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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.

Jane Alfred

Editor, Nature Reviews Genetics

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>

