New research helps explain why a deadly blood cancer often affects children with malaria

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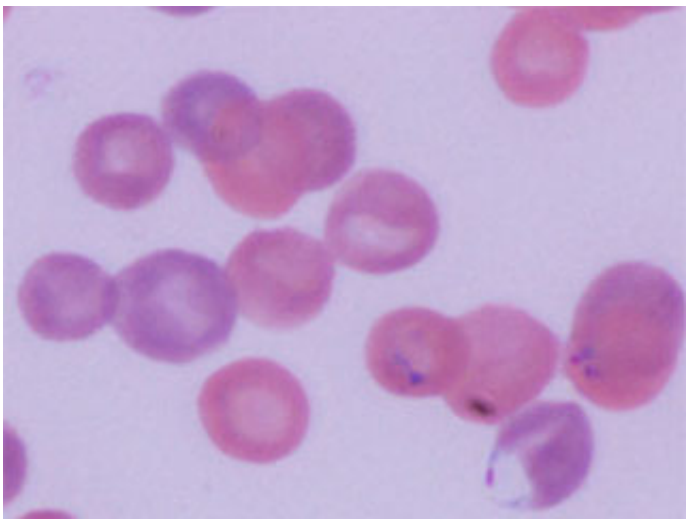

When a mouse's immune system reacts to red blood cells infected with the malaria parasite (dark spots within some of the pink cells above), changes occur in the DNA of B lymphocytes. These alterations, though beneficial in protecting from malaria, can occasionally lead to cancer. Credit: Laboratory of Molecular Immunology at Rockefeller University

In equatorial Africa, a region of the globe known as the "lymphoma belt," children are ten times more likely than in other parts of the world to develop Burkitt's lymphoma, a highly aggressive blood cancer that can be fatal if left untreated. That area is also plagued by high rates of malaria, and scientists have spent the last 50 years trying to understand

how the two diseases are connected.

The link has been a mystery: The parasite that causes malaria infects red blood cells and liver cells, while Burkitt's lymphoma originates in infection-fighting white blood cells called B lymphocytes. So how could a malaria infection increase a child's risk of developing this type of cancer?

A team of Rockefeller University researchers led by Michel Nussenzweig, the Zanvil A. Cohn and Ralph M. Steinman Professor and head of the Laboratory of Molecular Immunology, has helped explain why. Working in mice, they found that the same enzyme that helps create antibodies that fight off the malaria parasite also causes DNA damage that can lead to Burkitt's lymphoma. The research was published August 13 in *Cell*.

"I think of this process as a 'necessary risk,'" says Davide Robbiani, the first author of the study and an associate professor in Nussenzweig's lab. "The body needs this enzyme in order to produce potent antibodies to fight malaria. But in the process, the enzyme can cause substantial collateral damage to the cells that produce it, and that can lead to lymphoma," he adds.

In the study, the researchers infected mice with a form of the parasite that causes malaria, *Plasmodium chabaudi*. They immediately saw that the mice experienced a huge increase in germinal center (GC) B lymphocytes, the activated form of the white blood cells that can give rise to Burkitt's lymphoma. "In malaria-infected mice, these cells divide very rapidly over the course of months," says Robbiani.

As these cells rapidly proliferate, they also express high levels of an enzyme known as activation-induced cytidine deaminase (AID), which induces mutations in their DNA. As a result, these cells can diversify to

generate a wide range of antibodies—an essential step in fighting off various infections. But in addition to beneficial mutations in antibody genes, says Robbiani, AID can cause "off-target" damage and shuffling of cancer-causing genes. "In mice infected with the malaria parasite, these so-called chromosomal rearrangements occur very frequently in GC lymphocytes," says Robbiani, "and at least some of the changes are due to AID."

Next, the researchers bred mice lacking the p53 gene, which is known to protect cells from many types of cancer, including Burkitt's lymphoma. In analyzing mice that expressed AID but not p53, they found that every single one developed lymphoma. And when these mice were infected with the malaria parasite, they developed lymphomas specifically in mature B cells, similarly to what happens in Burkitt's lymphoma. "This finding sheds new light on a long-standing mystery of why two seemingly different diseases are associated with each other," says Robbiani.

Groups at Rockefeller and elsewhere are trying to understand how AID causes its off-target damage to DNA, which could lead to new treatments. "If we could somehow limit this collateral damage to cancer-causing genes without reducing the infection-fighting powers of B cells, that could be very useful," he says. "But first, we have to find out how the collateral DNA damage occurs in the first place."

There are no additional cancers associated with malaria, but lymphomas have been linked to other types of infections, and not just in Africa, says Robbiani. For instance, people with hepatitis C or the ulcer-causing bacterium Helicobacter pylori have a higher incidence of non-Hodgkin lymphomas, he notes. "It's possible that AID also plays a role in the association between these other infections and cancer," says Robbiani. "This is purely a speculation at this point, though highly suggestive."

More information: *Cell*, Robbiani et al.: "Plasmodium Infection Promotes Genomic Instability and AID-Dependent B Cell Lymphoma" dx.doi.org/10.1016/j.cell.2015.07.019