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How a Genetic Roll of the Dice Paves the Way for Lymphatic Cancers

For most cells, keeping DNA in optimal condition is a high priority. Most cells do not hesitate to halt their usual life cycle while they fix anything that is amiss, even resorting to suicide to stop damage from spreading. But the immune system persistently gambles, putting organisms at risk for cancer and other diseases as it prepares to defend against potential pathogens. A new study shows how loss of a single enzyme that performs two critical functions can create the potential for cancer when immune cells divide and mature.

Howard Hughes Medical Institute investigator Michel Nussenzweig; his brother, National Cancer Institute investigator Andre Nussenzweig; and their colleagues have shown that an enzyme called ATM kinase plays a dual role in preventing immune cells from propagating with damaged chromosomes. Their findings are reported in an online issue of the journal *Cell* published June 29, 2007.

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— Michel C. Nussenzweig

Their study shows that ATM kinase — which has stopped functioning in about 50 percent of cases of a blood cancer known as mantle cell lymphoma — both directly contributes to the repair of chromosome breaks and ensures that genetically damaged immune cells do not replicate their broken DNA ends. Without it, white blood cells with broken DNA can circulate through the body, potentially forming the substrate for lymphomas, one of the most common types of human cancers.

White blood cells called lymphocytes circulate through our bodies seeking out viruses, bacteria, and other antigens. When lymphocytes are born in the bone marrow as B or T cells, their DNA is broken during a process called V(D) J recombination, needed to assemble receptor molecules that can trigger an immune response when antigens are encountered. DNA breaks are also produced when a B cell encounters an antigen and responds by refining its antibodies. By deliberately pulling apart their DNA and then splicing it back together at another spot in the genome, lymphocytes expand the range of

invaders they are prepared to battle.

At the same time, however, this process introduces significant risks. Nature rolls the dice twice, at the birth of the immune cell and when it forms specialized antibodies, because our adaptive immune response is so important to our survival, Nussenzweig, an immunobiologist at Rockefeller University, says. There are millions of different pathogens and only around 20,000 genes. The specific response to all these different threats made possible by the programmed DNA damage allowed us to evolve and live a long life. But it's also not at all surprising that lymphatic cancer is so common.

This process of breaking DNA, shuffling it, and then putting it back puts lymphocytes—and our health—in a potentially precarious position. Broken chromosome ends are left exposed until the DNA re-knits at the precise location needed to assemble the appropriate antigen receptors; in the absence of the appropriate controls, these broken chromosomes can recombine with one another in inappropriate ways. Fortunately, a checkpoint system kicks in whenever the re-knitting and repair process fails, setting off apoptosis, or cellular suicide, to keep damaged lymphocytes from replicating.

Previous research by the Nussenzweig brothers and others has shown the importance of ATM and other enzymes in somatic recombination. However, the singular importance of ATM was not known. So in the new study, the scientists watched both types of somatic recombination processes in lymphocytes that lacked ATM, both in mice and in laboratory cultures.

In the absence of ATM, they found, mouse lymphocytes are unable to repair the double-strand DNA breaks that develop during somatic recombination. What surprised the investigators was that the mouse lymphocytes continued to divide and mature with the broken chromosomes for at least two weeks.

If the genome is not stable, says Nussenzweig, it should be repaired or the cell should die. However, no redundant failsafe system seems to correct the failure of the ATM pathway to initiate apoptosis. In other words, he says, You can think of programmed damage to the lymphocyte that does not get repaired as an endogenous carcinogen.