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Mutations Point the Way to New Leukemia Drugs

New research indicates that drugs that target a cell growth pathway known as the JAK-STAT pathway are likely to be effective against certain chronic leukemias.

Researchers recently discovered that a mutation in the *JAK2* gene is responsible for the majority of cases of three rare kinds of chronic leukemia, all of which are resistant to the leukemia drug Gleevec. The new study identifies a second mutation in the same pathway that can also cause the disease, leading researchers to think that drugs targeting JAK-STAT signaling should be effective against leukemias caused by either mutation.

"Now we have two targets that may be useful in the search for drug treatments to control chronic leukemia."

— Yana Pikman

In a study published July 18, 2006, in the online journal *Public Library of Science Medicine*, a team led by Yana Pikman, a Howard Hughes Medical Institute (HHMI) medical research fellow, and Ross L. Levine, a former HHMI medical research fellow, found a mutation in a gene called *MPL* in a subset of leukemias that lacked the more common *JAK2* mutation. HHMI medical research fellows are medical students who compete for the opportunity to spend a year doing full-time research.

D. Gary Gilliland, an HHMI investigator at Brigham and Women's Hospital and Harvard Medical School, is co-author of the paper.

We're excited about this finding because we hope to identify a common drug, an inhibitor of the *JAK2* pathway, to treat patients with these types of leukemia, said Gilliland, who in 2005 worked with Levine to identify the *JAK2* mutation responsible for most cases of myelofibrosis (MF), polycythemia vera (PV), and essential thrombocytosis (ET).

JAK2 normally encodes a protein that helps control the production of new blood cells. But when the gene is mutated, *JAK2*'s growth-stimulating signal gets turned on permanently, causing overproduction of one or another type of

blood cell. In different forms of the disease, the overabundant cells may be various kinds of white blood cells, platelets, or oxygen-carrying red blood cells.

Over time, this overproduction disrupts the balance of cells in the blood, hampers normal immune responses, overcrowds the bone marrow to make it dense and stiff, and forces blood formation to shift to the spleen and liver. Eventually those two organs become grossly enlarged; the end result is death.

Thus, the *JAK2* pathway is an important player in leukemia. Levine, Pikman, and Gilliland's new work shows that the pathway can be activated without a mutation in the *JAK2* gene itself. The new mutation they found lies in a gene called *MPL*. *MPL* encodes a receptor protein that sits on the surface of some blood cells and receives growth signals, communicating to *JAK2* when a signal has arrived. Mutated *MPL*, however, constantly tells *JAK2* to trigger growth—whether or not the appropriate signal has reached the cell. Thus, the end result is the same as that of a mutation that activates *JAK2* directly: uncontrolled growth and an imbalance of blood cells.

Now we have two targets that may be useful in the search for drug treatments to control chronic leukemia," said Pikman, lead author of the *PLoS Medicine* article and a student at Harvard Medical School. This new mutation is interesting because when we express it in mice, they get a very similar disease, so it may be a good model for testing drugs against leukemia," Pikman added. She said a search is already under way to identify small molecules that might be effective in overcoming the damage caused by the mutations.

The leukemias that the researchers study cannot be controlled by Gleevec, one of the first treatments that targets a known molecular defect. Gleevec, developed by HHMI investigators Brian J. Druker and Charles L. Sawyers, is very effective against the most common form of chronic leukemia, chronic myelogenous leukemia (CML), but there are many cases of chronic leukemia that Gleevec cannot control. Gleevec works by targeting the Philadelphia chromosome, a mutation that triggers excessive cell growth in many leukemias but does not exist in MF, PV, and ET.

The first mutation in *JAK2* stimulating the JAK-STAT pathway was discovered in 2005 by Gilliland and Levine, an instructor at Harvard Medical School and the senior author of the *PLoS Medicine* paper, and was also reported by several other laboratories in the United Kingdom, France, and Switzerland. That first mutation accounts for about half of the patients who have the three sub-types of chronic leukemia that Gleevec cannot control.

But we had found a significant number of patients who didn't have that mutation, Levine said. So this (new discovery) represents our first insight into the cases not attributable to the first mutation. It doesn't explain all of them, but it tells us more about this whole family of disorders. Gilliland said there probably are other mutations in the same pathway that explain additional

cases of leukemia.