CANCER GENETICS

It doesn't always take two

It takes two, so the song goes, and this is often so for genes. Recessive disorders, for example, require both copies of a gene to be lost. However, some diseases and traits can occur when one wild-type allele is still present. Now, two papers report that a *BLM* gene mutation — which, when homozygous, causes the recessive, cancer-predisposition disease Bloom syndrome (BS) — surprisingly predisposes mice and humans to intestinal cancer when haploinsufficient. Because BLM is a helicase that maintains genome stability, these papers highlight the crucial role of genome instability in both cancer pathogenesis and predisposition.

Heppner Goss *et al*. generated a new BS mouse model by targeting the mouse *Blm* gene with a mutation (Blm^{Cin}) that causes a premature truncation. This mutation acts as a null allele and simulates a founder mutation (BLM^{Ash}) that is present in 1% of Ashkenazi Jews.

The authors used two approaches to investigate the effect of *Blm* haploinsufficiency on tumorigenesis in these mice. First, they injected them with murine leukaemia virus (MLV). Both wild-type and $Blm^{Cin/+}$ mice developed metastatic T-cell lymphoma on exposure to this virus, but mutant mice died earlier, despite tumour morphology being the same in both sets of mice. Next, they crossed $Blm^{Cin/+}$ mice to Apc^{Min} mice — a mouse model of familial adenomatous polyposis coli. (The *Min* mutant was chosen because the gastrointestinal (GI) tract is where cancer commonly develops in BS patients.) Double heterozygous mutant mice developed twice as many GI adenomas as did $Apc^{Min}/Blm^{+/+}$ animals, and many $Apc^{Min}/Blm^{+/-}$ mice had tumours with high-grade dysplasia. Tumours in both $Apc^{Min}/Blm^{+/+}$ and $Apc^{Min}/Blm^{+/-}$ also showed *Apc* loss of heterozygosity (LOH). In both mutants, *Apc* LOH seemed to occur predominantly through the loss of chromosome 18, where *Apc* is located. However, in some $Apc^{Min}/Blm^{+/-}$ tumours, *Apc* loss also occurred through somatic recombination. No neoplasias were seen outside the GI tract, and *Blm* LOH was not evident in tumour tissue.

The results of Gruber *et al*. lend further weight to these findings. In a study of 1,244 Ashkenazi Jews with colorectal cancer (CRC), those with CRC were found to be twice as likely to carry the BLM^{Ash} allele as those Ashkenazi Jews without CRC. These findings, and those of Heppner Goss *et al*., indicate that BLM haploinsufficiency might compromise the maintenance of genomic integrity, perhaps by causing an increased mutation rate in heterozygous cells, so speeding their progression to tumorigenesis.

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References and links

ORIGINAL RESEARCH PAPERS Heppner Goss, K. *et al*. Enhanced tumour formation in mice heterozygous for *Blm* mutation. *Science* **297**, 2051–2053 (2002) | Gruber, S. B. *et al*. *BLM* heterozygosity and the risk of colorectal cancer. *Science* **297**, 2013 (2002)

WEB SITE

Joanna Groden's lab: http://www.hhmi.org/research/investigators/groden.html