Efficient identification of candidate tumor suppressor genes using retroviral insertional mutagenesis in mice with genomic instability

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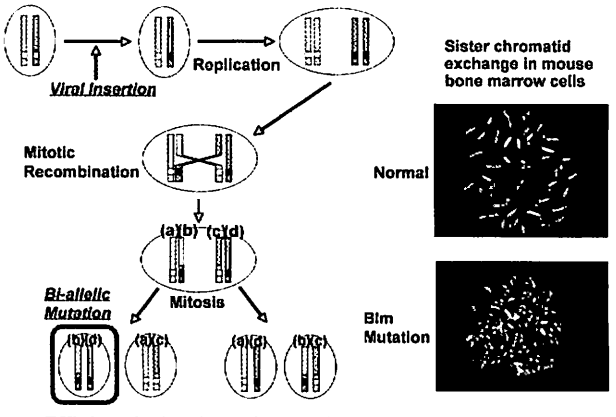
Retroviral insertional mutagenesis in mice is one of the important strategies for efficient and high-throughput identification of cancer-causing genes. However, there was one limitation to the use of retroviral tagging for gene discovery. Viral integrations primarily identify proto-oncogenes rather than tumor suppressor genes. This is presumably because a single retroviral induced mutation is sufficient to activate an oncogene and initiate a tumor, while two mutations are needed to inactivate a tumor suppressor gene. To overcome this limitation, we utilized the mice that have genomic instability so that viral integration in one allele could be efficiently rendered homozygous. Mice carrying mutations in the Bloom syndrome (Blm) gene have a high frequency of spontaneous mitotic recombination and loss of heterozygosity (LOH). Thus, MuLV (murine leukemia virus)-infected mice with Blm mutation are thought to be more apt to carry retroviral integrations in tumor suppressor genes.

In fact, the MuLV-infected Blm mutant mice showed earlier onset of lymphoma than Blm wild type mice. Using the high-throughput retroviral tagging, we have isolated so far more than 150 candidate disease genes including the genes whose coding regions are consistently disrupted by multiple retroviral integrations. Most of the 'disrupted' candidate genes showed the evidences of bi-allelic mutations in the tumors. Those genes included the known genes that were reported to function as tumor suppressors (Rb family, Cdk inhibitors etc.), and also novel interesting candidate genes (JmjC domain family). Thus, the MuLV-infected mouse with genomic instability is a useful animal model that makes us enable to isolate candidate tumor suppressor genes efficiently.



Efficient induction of bi-allelic mutations in retrovirus-infected Bloom syndrome model mice