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Molecular network influences development of chronic lymphocytic leukemia

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A study shows for the first time that the three most common chromosome changes seen in chronic lymphocytic leukemia disrupt a molecular network that includes several important genes and strongly influences the outcome of the disease.

The research was led by investigators at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) and at University of Texas M.D. Anderson Cancer Center, working in collaboration with investigators at seven other centers in Italy and the United States. The findings were published recently in the *Journal of the American Medical Association* (*JAMA*).

The network involves genes on chromosome 13, chromosome 11 and chromosome 17, along with the important tumor-suppressor gene TP53, the prognostically important molecule called ZAP-70 and two sets of regulatory molecules called microRNA.

"Our findings might allow doctors to better identify which CLL patients need closer follow-up or earlier treatment," says first author Dr. Muller Fabbri, a research scientist at the OSUCCC – James. "Moreover, our study provides important new information about how CLL develops and identifies new molecular targets for the development of new treatments."

CLL is the most common leukemia in the U.S., where 15,000 new cases were expected in 2010, along with 4,400 deaths from the disease.

The disease has an extremely variable clinical outcome, Fabbri notes. While most patients have a slowly progressing form of the disease that requires little or no treatment for many years, others have aggressive disease that requires immediate therapy.

Chromosome damage is common in CLL, and it often involves the loss of pieces of chromosome 13. The loss of pieces of chromosomes 11 and 17 may also occur. More specifically, these changes are called the 13q deletion, and the 11q and 17p deletions.

"Patients with a 13q deletion generally have a better prognosis than patients with the 11q or 17p deletion," Muller says. "But we don't know why the loss of part of chromosome 13 results in a better prognosis. Our discovery helps unravel this mystery. It identifies a molecular mechanism that explains why these deletions affect patient outcome."

This study, led by Dr. Carlo M. Croce, professor of molecular virology, immunology and medical genetics, and director of the Human Cancer Genetics program at the OSUCCC – James, shows that loss of chromosome 13q interrupts a biochemical network that involves two families of microRNA and the TP53 tumor-suppressor gene. The interruption leads to greater activity of two genes (BCL2 and MCL1), which prevents cancer cells from dying when they should, and to less activity by a gene called ZAP70. Low levels of ZAP70 are associated with milder disease, while high levels are associated with aggressive disease.

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