

New clue in leukemia mystery: Researchers identify 'poison' employed by deadly enzyme mutations

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There is new hope for people with acute myelogenous leukemia (AML), a fast-growing cancer of the blood and bone marrow. Research led by Weill Cornell Medical College and published today in the online edition of the journal *Cancer Cell* reveals a surprising and unexpected cancer-causing mechanism. The investigators discovered that newly identified mutant enzymes in AML create a chemical poison to cause leukemia. Their findings should prove useful in treating patients by providing a molecular target against which to develop new drugs against one subset of AML as well as other cancers.

AML is one of the most common types of leukemia among adults, with an estimated 12,300 new cases diagnosed in the United States each year and 8,950 deaths, according to the American Cancer Society. People with AML have abnormal cells inside their bone marrow that quickly multiply, replacing healthy blood cells in the bone marrow and leading to infections, bleeding and severe anemia.

The large-scale, international, collaborative research effort scrutinized the genomes of 750 AML patients from the United States and Europe for chemical clues to better understand how leukemia arises from normal [bone marrow cells](#). Using computational tools to sift through millions of data points, they discovered a unique [chemical signature](#) in the genomes of patients with mutations in either of two enzymes called IDH1 and IDH2, which occur frequently in AML.

Dr. Ari Melnick of Weill Cornell Medical College and his principal co-authors -- including Dr. Craig B. Thompson, president of Memorial Sloan-Kettering Cancer Center (MSKCC), and Dr. Ross L. Levine, also of MSKCC -- discovered this chemical signature: a massive accumulation of

[DNA methylation](#) that causes genes to function abnormally, leading to AML. They went on to show that IDH1 and IDH2 mutations generate a "poison" that blocks the ability of a protective factor called TET2 to remove the methylation from the genome. Interestingly, the researchers also showed that many AML patients have mutations that inactivate TET2, and this causes the same abnormal DNA methylation effect as IDH1 and IDH2 mutations.

"One of the great surprises of this study was that IDH1 and IDH2, which are normally involved in energy metabolism and located far away from DNA and outside of the cell nucleus, could become subverted to make a substance that poisons the genome," says Dr. Ari Melnick, the study's senior author and associate professor of medicine and director of the Raymond and Beverly Sackler Center for Biomedical and Physical Sciences at Weill Cornell Medical College.

"Our study shows for the first time that metabolic enzymes not only help to fuel tumor growth but when mutated can also directly 'rewrite' the instructions that govern the genome," Dr. Melnick continues. One important implication of this work is that it appears technically feasible to create drugs that can specifically stop mutant IDH1 and IDH2 from making the cancer-causing poison. Such inhibitors have the potential to fundamentally restore normal functioning to the genome and thus help to treat leukemias. IDH1 is also frequently mutated in malignant brain tumors, suggesting that the current study has broad implications for several types of cancer.

"These discoveries were only possible thanks to the collaboration of a large team of scientists with expertise in different disciplines from around the world," emphasizes Dr. Melnick, "and thanks to an unusual alliance between multicenter clinical trials

groups from Europe and the United States. This spirit of cooperation allowed for the collection and analysis of the massive genomic datasets required for these discoveries to be made. Working together, it will be possible to accelerate the pace of discovery and development of better treatments."

Provided by New York- Presbyterian Hospital

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