Researchers identify key mechanism that occurs at the inception point of many human lymphomas

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Researchers at the Keck School of Medicine of the University of Southern California (USC) have explained how certain key mutations occur in human lymphomas—a process that has, until now, remained a mystery.

The findings of the study, published in the Dec. 12 issue of the journal Cell, will have a significant impact on future study of how human lymphoma occurs.

Chromosomal translocations, in which segments of DNA are moved around the genome, are DNA mutations frequently found in blood cancers. They occur when two chromosomes break and the resulting fragments are reassembled in an exchange, says Michael R. Lieber, M.D/Ph.D., Rita and Edward Polusky Professor in Basic Cancer Research at the Keck School of Medicine and the study's principal investigator.

"Our study provides new insight into understanding how these translocations occur and describes a key and informative fingerprint at these chromosomal break sites," Lieber says.

The fingerprint had been overlooked for decades because chromosomal break sites typically suffer damage that obscures the fingerprint, he says.

"The precise steps leading to this pathologic rearrangement process—especially how the DNA is broken—have been a mystery for 25 years, in large part because these events occur long before the cancer becomes clinically apparent, and conventional experimental techniques do not reflect the process as it occurs naturally," says Albert Tsai, M.D/ Ph.D. candidate at the Keck School of Medicine and the lead author of the study.

Expanding on previous work done at the Keck School and USC Norris Comprehensive Cancer Center and elsewhere, researchers studied patient tumor chromosomal translocations to gain an important clue as to how the most common lymphomas are caused. The study demonstrated that these breaks are focused at CpG sites, short special sequences in the genome, within restricted breakage zones. The CpG localization occurs in early B-cells, but not in translocations before or after that stage.

Their findings implicated roles for two enzymes—AID and RAG complex—which are normally present in lymphocytes and that function to diversify the immune system to defend against attack by bacteria, viruses and parasites, Lieber says. The diversification process involves altering the DNA which encodes antibodies, by cutting and rejoining the DNA in a way that sometimes goes awry. This appears to be what causes the chromosomal translocations, he says.

"Based on previous clues, we did a number of biochemical studies to verify our hunch about the mechanism of translocation," Lieber says. "Our study demonstrates the biochemical feasibility of the sequence of events proposed, and this matches the fingerprint left by the chromosomal translocations."

Source: University of Southern California