A new target for lymphoma therapy

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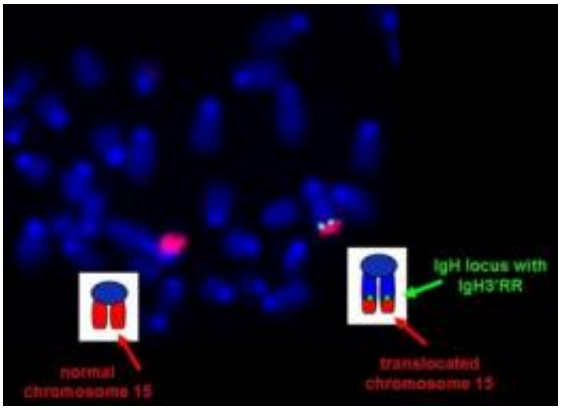

This image shows how the movement of genes, or translocation, is responsible for cancers that arise from mature B-cells, such as Burkitt's lymphoma. Chromosome 15 (in red) contains c-myc, a known oncogene. If a part of chromosome 15 becomes connected to the IgH region of the DNA, the gene regulator IgH3'RR (green) can over-activate c-myc, leading to tumors. Credit: Courtesy of Monica Gostissa, PhD, PCMM/IDI

Researchers at the Program in Cellular and Molecular Medicine and the Immune Disease Institute at Children's Hospital Boston (PCMM/IDI) have found a link between a common mutation that can lead to cancer and a distant gene regulator that enhances its activity. Discovery of this relationship could lead to drugs targeting B-cell lymphomas, including Burkitt's lymphoma, an aggressive cancer in children, as well as multiple myelomas and other blood-related cancers.

Lymphomas often originate in B cells, the same cells that produce

antibodies to help fight infections. A B cell can become cancerous if a gene known as c-myc leaps to another section of DNA (the IgH region, responsible for building antibodies), fuses with it, and somehow becomes over-activated. Scientists have wondered for years how this oncogenic activation occurs, in particular what component in the IgH region activates c-myc. The new study, published in the Dec. 10 issue of *Nature*, identifies this regulatory component, and marks the first time researchers are able to understand how this movement of genes, or "chromosomal translocation," can hijack a B cell's operation badly enough to lead to cancer.

"IgH-to-myc translocation is the classic example of activation of an oncogene in cancer," says Frederick Alt, PhD, scientific director of PCMM/IDI and senior author of the study. "But nobody really understood how it works."

Aberrant DNA translocations can occur during two different stages of a B cell's development: during a process known as VDJ recombination, when a progenitor B cell creates an antibody to fight a specific pathogen, or during class switch recombination, when a mature B cell gives its antibody a different strategy to fight infection (changing from an IgM to an IgG antibody, for example). Based on their past research , Alt and his colleagues decided to focus on one part of the IgH region called IgH 3' regulatory region (IgH3'RR). They had already shown IgH3'RR to be a far-reaching gene regulator that enhances the transcription of neighboring genes in the IgH region during class switch recombination.

To investigate the relationship between IgH3'RR and lymphoma, the team, led by Alt and first author Monica Gostissa, PhD, of PCMM/IDI, deleted the IgH3'RR in a line of mutant mice previously generated in the Alt lab. These mice routinely develop a B-cell lymphoma in which c-myc is translocated to the IgH region of the DNA. However, without IgH3'RR, mature B cells did not become cancerous, suggesting that

mature B cells -- from which most human lymphomas originate -- need IgH3'RR in order to develop into lymphoma.

"The study shows that the IgH3'RR is a key element for turning on the cancer-causing activity of c-myc after it is translocated to the IgH locus," says Alt. He noted that the study also shows that the cancer-causing activity of the IgH3'RR on c-myc can extend over surprisingly long chromosomal distances.

The study suggests the IgH3'RR as a new target for arresting lymphomas and other blood-related cancers that arise from mature B cells. Though inactivating IgH3'RR can impair a B cell's versatility in creating different classes of antibodies, it would not leave a patient immune-deficient because the B cells would retain some of their activity, says Gostissa. Furthermore, such a treatment would be reversible.

The next step is for the researchers to see what eliminating IgH3'RR will do to existing tumors, and then to create a cell-based drug screening assay to test for possible IgH3'RR inhibitors.

More information: Monica Gostissa, Catherine T. Yan, Julia M. Bianco, Michel Cogne, Eric Pinaud and Frederick W. Alt. "Long-range Oncogenic Activation of IgH/c-myc Translocations by the IgH 3' Regulatory Region." *Nature*. Dec. 10, 2009.

Source: Children's Hospital Boston (news : web)