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New study offers insight into possible cause of lymphoma

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The immune system's powerful cellular mutation and repair processes appear to offer important clues as to how lymphatic cancer develops, Yale School of Medicine researchers report this week in *Nature*.

"The implications of these findings are considerable," said David Schatz, a Howard Hughes Medical Institute investigator, professor of immunobiology at Yale, and senior author of the study. "It now seems likely that anything that compromises the function of these DNA repair processes could lead to widespread mutations and an increased risk of cancer."

The lymph system is made up of infection-fighting B cells. Schatz and his colleagues examined the somatic hypermutation (SHM) process, which introduces random mutations in B cells' antibody genes to make them more effective in fighting infection.

SHM occurs in two steps: First, a mutation initiator, or activation-induced deaminase (AID), causes genetic mutations. Second, DNA repair enzymes spot the changes and begin making "sloppy" repairs, which lead to yet more mutations. The two steps combined, Schatz said, present a major risk to genomic stability.

Interestingly, these same repair enzymes recognize mutations in many other types of genes in the B cells, but they fix the genes in a precise, or, "high fidelity," manner.

Up until now it was thought the risk to genomic stability was avoided for the most part because the first step of the SHM process only happened in antibody genes. But this study found that AID acts on many other genes in B cells, including genes linked to lymphatic cancer and other malignancies.

"And then we had another surprise," Schatz said. "Most of these non-antibody genes do not accumulate mutations because the repair, for whatever reason, is precise, not sloppy."

What this means, Schatz said, is that researchers studying lymphatic cancer must understand both the first and the second step-the original mutations and then the repair process.

"If the precise, or high fidelity, repair processes break down, this would unleash the full mutagenic potential of the initial mutation, resulting in changes in many important genes," Schatz said. "We hypothesize that exactly this sort of breakdown of the repair processes occurs in the early stages of the development of B cell tumors."

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