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Discovery of Mutation in Blood Stem Cells Provides Clues to Cancer Development

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A mutation in blood stem cells occurs in patients with a blood disorder called *polycythemia vera* (PV), scientists at the Moores Cancer Center at the University of California, San Diego (UCSD) and the Institute for Stem Cell Biology and Regenerative Medicine and Comprehensive Cancer Center at Stanford University School of Medicine have confirmed.

The discovery suggests that development of a very specific inhibitor at the stem-cell level, to interfere with the pathway leading to the disease, could improve treatment for the cancer-causing disorder.

According to research published in the April 3-7 early on-line edition of *Proceedings of the National Academy of Sciences*, patients with PV - a disease in which the patient's body makes too many red blood cells and which can lead to acute leukemia - have a mutation expressed in the stem cell, the point at which the body's blood cells become structurally and functionally specialized.

The scientists discovered that a mutation in the JAK2 signaling pathway allows the cells to bypass the body's usual mechanism of red blood-cell production, the binding of the hormone erythropoietin (EPO) to its receptor, a process which normally regulates the production of red blood cells. As a result of this intrinsic defect, the bone marrow produces excessive numbers of red blood cells.

"This discovery is important because if we can pinpoint an inhibitor that directly targets the JAK2 mutant allele, we can fight the disease without inhibiting normal stem cell differentiation. These patients could then still produce normal red blood cells, normal platelets and white blood cells," said Catriona H.M. Jamieson, M.D., Ph.D., assistant professor of medicine and Director for Stem Cell Research at UCSD's Moores Cancer Center.

"The body is very utilitarian," added Jamieson, first author of the study. "There are primal pathways that are important for regenerating cells and tissues, and those are the same pathways that cancers use, subverting normal processes and using them for the wrong purpose. The discovery of this mutation means we can look toward interrupting these pathways, systematically, without wiping out the patient's normal blood cells."

PV is diagnosed in approximately 10,000 to 15,000 people in the United States per year, but the disease has a high prevalence, meaning that people suffer from the disease over a long period of time. The major clinical consequence of PV is the development of thrombosis, in part related to the increased viscosity of the blood. The disorder can also lead to scarring of the bone marrow and acute leukemia. Currently, patients are treated by bleeding them (phlebotomy) or administering low-dose chemotherapy.

Co-author Jason Gotlib, M.D., M.S., assistant professor of medicine at the Stanford University School of Medicine said, "We now appreciate that the challenge in fighting certain forms of blood cancer is partly due to a reservoir of leukemic stem cells that are resistant to current therapies. The discovery of the *JAK2* mutation in stem cells in patients with PV is an important first step in developing treatments which target the earliest population of cells which propagate the disease."

The research also provides more insight into why some patients develop leukemia or other malignancies, while others don't, by identifying determinant cancer genes and the signaling pathways leading to the disease.

"It will tell us more about cancer and how cancer progresses," Jamieson added. "Usually, cancer isn't just there all of a sudden overnight; it develops by a series of mutations."

The next steps are to see how other stem cell functions on this pathway - such as self-renewal, survival and proliferation, are affected - and to duplicate this in-vitro research in mouse models. Working with specific inhibitors developed by local pharmaceutical companies, the UCSD and Stanford researchers plan to conduct clinical trials in the near future and are working with colleagues at Harvard University, the Mayo Clinic, and the M.D. Anderson Cancer Center in Houston to help expedite these trials.

The study's principle investigator was Irving L. Weissman, M.D., Director, Institute for Stem Cell Biology and Regenerative Medicine and the Virginia & D.K. Ludwig Professor for Clinical Investigation in Cancer Research at Stanford University. Additional contributors include Mark P. Chao, Carol Jones, Marla Lay, M. Rajan Mariappan, and James L. Zehnder at Stanford University; and Jeffrey A. Durocher and Stan L. Lilleberg at Transgenomic, Inc., Gaithersburg, MD.

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