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An enzyme that mutates antibodies also targets a cancer-causing oncogene

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The human immune system is in a perpetual state of self-experimentation. It expertly mutates and shuffles the DNA of its own cells to evolve new defenses against the vast array of microbes that try to invade our bodies. But when the genetic experiment goes awry, the result can be a deadly cancer.

Now, Rockefeller University scientists have discovered that the same enzyme that enables the immune system's defensive creativity is also responsible for a particular genetic malfunction — a translocation of one piece of DNA to the wrong chromosome — that causes Burkitt's lymphoma. The findings, to be published in the December 12 edition of *Cell*, suggest the enzyme, called activation-induced deaminase (AID), is probably involved in a broader range of cancers as well.

"We strongly suspect that many or all of the translocations of human lymphomas in mature B cells are the product of this enzyme," says Michel C. Nussenzweig, Sherman Fairchild Professor and head of the Laboratory of Molecular Immunology. "And there's more and more data to show that it may be involved in other cancers as well. It's been identified in stomach cancers, for instance."

A very specific translocation causes Burkitt's lymphoma, a cancer that plagues children in equatorial Africa. It involves a DNA break in an immune system antibody gene and the much more rare break in a cancer-promoting gene called c-myc. Previous work had shown that AID was responsible for breaking antibody genes but not c-myc. In fact, scientists

thought a host of other factors might be involved in the c-myc break, but AID had been all but ruled out.

Despite the prior studies, Davide Robbiani, a research associate in Nussenzweig's lab and a Leukemia and Lymphoma Society Fellow, believed AID was the culprit. To prove it, he and his colleagues started by deleting the promoter region of the c-myc oncogene, rendering the gene inactive, in a mutant line of mice. By looking for — and not finding — the specific translocation in these mice, he showed that c-myc had to be active in order for its DNA break to take place.

He then inserted a DNA tag into the mouse genome that allowed him to induce a break at the c-myc gene, which occurs only very rarely if left to its own devices. He found that his artificially created breaks were comparable in most every way to the breaks caused by AID, but when he looked for the translocation in mice that didn't produce this enzyme, they were nowhere to be found.

"This is a definitive study," says Nussenzweig, who is also a Howard Hughes Medical Institute investigator. "We now know AID is causing damage in other parts of the genome, not just in antibody genes."

Because AID normally enables the genetic experimentation that's critical to an effective immune response, shutting it down even to fight cancer is perilous. "As a general rule, you wouldn't want to give an AID inhibitor to everyone because immune systems would not be working so well," Nussenzweig says. Still, a pharmaceutical AID inhibitor, if developed, might prove useful in treating certain tumors that are expressions of this powerful gene mutator.

The next step is to figure out exactly how AID works and identify other genetic sites where AID is active. "We are now developing the tools to do exactly that," Robbiani says.

Source: Rockefeller University