In 2008, two research groups in Europe made an intriguing discovery: A significant number of people with leukemias carry a mutation in a gene called *TET2*. However, it was not clear how *TET2* mutations contribute to the disease or how *TET2* functions in healthy cells. Now a study led by researchers at Memorial Sloan Kettering Cancer Center and New York University has shown that *TET2* loss enhances the function of blood stem cells, causing them to renew themselves more efficiently than normal blood stem cells. These mutant cells outcompete the normal cells, a condition that progresses to leukemia.

The finding, published in the July issue of *Cancer Cell*, provides a key insight into what initially goes wrong in the development of many leukemias. [PubMed Abstract ] "For the first time, we have definitive proof for what a *TET2* mutation by itself does to the blood cells," says medical oncologist Ross L. Levine , a member of the Human Oncology Pathogenesis Program and the Leukemia Service at Memorial Sloan Kettering, who led the study along with Iannis Aifantis of the NYU Cancer Institute. "After proving *TET2* loss confers a new capacity on the stem cells, we can start investigating whether existing or novel therapies might block that effect."

Critical to the discovery was the development of a mouse model that lacks *TET2* function in blood cells — the same cells that become cancerous in leukemia. The loss of *TET2* in the animals had two dramatic effects: The blood stem cells had enhanced reproductive capabilities, and the mice went on to develop myeloid leukemia within six months. "These mice will serve as a valuable research tool allowing us to look for therapeutic targets that might be effective against leukemias caused by the *TET2* mutation," Dr. Levine says.

The Cancer Cell study is one of several recently published that shed light on how certain mutations may contribute to leukemia by modifying DNA methylation — a mechanism that allows a cell to chemically modify its genes leading to changes in gene expression. A related gene, *TET1*, was recently found to affect DNA methylation, and the researchers suspect *TET2* has a similar function. There already are cancer drugs in clinical testing that target methylation, so such therapies might be effective against leukemia.