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Researchers Closer to Understanding How One Mutation Causes Three Different Blood Disorders

A fresh look at the delicate dance of enzymes within living cells has provided insights into how one genetic mutation can lead to three distinct blood disorders.

The discovery “provides new and important insights into how this gene contributes to the development of myeloproliferative disease,” said D. Gary Gilliland, a Howard Hughes Medical Institute researcher at Brigham and Women's Hospital and Harvard Medical School. “It should provide an important foundation for subsequent development of new drugs,” he added.

The new research results, found in collaboration with biologist Harvey Lodish's team at the Whitehead Institute for Biomedical Research, were announced December 19, 2005, in an immediate early online publication in the *Proceedings of the National Academy of Sciences*.

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- D. Gary Gilliland

What the teams of scientists are trying to decipher is the molecular explanation for how the protein encoded by this single gene - called *JAK2V617F* - can be the culprit in three different leukemia-like diseases. They want to know how and why the protein produced by this gene cooperates with other signaling proteins to touch off disease.

The three leukemia-related disorders caused by the mutation are each characterized by abnormal growth of blood system cells. The first, polycythemia vera, involves ultra-high red blood cell counts. The second, essential thrombocythemia, results from excess growth of blood platelets. And the third, myelofibrosis with myeloid metaplasia, stems from abnormal

growth of fibroblast cells, making the bone marrow abnormally dense.

Patients who have these disorders are generally older, and there are about 100,000 in the United States. At present, patients with any of the three disorders receive empirically derived drug treatments similar to those that used to be used to treat chronic myelogenous leukemia (CML).

The three blood disorders can all become dangerous forms of adult leukemia. “They are technically cancers in their own right,” Gilliland explained. They tend to be slow-growing, and they are sometimes detected before severe symptoms arise, as is true with CML. Although relatively rare individually, together these disorders are about five times more common than CML, Gilliland said.

The research teams hope their findings will help them develop targeted drug therapies for the three disorders, similar to what has already been achieved for CML with the drug Gleevec.

In earlier work, Gilliland and three other teams of investigators found that the damaging mutation in the gene for JAK2V617F occurs later in life - and is acquired rather than inherited. It is not yet known why this single gene mutation causes different disorders in different patients, but it does show that those disorders have much in common. Other, more aggressive leukemias are known to result from different kinds of genetic damage, such as gene rearrangements caused by chromosome breakage.

The two research teams at Harvard and the Whitehead Institute studied the mutation, which occurs in a gene that makes an enzyme called a kinase. This particular kinase is one link in a chain - a kinase cascade—that sends a signal from the cell surface to the nucleus, spurring a reaction such as cell division.

The kinase is normally pressed into action by the arrival of a molecule that docks with a specific receptor sitting on the cell's surface. Arrival of the outside signal, like guests ringing a doorbell, sets off a cascade of events inside the cell. The kinase's job, once the doorbell is rung, is to add a phosphate group to another protein. This sends a message that eventually reaches the nucleus and sets off some action, such as cell division.

The problem is that a strategic mutation can change everything. In these three blood disorders, for example, the mutant gene makes an abnormal kinase, like a faulty doorbell that won't shut off, and the kinase constantly transmits a signal down the chain of command, whether it's needed or not. The signal thus spurs abnormal activity - and too much growth causes overgrowth of a particular type of blood cell, leading to leukemia.

The researchers demonstrated that the faulty kinase can only trigger this excessive growth in cells that have its corresponding receptor. Since this receptor is found only in certain types of blood cells, their work helps explain

why a mutation in *JAK2V617F* can trigger three distinct blood disorders - but has not been found to be associated with disorders originating in other types of blood cells.

Although more research is needed, “these studies advance our understanding of the basis of myeloproliferative diseases,” Gilliland said. “Ultimately it's going to lead to curative strategies - we hope.”