Researchers discover key mutation in acute myeloid leukemia

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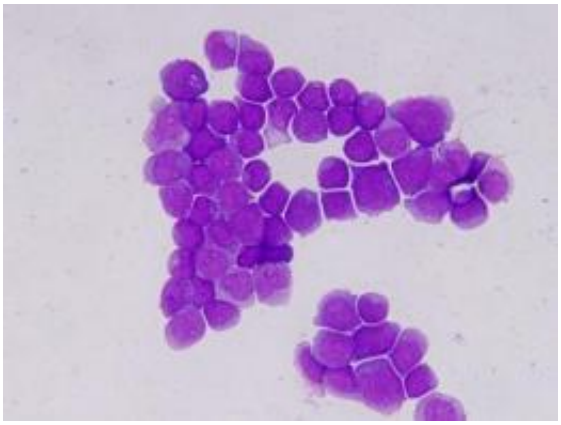

These are acute myeloid leukemia cells. Credit: Washington University

Researchers have discovered mutations in a particular gene that affects the treatment prognosis for some patients with acute myeloid leukemia (AML), an aggressive blood cancer that kills 9,000 Americans annually. The scientists report their results in the Nov. 11, 2010, on-line issue of *The New England Journal of Medicine*.

The Washington University School of Medicine in St. Louis team initially discovered a mutation by completely sequencing the genome of a single AML patient. They then used targeted DNA sequencing on nearly 300 additional AML patient samples to confirm that mutations discovered in one gene correlated with the disease. Although genetic changes previously were found in AML, this work shows that newly

discovered mutations in a single gene, called DNA methyltransferase 3A or DNMT3A, appear responsible for treatment failure in a significant number of AML patients. The finding should prove rapidly useful in treating patients and which may provide a molecular target against which to develop new drugs.

"This is a wonderful example of the ability of the unbiased application of whole-genome, DNA sequencing to discover a frequently mutated gene in cancer that was previously unknown to be correlated with prognosis," said Eric D. Green, M.D., Ph.D., director of the National Human Genome Research Institute (NHGRI), a part of the National Institutes of Health, which co-funded this study. "This may quickly lead to a change in medical care because physicians may now screen for these mutations in patients and adjust their treatment accordingly."

The study was carried out by researchers from the Washington University Genome Center and the Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine. In the study, the researchers found DNMT3A mutations in 21 percent of all AML patients studied and in 34 percent of the patients classified as having an intermediate risk of treatment failure based on widely used laboratory tests of their leukemia cells. More than half of AML patients are classified as having an intermediate risk and are then typically treated with standard chemotherapy.

For patients with the DNMT3A mutation, however, chemotherapy may not be the best first treatment. "We have not had a reliable way to predict which of these patients will respond to the standard treatment," said lead author and hematologist Timothy Ley, M.D., the Lewis T. and Rosalind B. Apple Professor of Medicine at Washington University School of Medicine. "In the cases we studied, mutations in the DNMT3A gene trump everything else we've found so far to predict adverse outcomes in intermediate-risk AML."

Patients with the mutation survived for a median of just over a year, compared to median survival of nearly 3.5 years among those without the mutation. "Based on what we found, if a patient has a DNMT3A mutation, it looks like you're going to want to treat very aggressively, perhaps go straight to bone marrow transplantation or a more intensive chemotherapy regimen," says senior author Richard K. Wilson, Ph.D., director of Washington University's Genome Center.

As part of the new research, the investigators looked to see which treatments the patients received and how they fared. Those with DNMT3A mutations treated with bone marrow transplants lived longer than those who received only chemotherapy, but the Washington University investigators caution that the sample size was small and follow-up studies will be needed to confirm these initial findings.

"This discovery is a clear example of the power of comprehensive analysis of cancer genomes," said Francis S. Collins, M.D., Ph.D., director of the National Institutes of Health. "By using high-throughput DNA sequencing, researchers will be able to discover all of the common genetic changes that contribute to cancer. With that knowledge, a growing list of targeted treatments will be developed, based on a firm biological understanding of the disease."

Launched in 2006 as a partnership between the National Cancer Institute and the National Human Genome Research Institute, both NIH components, The Cancer Genome Atlas (TCGA) has developed a comprehensive strategy for comparing the genome of cancer cells to the genome of normal cells from the same patient. This allows the identification of genetic changes that cause the uncontrolled growth of a cancer cell. TCGA also biologically characterizes the tumors in several other ways. Together, the TCGA data can be linked to clinical data to help researchers understand the characteristics of the tumor being studied. The project plans to analyze up to 500 patient samples of tumor

and normal tissue in 20 major types of cancer over the next five years.

"Cancer is a genetic disease," said NCI Director Harold Varmus, M.D. "Every discovery teaches us more and more about the many ways genes can be deranged in a tumor cell to make it grow out of control. While we generally describe some 200 types of cancer based on where they originate in the body, genetics may show us that there are thousands of different types, each requiring different treatments. Fortunately, we are now acquiring the tools we need to understand them and to make important progress."

Washington University is a TCGA participant and has pioneered the use of comprehensive, genome-wide approaches to study cancer. Although the AML study just reported was not part of TCGA, the Washington University team has donated nearly 200 AML samples for comprehensive genomic analysis to the TCGA program. The AML results and all TCGA analyses can be found at its data portal, http://cancergenome.nih.gov/dataportal, which provides direct access to the genomic analytic datasets, with selected patient genetic and clinical data limited to researchers qualified through an NIH review and approval process designed to safeguard participant privacy.

"This work represents the culmination of years of collaborative research that has focused on cataloging the mutations involved in AML," says co-author John Dipersio, M.D., Ph.D., chief of the division of oncology and deputy director of the Siteman Cancer Center. "This work provides a pathway and a foundation for doing the same in all other malignancies that could potentially lead to more effective, targeted therapies.

AML is a cancer of the blood. Like most cancers, it develops from mutations that occur in cells over the course of many years during a person's life and not from inherited genetic errors present at birth. AML strikes some 13,000 Americans annually, killing 9,000. The disease

occurs most often in adults and becomes more difficult to treat as patients age. The five-year survival rate for adults with AML is about 20 percent.

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