Marker distinguishes more-aggressive from less-aggressive forms of chronic leukemia

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Researchers have identified a prognostic marker in the most common form of chronic leukemia that can help to distinguish which patients should start treatment quickly from those who can safely delay treatment, perhaps for years.

The study, led by researchers at the Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC - James), focused on chronic lymphocytic leukemia (CLL), a malignancy expected to occur in 16,000 Americans this year and cause 4,600 deaths.

The researchers examined a gene called ZAP-70 in CLL cells for a chemical change called methylation. They found that when the gene in leukemia cells is methylated, patients are likely to have the slow-progressing form of CLL, and when the ZAP-70 gene is unmethylated, patients are likely to have aggressive disease and should consider beginning treatment immediately.

Currently, doctors must simply observe newly diagnosed patients to determine which type of CLL they have. This can delay the start of treatment in patients with aggressive disease, or it can lead to treating patients who don't yet require it.

The findings are published in the *Journal of Clinical Oncology*.

"This study demonstrates that ZAP-70 methylation status is a highly predictive, reproducible biomarker of poor prognosis in this disease, and a clinically useful prognostic test for CLL," says principal investigator Dr. John Byrd, a CLL specialist and professor of Medicine, of Medicinal Chemistry and of Veterinary Biosciences at the OSUCCC - James.

Currently, the presence of mutations in a gene called IGVH (immunoglobulin heavy chain variable region gene), and the amount of protein produced by the ZAP-70 gene in CLL cells are sometimes used to predict prognosis and response to treatment in people with this disease, "but these assays are expensive and difficult to perform," says coauthor and researcher Dr. David Lucas, research assistant professor and CLL specialist at the OSUCCC - James.

"In all cells, some areas of DNA undergo methylation, which controls how that DNA is used," Lucas says. "In cancer cells, the pattern of DNA methylation is often different from that of healthy cells, and this influences how much protein is produced by ZAP-70 and other genes."

Because the protein produced by the ZAP-70 gene is often present at different levels in leukemia cells, Byrd, Lucas and their colleagues hypothesized that changes in ZAP-70 methylation status could explain decreases in the gene's expression and a more favorable clinical outcome.

The researchers examined CLL cells from 247 patients obtained through four independent clinical trials. Project co-leader, Dr. Christoph Plass, of the Division of Epigenomics and Cancer Risk Factors, German Cancer Research Center in Heidelberg, Germany, used a new mass spectroscopy-based technique to assess DNA methylation of the ZAP-70 regulatory region.

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