Connecting cancer genes

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A large genetic study in mice has identified hundreds of genes involved in the development of cancer by examining the DNA of more than 500 lymphomas to find the cancer causing mutations.

The study found just over 10,000 mutations in total, which together implicate almost 350 regions in the mouse genome in cancer formation. 50 of these regions correspond to genes known to be involved in human cancers while the other regions were novel, adding to our picture of the complex set of diseases that are cancers.

The results were obtained by an international consortium of researchers, led by Drs Anton Berns, Maarten van Lohuizen and Lodewyk Wessels from the Netherlands Cancer Institute (NKI), and Dr David Adams, Experimental Cancer Genetics, from the Wellcome Trust Sanger Institute and are published in *Cell*.

The team used a virus called the murine leukaemia virus to produce mutations in cancer genes: the virus targets white blood cells, resulting in lymphoma, a common tumour of the blood system.

"Human cancers are generally thought to be formed by the stepwise accumulation of mutations that disrupt genes within a cell, and the virus mimics this process as it inserts itself into the mouse genome," explains Dr David Adams, senior author on the paper. "The virus then acts as a 'tag', allowing us to identify where it has integrated and which gene or genes have been disrupted.

"By finding an average of 20 mutations from each of the 500 tumours, not only did we find many new cancer genes, but we can see which genes work together in the same cell to transform it into a lymphoma." Said Dr. Jaap Kool, co-first author on the paper from the NKI.

The infected mouse lines carried mutations in genes called p53 and p19, which are known to suppress the development of cancer and are among the most commonly mutated genes in human cancers. The team were able to identify a rich set of novel genes implicated in cancer, including additional genes that might act to suppress tumour development, which are not readily detected in most surveys.

Human cancer cells frequently contain many mutations that are not involved in the development of cancer – do not drive cancer development – but are produced by increased mutation rates in cancer cells and are 'passengers'. Discerning which are driver and which are passenger mutations is a challenge for human cancer gene studies.

"The benefit of our system in the mouse is that, unlike human tumours, which usually contain many different types of genetic alternations, the causal mutations that initiate these tumours in mice can be easily identified and studied," explains Dr Adams, "These studies are complementary to and enrich the analysis of human cancers."

The project was made possible by the Sanger Institute's high-throughput sequencing and computational resources, which allowed the team to identify new potential cancer genes in the mouse. By comparing their data to genome-wide human cancer datasets generated by the Sanger Institutes' Cancer Genome Project, they could show that at some of the of the newly identified genes were potentially relevant to human cancer formation.

The team are currently carrying out other cancer screens using viruses

and additional methods to disrupt cancer genes. These screens are searching for genes and gene interactions in the formation of bowel, lymphoid and breast cancers.

Source: Wellcome Trust Sanger Institute