

Researchers identify DNA mutation that occurs at beginning point of T-cell lymphoma

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Researchers at the Keck School of Medicine of the University of Southern California (USC) have identified a key mechanism that causes chromosomes within blood cells to break—an occurrence that marks the first step in the development of human lymphoma.

The study provides researchers with the clearest insight yet into why these breakages—called chromosomal translocations—occur at a specific points in the chromosome, says principal investigator Michael R. Lieber, M.D., Ph.D., Rita and Edward Polusky Professor in Basic Cancer Research at the Keck School of Medicine.

The study appears as the featured cover article in the June 12 issue of the journal *Molecular Cell*. The study is the second led by Lieber to appear on the cover of a Cell journal in the past six months.

"The new findings go to the heart of why cancers begin. This is an opportunity to see the very beginning step of human lymphoma," Lieber says. "With this information, we can now begin to look at ways to interfere with this process in order to stop the lymphoma and to develop more targeted therapies for treatment."

There are two types of lymphoma: B cell lymphomas and T cell lymphomas. Both B cells and T cells perform vital functions in the immune system by creating antibodies and destroying virus-infected cells. However, the beginning point, or inception, of most human lymphomas occurs when two [chromosomes](#) break and the resulting

fragments are reassembled in an exchange.

Researchers specifically looked at T cell acute lymphoblastic lymphomas (ALL). ALL accounts for half of all childhood cancers under the age of five, and T cell ALL represents about 10 percent of ALL. The USC scientists identified a specific enzyme known as the RAG complex that occasionally cuts the chromosome at an off-target site, causing lymphocyte (blood) cells to proliferate uncontrollably.

They showed that the RAG complex selects the wrong target largely because the proteins in which the wrong chromosome is wrapped (called chromatin) lures the RAG complex to the wrong site.

"The immune system is very good at its job," Lieber says. "More than ninety-nine percent of the time it gets it right, but it only takes one mistake in one of a hundred million [cells](#) to cause a problem. "

The paper follows a similar study, published in the December issue of the journal Cell, in which Lieber and colleagues determined how the most common chromosomal translocation in B cell lymphoma occurs. Researchers at USC have been working for many years to understand the underlying mechanisms that cause blood cancers.

"The goal is to understand translocations in various different forms of [lymphoma](#)," Lieber says. "The two papers cover more than half of all human lymphomas. That represents a major step forward in understanding this disease."

Source: University of Southern California ([news](#) : [web](#))

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