Novel test identifies leukemia patients likely to respond to new therapy

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Researchers at the Albert Einstein College of Medicine of Yeshiva University have discovered a genetic signature identifying cases of lymphoma that are uniquely susceptible to a newly developed molecular targeted therapy. As a result, physicians organizing clinical trials of the new therapy will be able to enroll patients who'll be most likely to benefit from it.

The research was led by Dr. Ari Melnick, assistant professor of developmental & molecular biology and medicine at Einstein, who also developed the new lymphoma therapy. The study appears in the February 20 issue of the *Proceedings of the National Academy of Sciences*.

Each year more than 60,000 Americans are diagnosed with B cell lymphomas—tumors of cells of the immune system that include Hodgkin's and non-Hodgkin's lymphomas. B cells are the immune-system cells that make antibodies. Genetic aberrations can cause B cells to multiply uncontrollably, causing B cell lymphomas.

Dr. Melnick's study focused on a gene called BCL6. The protein it codes for is a transcriptional repressor, which means that it can shut off the functioning of genes in B cells and other cells of the immune system and prevent them from being expressed. The BCL6 protein is normally produced only during a specific stage of B cell development and is never made again. But deregulation of BCL6 can cause the protein to be produced when it shouldn't be. The unwelcome presence of the BCL6

protein blocks the expression of important genes that normally protect cells from becoming cancerous. As a result, malignant B-cell lymphomas occur.

Mutations or chromosomal rearrangements that deregulate BCL6 are responsible for many cases of diffuse large B cell lymphoma—an aggressive cancer that accounts for up to 30 percent of newly diagnosed non-Hodgkin's lymphoma cases. In a 2004 Nature Medicine article, Dr. Melnick and colleagues described a peptide, which they dubbed BPI, that showed promise in treating B-cell lymphomas by specifically blocking the cancer-causing effects of the BCL6 protein. But until now, there has been no way to distinguish between diffuse large B cell lymphomas that are caused by BCL6 deregulation and those cases in which BCL6 is expressed but doesn't actually drive the cancer.

Dr. Melnick reasoned that those diffuse large B cell lymphomas that are caused by BCL6 deregulation should have a characteristic "signature" in which the genes targeted by the BCL6 protein are either expressed (turned on) or not expressed. The researchers used state-of-the-art genomics technology to analyze a panel of diffuse large B cell lymphoma cell lines. They found a set of 485 BCL6-controlled genes and confirmed that all lymphomas with the BCL6 signature are killed by BPI while lymphomas without the signature are resistant to the therapy.

"Suitable lymphoma patients—those whose tumor cells exhibit this BCL6 signature --will now have access to a potent and specific therapy that is unlikely to cause the side effects associated with chemotherapy drugs," says Dr. Melnick. "At the same time, lymphoma patients who don't fit this genetic profile will be spared a drug treatment that would be ineffective for them."

Source: Albert Einstein College of Medicine