Gene shut-down may offer early warning of chronic leukemia

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A new study shows that certain genes are turned off early, before clinical signs of the disease appear, in the development of chronic leukemia.

The study, led by researchers at the Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute, examined cancer cells from patients with chronic lymphocytic leukemia (CLL) and from a new strain of mice that develops a very similar disease.

The findings suggest that changes called epigenetic alterations, which silence a gene's ability to make its protein, might serve as markers for detecting CLL early and for monitoring its progression. They also point to a strategy for treating the disease earlier using drugs that reverse such changes, and further confirm the value of the mouse model for studying CLL causes and treatment, researchers say.

The research revealed that a gene called FOXD3 likely plays a key role in CLL, and that the gene is silenced early, followed by the silencing of other genes.

The findings are published online in the Proceedings of the National Academy of Sciences Early Edition.

"Our data suggest that the silencing of FOXD3 might represent a very early gene involved in the initiation of CLL that we can potentially target for re-expression with specific drugs," says study leader Dr. John C.

Byrd, professor of internal medicine, director of the hematologic malignancies program at the James Cancer Hospital and Solove Research Institute and a CLL specialist. "Next, we need to learn whether therapy to reverse this silencing can delay or prevent CLL progression."

An estimated 15,500 Americans are expected to develop CLL in 2009, and about 4,400 people will die of the disease. The malignancy usually strikes people aged 50 or older, causing white blood cells called B lymphocytes to proliferate. This can lead to severe anemia and dangerous viral, bacterial and fungal infections. Average survival is eight to 12 years from diagnosis.

The animal model, called the TCL1 transgenic mouse, was developed by Ohio State cancer researcher Dr. Carlo M. Croce and a group of colleagues in 2002. An earlier study by Byrd and his laboratory showed that the disease in the mouse has many of the same molecular and genetic features as human CLL, responds to drugs used to treat the disease and develops drug resistance, as CLL patients often do.

"Data from this new study demonstrate a strong similarity in gene silencing patterns in the mouse leukemia and in human CLL, suggesting that the changes in the mice mimic critical changes in different stages of the human disease," says Byrd, who worked closely on the study with first author and graduate student Shih-Shih Chen, co-senior author Christoph Plass at the German Cancer Research Center in Heidelberg, and other colleagues.

"We know that human CLL involves the silencing of a number of genes, but we can look at human CLL only after patients develop the disease," he says.

"This mouse model now allows us to look at events leading up to the disease and perhaps identify markers for early disease detection and the

testing of new therapies."

Source: Ohio State University Medical Center