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Chemical stem cell signature predicts treatment response for acute myeloid leukemia

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Researchers at Albert Einstein College of Medicine of Yeshiva University and Montefiore Medical Center have found a chemical "signature" in blood-forming stem cells that predicts whether patients with acute myeloid leukemia (AML) will respond to chemotherapy.

The findings are based on data from nearly 700 AML patients. If validated in clinical trials, the signature would help physicians better identify which AML patients would benefit from chemotherapy and which patients have a prognosis so grave that they may be candidates for more aggressive treatments such as bone-marrow transplantation. The paper was published today in the online edition of the *Journal of Clinical Investigation*.

Sparing Patients from Debilitating Side Effects

According to the American Cancer Society, AML accounts for nearly one-third of all new leukemia cases each year. In 2013, more than 10,000 patients died of AML.

"AML is a disease in which fewer than 30 percent of patients are cured," said co-senior author Ulrich Steidl, M.D., Ph.D., associate professor of cell biology and of medicine and the Diane and Arthur B. Belfer Faculty Scholar in Cancer Research at Einstein and associate chair for translational research in oncology at Montefiore. "Ideally, we would like

to increase that cure rate. But in the meantime, it would help if we could identify who won't benefit from standard treatment, so we can spare them the debilitating effects of chemotherapy and get them into clinical trials for experimental therapies that might be more effective."

Analyzing Methylation Patterns

The Einstein study focused on so-called epigenetic "marks" – chemical changes in DNA that turn genes on or off. The researchers focused on one common epigenetic process known as methylation, in which methyl (CH_3) groups attach in various patterns to the genes of human cells. Researchers have known that aberrations in the methylation of hematopoietic, or blood-forming, stem cells (HSCs) can prevent them from differentiating into mature blood cells, leading to AML.

Dr. Steidl suspected that comparing how closely the DNA methylation patterns in the cancerous white blood cells of AML patients resembled the patterns found in healthy individuals' HSCs might foretell the patients' response to treatment. To find out, he and his colleagues at the Albert Einstein Cancer Center carried out a novel DNA methylation analysis on 561 genes in healthy HSCs at various stages of differentiation. This new technique, developed by co-senior author Amit Verma, M.D., allows researchers, for the first time, to study DNA methylation of cells such as HSCs that can be found only in small quantities. Dr. Verma is associate professor of medicine and of developmental & molecular biology at Einstein and director, hematologic malignancies at the Montefiore Einstein Center for Cancer Care.

The researchers first analyzed HSCs from three healthy individuals to determine normal methylation patterns. They found that in the HSCs of healthy people, most DNA cytosines (one of four main components of DNA) are methylated. They noted that where demethylation (removal of

methyl groups) occurs, it's limited mainly to one particular stage of HSC differentiation.

Using Epigenetic Signatures to Predict Survival

The researchers hypothesized that by comparing the "epigenetic signature" of healthy people's HSCs with that of AML patients' cancerous white blood cells, they could predict survival of AML patients. In other words, patients with a methylation pattern resembling that of healthy people's HSCs (i.e., a "low score") would be more likely to live longer – and therefore benefit more from chemotherapy – than patients with a high score.

The researchers then tested their scoring method using data on 688 AML patients in three different clinical trials, In each of these groups, patients with low scores (methylation patterns similar to normal HSCs) had approximately twice the median survival time of patients with high scores. "Our epigenetic stem cell signature was clearly superior to similar tests that have been used," said Dr. Steidl.

Dr. Steidl and his colleagues are now studying the genes that are included in the aberrant signatures to determine if they play a role in causing AML.

More information: "HSC commitment-associated epigenetic signature is prognostic in acute myeloid leukemia," *Journal of Clinical Investigation*, 2014.

Provided by Albert Einstein College of Medicine