Seemingly suicidal stunt is normal rite of passage for immune cells

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Researchers have shown that self-induced breaks in the DNA of immune cells known as lymphocytes activate genes that cause the cells to travel from where they're made to where they help the body fight invaders.

Scientists have known for two decades or more that lymphocytes can break their own DNA in this fashion, creating splits in both of the two strands. However, the new finding is the first to link such serious damage to activation of genes not directly involved in the cells' attempts to either fix the harm or self-destruct to stop themselves from becoming cancerous.

When genes are activated is critical to the ability of cells to take on specialized roles in the body, and the finding, published online in *Nature,* left researchers wondering if other developmental pathways in different cell types are also triggered by DNA damage.

"It's also interesting to note that the cell sees the genetic material of some invaders, such as DNA viruses, as damaged DNA," says senior author Barry Sleckman, M.D., Ph.D, director of the Division of Laboratory and Genomic Medicine and an expert in DNA repair. "Could pathogens be taking advantage of these pathways outside of the previously recognized responses to DNA damage? We don't know yet."

The finding immediately improved scientists' understanding of ataxia telangiectasia, a rare genetic disorder that, among other symptoms, can weaken the immune system. Patients with the disorder have a mutation

in a gene, ATM, that normally helps the cell sense DNA damage.

"This explains why the lymphocyte counts in these patients drop so sharply," Sleckman says. "Not only is the cell's ability to repair DNA damage slowed down, the lymphocytes can't activate the genes that get them to where they need to be."

Cells have built-in safeguards that regularly look for DNA damage. They can then repair it, or if that's not possible, push the cell to self-destruct. Both mechanisms help prevent DNA damage from turning a cell cancerous. For years, scientists assumed that a cell would view a break in both strands of DNA as serious damage and commit to self-destruction.

To their surprise, immunologists discovered two decades ago that breaking DNA was the source of one of the immune system's great strengths. Human DNA contains only 30,000 human genes, but the immune system makes proteins known as antibodies that recognize billions of different foreign substances. Immunologists showed that this was because lymphocytes create double-strand DNA breaks that allowed them to splice together their genetic materials in new ways. Material created from the new genetic combinations is used to generate antibodies and other defensive mechanisms that help the body defend itself against a much greater variety of invaders.

Sleckman wanted to examine the implications of DNA breaks in lymphocytes. In a cell line developed in his lab, researchers induced double-stranded breaks in lymphocyte DNA using the same enzymes the cells normally use to create the breaks. They then analyzed the genes activated as a result.

As expected, the breaks turned on two groups of genes: one, headed by the p53 protein, pushes the cell toward self-destruction; the other, headed by the NFKappa-B proteins, pushes for survival of the cell and

repair of the damaged DNA. These groups of genes are normally activated in any cell that experiences DNA damage.

But Sleckman and his colleagues also found several lymphocyte-specific genes activated by the breaks.

"Several of these genes are involved in the migration and homing of lymphocytes," says Sleckman. "Lymphocytes are made in the bone marrow and the thymus, and they have to move to other niches, including the lymph glands, to do their work."

In addition to the young lymphocyte, scientists are aware of other instances where DNA is normally and regularly broken, such as the replication of DNA during cell division or the creation of reproductive cells like the sperm and the egg. Ionizing radiation and chemotherapy drugs also can cause similar damage to DNA. Finally, DNA strands from infectious agents that enter the cell can mimic damaged host DNA.

"It's entirely possible that some of these breaks are activating genetic mechanisms that are unrelated to DNA repair or cell survival, like the mechanisms we identified in lymphocytes," says Sleckman. "Understanding the broader scope of the cells' responses to DNA damage could potentially be important in a wide variety of contexts."

Citation: Bredemeyer AL, Helmink BA, Innes CL, Calderon B, McGinnis LM, Mahowald GK, Gapud EJ, Walker LM, Collins JB, Weaver BK, Mandik-Nayak L, Schreiber RD, Allen PM, May MJ, Paules RS, Bassing CH, Sleckman BP. DNA double-strand breaks activate a multi-functional genetic program in developing lymphocytes. *Nature*, online Oct. 12, 2008.

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