

Gene mutation contributes to leukemia by enhancing function of blood stem cells

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Researchers at Memorial Sloan-Kettering Cancer Center and New York University have discovered how a mutation in the gene known as TET2 contributes to the development of some leukemias. When a mutation in TET2 occurs, it enhances the function of blood stem cells in the bone marrow, causing them to renew themselves more efficiently than normal blood stem cells. This results in a greater number of mutant cells than normal blood stem cells, a condition that leads to leukemia.

The discovery, published in the July issue of *Cancer Cell*, provides a key insight into what first goes wrong in the development of many leukemias. The finding was made by a research group led by Ross L. Levine, MD, a member of the Human Oncology Pathogenesis Program and the [Leukemia](#) Service at Memorial Sloan-Kettering, and Iannis Aifantis, PhD, a member of the NYU Cancer Institute.

Central to the discovery was the development of a mouse model lacking TET2 function, which will serve as a valuable research tool. "We now have a model that will allow us to look for therapeutic targets that might be effective against leukemias caused by the TET2 mutation," said Dr. Levine. "After proving that TET2 loss confers a new capacity on these [stem cells](#), we can start investigating whether existing or novel therapies might block that effect."

Researchers have known that mutations in the TET2 gene are common in many [blood cancers](#), but other gene mutations are associated with leukemias as well, so the role of TET2 in leukemia development was

unclear. Drs. Levine and Aifantis created the first TET2-deficient [mouse model](#) to answer this question.

"This study is a chapter in a story that is evolving very rapidly. Many other research groups are studying the basic biology of epigenetic regulators like TET2 in parallel to us, so what we and others learn about the mechanism is laying the groundwork for the development of novel therapies for leukemia patients," said Ross L. Levine, MD, a member of the Human Oncology Pathogenesis Program and the Leukemia Service at Memorial Sloan-Kettering.

Because TET2 appeared to be relevant to blood cancers, the mice were engineered to carry a TET2 mutation in blood cells only. The loss of TET2 had two dramatic effects: 1) it increased the function of [blood stem](#) cells, which in turn allowed these [mutant cells](#) to accumulate in the bone marrow and outnumber normal stem cells, and 2) over the next six months, the mice went on to develop myeloid leukemia.

"For the first time, we have definitive proof for what a TET2 mutation by itself does to the blood cells," said Dr. Levine, noting that while this mutation alone may not always lead to leukemia -- unknown mutations in other genes may need to occur as well -- the results of the experiment prove that TET2 plays a critical role.

The study also provides a glimpse into how mutations in genes known as epigenetic regulators contribute to leukemia development. These types of genes, which include TET2, function by modifying how other genes are expressed without altering their DNA sequence. Instead, epigenetic regulators modify the structure of molecules that surround DNA. Dr. Levine and his colleagues are now trying to further define exactly how TET2 deficiency changes gene expression in the mutant stem cells, spurring them to outperform the normal stem cells.

Although the mice in the study specifically developed myeloid leukemia, the researchers say it is likely that TET2 deficiency plays a role in many blood cancers and may contribute to other types of cancer as well. Because mutations in TET2 frequently occur with mutations in other genes that are linked to cancer, Dr. Levine is working on creating mouse models that carry multiple mutations.

"This study is a chapter in a story that is evolving very rapidly," Dr. Levine said. "Many other research groups are studying the basic biology of epigenetic regulators like TET2 in parallel to us, so what we and others learn about the mechanism is laying the groundwork for the development of novel therapies for leukemia patients."

Provided by Memorial Sloan-Kettering Cancer Center

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