The gene processes that drive acute myeloid leukaemia

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Researchers have described how the most common gene mutation found in acute myeloid leukaemia starts the process of cancer development and how it can cooperate with a well-defined group of other mutations to cause full-blown leukaemia.

The researchers suggest that three critical steps are required to transform normal blood cells into leukaemic ones, each subverting a different cellular process. By charting the route towards cancer, the study identifies processes that might serve as targets for new treatments to halt the cancer's development in its tracks and even reverse it.

Acute myeloid leukaemia is a rare but devastating disease, which can take hold in a matter of just days or weeks. Every year, 2,000 adults in the UK are diagnosed with acute myeloid leukaemia: only about three in ten adults survive for five years.

In recent years researchers have identified a number of genes involved in the development of acute myeloid leukaemia. The most common is NPM1, a gene with many known functions. The new research shows that mutation in NPM1 is a key event in the development of a large proportion of cases of acute myeloid leukaemia and that it exerts its effect by helping cells to self-renew, a process that can be thought of as the first step towards leukaemia. The team also identify two subsequent events that are required to cooperate with NPM1 to drive cells to become cancerous.

"We have used targeted gene disruption to look at the way acute myeloid leukaemia develops in mice," says Dr George Vassiliou, Consultant Haematologist, cancer researcher and first author on the study from the Wellcome Trust Sanger Institute, "and have found critical steps that take place when the cancer develops. Identifying the biological steps in turn means we can look for new drugs to reverse the process."

The team started by developing a strain of mice that contained a 'control switch', that allowed the researchers to turn on mutations in the acute myeloid leukaemia gene Npm1.

When they switched on the Npm1mutations in the mice, the team saw that the mutation gave normal blood cells the ability to renew themselves more efficiently and boosted the production of a group of blood cells known as myeloid cells.

However, the team found that, despite mutations in this most frequently mutated leukaemia gene, only three out of every ten mice developed leukaemia and the disease developed only after a long time. The results suggest that the Npm1 mutation can start the leukaemic process but cannot, on its own, drive cells towards cancer.

To try to find the events that conspire to cause acute myeloid leukaemia, the team studied the same mice using a technique called 'insertional mutagenesis', in which tagged DNA is inserted into the mouse genome. Using this specialised technique, researchers can accelerate the development of cancers by causing mutations in genes at random, while at the same time 'tagging' the altered genes, making them easy to identify. When the process hits a gene that drives cancer, it leads to tumours in the mice - the team can then use the tag to see which genes were mutated.

By applying the technique to the mice that already had the Npm1

mutation, the team could search for additional genes that work with Npm1 to promote cancer development. As they had anticipated, the team found that more than four in five of these mice rapidly developed acute myeloid leukaemia.

Looking at the new gene mutations, the team identified three distinct processes that the mutated genes seemed to govern. While the team were able to confirm the role of Npm1 mutations in cellular self-renewal, they found other genes, which were routinely involved in one of two other processes. The first group of genes controlled the way that cells proliferate; the second group played a role in orchestrating the genetic activity in the cells.

"In our mice two or, in most cases, all three of these cellular processes were subverted," says Allan Bradley, from the Sanger Institute and senior author on the paper. "In concert, these genetic mutations, which were concentrated on a tiny number of genes, transformed normal to leukaemic cells. These findings give a much clearer view of how this difficult cancer develops and propagates.

"Our studies in the mouse, using novel methods to alter genes, complement the work of human cancer genomics. Together, we can more rapidly give biological context about just how genetic changes can cause the disease."

Researchers can now look in closer detail at the processes identified and divide them into complementary groups, a crucial first step to developing effective anti-cancer drugs.

"The two main therapeutic options for acute myeloid leukaemia have remained unchanged for more than 20 years," says Brian Huntly, MRC Senior Clinical Fellow at the University of Cambridge. "Although our ability to better use existing agents has led to modest improvements in

patient survival, we desperately need new treatments to combat this disease and this relies heavily on us understanding the biological processes behind leukaemia development.

More information: Vassiliou GS, et al. (2011) Mutant nucleophosmin and cooperating pathways drive leukemia initiation and progression in mice. *Nature Genetics*. Published online at doi: 10.1038/ng.796