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Study shows how chronic inflammation can cause cancer

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A hormone-like substance produced by the body to promote inflammation can cause an aggressive form of leukemia when present at high levels, according to a new study by researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

The study shows that high levels of interleukin-15 (IL-15) alone can cause large granular lymphocytic (LGL) leukemia, a rare and usually fatal form of cancer, in an animal model. The researchers also developed a treatment for the leukemia that showed no discernible side effects in the animal model.

Published in the journal *Cancer Cell*, the findings show that IL-15 is also overexpressed in patients with LGL leukemia and that it causes similar cellular changes, suggesting that the treatment should also benefit people with the malignancy.

"We know that inflammation can cause cancer, but we don't know the exact mechanism," says principal investigator Dr. Michael A. Caligiuri, CEO of The James Cancer Hospital and Solove Research Institute, and director of Ohio State's Comprehensive Cancer Center.

"Here, we show one way it can happen, and we used that information to potentially cure the cancer."

Normally, the body releases IL-15 to stimulate the development, survival

and proliferation of natural-killer cells, which are immune cells that destroy cancer and virus-infected cells. This research shows that when IL-15 is present in high amounts in the body for prolonged periods, such as during chronic inflammation, it can cause certain immune cells called large granular lymphocytes, or LGLs, to become cancerous.

This malignant transformation begins when IL-15 attaches to receptors on the surface of normal LGLs, an event that boosts levels of a cancer-causing protein called Myc (pronounced "mick") inside the cells. The high Myc levels, in turn, bring changes that cause chromosome instability and additional gene mutations. The high Myc levels also activate a process called DNA methylation, which turns off a variety of genes, including important genes that normally suppress cancer growth.

"We stand the best chance of curing cancer when we understand its causes," says first author Anjali Mishra, a postdoctoral researcher in Caligiuri's laboratory. "Once we understood how this inflammatory hormone causes this leukemia, we used that information to develop a treatment by interfering with the process."

Caligiuri and Mishra were joined in this study by Dr. Guido Marcucci, associate director for Translational Research at the OSUCCC – James, Dr. Robert Lee, professor of pharmaceutics and pharmaceutical chemistry in Ohio State's College of Pharmacy and a group of collaborators. The investigators conducted the research using cells isolated from patients with LGL leukemia and a mouse model of the disease. Key findings include:

- Exposing normal, human, large granular lymphocytes to IL-15 caused cell proliferation, chromosomal instability and global DNA hypermethylation;
- Excessive IL-15 activated the cancer-causing Myc oncogene in

large granular lymphocytes, leading to genetic instability, DNA hypermethylation and malignant transformation;
- Details of how Myc upregulation causes the genetic instability and hypermethylation.

Lee developed a liposomal formulation of the proteosome inhibitor bortezomib that shuts down the cancer-causing pathway, potentially curing the malignancy. Leukemic mice treated with the liposomal bortezomib showed 100 percent survival at 130 days versus 100 percent mortality at 60-80 days for control animals.

"We now plan to develop this drug for clinical use," says Marcucci, who holds the John B. and Jane T. McCoy Chair in Cancer Research in Cancer Research.

Provided by Ohio State University Medical Center