Trp53*$^{-/-}$ *Rad50*$^{S/S}$ mice developed tumours and died much earlier than *Trp53*$^{-/-}$ mice alone, again supporting the idea that the *Rad50*^{K22M} mutation causes genotoxic stress.

A final confirmation came when the authors analysed various indices of genotoxic stress. Levels of phosphorylated histone H2AX — which correlate with levels of DNA damage — were the same in unirradiated *Rad50*$^{S/S}$ cells as in irradiated wild-type cells. And karyotype analyses of *Rad50*$^{S/S}$ thymic lymphoma cells revealed increased chromosome breaks and rearrangements (including telomeric short-arm fusions) compared with wild-type cells. So, as the authors conclude, "the data clearly indicate that the Mre11 complex exerts a profound influence on homeostasis in mammalian tissues, even when its checkpoint and DNA recombination functions are not overtly impaired".

Alison Mitchell
Editor, Nature Reviews Molecular Cell Biology

References and links

ORIGINAL RESEARCH PAPER Bender, C. F. *et al*. Cancer predisposition and hematopoietic failure in *Rad50*$^{S/S}$ mice. *Genes Dev*. **16**, 2237–2251 (2002)
FURTHER READING D'Amours, D. & Jackson, S. P. The Mre11 complex: at the crossroads of DNA repair and checkpoint signalling. *Nature Rev. Mol. Cell Biol*. **3**, 317–327 (2002)
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WEB SITE
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IN BRIEF

GENETIC SCREENING

High-throughput retroviral tagging to identify components of specific signalling pathways in cancer.

Mikkers, H. *et al. Nature Genet.* **32**, 153–159 (2002)

This paper, together with two more letters in the September issue of *Nature Genetics*, describes the first *in vivo* mammalian genetic screens used to identify genes underlying human cancer. Mikkers *et al*. show the power of using retroviral insertional mutagenesis, together with the complete mouse genome sequence, by identifying genes that can substitute for *Pim1* and *Pim2* in lymphomagenesis. This strategy is the mammalian equivalent of the powerful yeast, *D. melanogaster* and *C. elegans* genetic screens.

ONCOGENES

RAF/*RAS* oncogenes and mismatch-repair status.

Rajagopalan, H. *et al*. *Nature* **418**, 934 (2002)

Activating mutations in a member of the RAF family, *BRAF*, have been found in a high proportion of melanomas and in other cancers. Rajagopalan *et al*. report that *BRAF* mutations in colorectal cancers occur only in tumours that do not carry mutations in *KRAS*, and that mutations in *BRAF* are linked to the ability of these tumours to repair mismatch bases in DNA. These results indicate that mutations in *BRAF* and *KRAS* exert equivalent effects in tumorigenesis.

EPIDEMIOLOGY

On the use of familial aggregation in population-based case probands for calculating penetrance.

Begg, C. B. *J. Natl Cancer Inst*. **94**, 1221–1226 (2002)

High-risk families with multiple cases of breast cancer or case probands are often used in population-based penetrance studies of *BRCA1* and *BRCA2* mutations. Begg reviews eight published studies and shows that penetrance estimates from case proband studies are biased towards increased risk. This paper highlights the need to improve the methods that are used to predict cancer risk.

ONCOGENES

Distinct requirements for *Ras* oncogenesis in human versus mouse cells.

Hamad, N. M. *et al*. *Genes Dev*. **16**, 2045–2057 (2002)

Oncogenic Ras stimulates three main classes of effector proteins — Rafs, PI3-kinase and RalGEFs — with Rafs generally being the most potent at transforming mouse cells. However, using oncogenic *Ras* mutants, Hamad *et al*. found that RalGEF is sufficient for Ras transformation in human cells. The findings indicate that signal-transduction biochemistry studies in mice might have to be revisited to assess applicability to humans, and that RalGEF could be a promising target for anticancer therapies.