Biomarkers of behavior, therapeutic targets for adult B-acute lymphoblastic leukemia identified

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New insight into the aggressive behavior of certain adult B-acute lymphoblastic leukemias has provided researchers with a potential new prognostic biomarker and a promising new therapeutic target.

The research, conducted by Ari Melnick, M.D., associate professor of medicine and director of the Raymond and Beverly Sackler Center for Biomedical and Physical Sciences at Weill Cornell Medical College and a hematologist-oncologist at New York-Presbyterian Hospital/Weill Cornell Medical Center, and colleagues, was published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

Although B-acute lymphoblastic leukemia is highly curable in children, the disease is usually fatal in adults, and researchers have yet to identify why this is the case. Part of the explanation for the poorer outcomes in adults is the higher frequency of genetic alterations associated with unfavorable prognosis.

In order to better understand why these genetic alterations are associated with poor outcomes, Melnick and colleagues studied 215 diagnostic specimens obtained from adults with B-acute lymphoblastic leukemia who were participating in a large Eastern Cooperative Oncology Group phase III clinical trial.

"We performed an integrative epigenomics study to decode the

instructions that determine how these cells behave," Melnick said. "The hope was that this would allow us to identify better survival biomarkers and new therapeutic targets."

In many cancers, genetic alterations work in conjunction with epigenetic changes (changes in the way that DNA is modified and packaged) to promote cancerous behaviors. Looking at the B-acute lymphoblastic leukemia specimens, Melnick and colleagues found that many of the leukemias' bad traits were a result of changes in the epigenetic code. In many cases, the epigenetic changes were directly linked to the proteins generated from the genetic alterations and could be used to identify key master regulators required for the leukemic cells to live, according to Melnick.

"For example, we found that a cell surface molecule called CD25 was an extremely powerful indicator of the presence of the most aggressive and fatal cases," Melnick said.

The researchers also discovered that abnormal forms of the E2A and MLL proteins occurring in B-acute lymphoblastic leukemias directly reprogram epigenetic settings at their binding sites throughout the genome.

Most notably, the researchers found that mutant forms of MLL epigenetically reprogramed leukemia cells to express the powerful oncoprotein BCL6, and that BCL6 was required to maintain the proliferation and survival of the leukemia cells.

"We then designed inhibitors of BCL6 and showed that we could kill leukemia cells from patients enrolled in the clinical trial by blocking its function," Melnick said.

Based on these results, the researchers plan to use CD25 as a biomarker

to identify those patients who have the worst disease in the next set of clinical trials, and to tailor treatment appropriately. In addition, BCL6 inhibitors are currently being translated for use in humans, and they hope to develop clinical trials targeting BCL6 in MLL-rearranged leukemias.

"These results will ultimately lead to biomarkers that help guide treatment and to the development of therapies that will be more effective for patients with this aggressive form of leukemia," Melnick said.

Provided by American Association for Cancer Research

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