Scientists Uncover Indicator that Warns Leukemia is Progressing to More Dangerous Form

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(PhysOrg.com) -- Scientists at the Moores Cancer Center at the University of California, San Diego, Stanford University School of Medicine and other centers have identified a mechanism by which a chronic form of leukemia can progress into a deadlier stage of the disease. The findings may provide physicians with an indicator of when this type of cancer - chronic myeloid leukemia (CML) - is progressing, enabling them to make more accurate prognoses for the disease and improved treatment choices.

“If we can predict when a patient is moving from the chronic phase in CML to the blast crisis stage, then we can hopefully intervene before it’s too late,” said Catriona H.M. Jamieson, MD, PhD, assistant professor of medicine at the UC San Diego School of Medicine and Director for Stem Cell Research at the Moores UCSD Cancer Center.

The findings, reported online during the week of February 16, 2009 in the Proceedings of the National Academy of Sciences, also shed light on the development of potentially treatment-resistant leukemia stem cells and provide insights for new strategies against CML and other cancers.

Led by Jamieson and Irving Weissman, MD, director of the Stem Cell Biology and Regenerative Medicine Institute at the Stanford University School of Medicine, the researchers discovered that when a molecular off-switch called glycogen synthase kinase (GSK) 3 beta becomes faulty in chronic stage CML cells, it fails to turn off another protein, beta-catenin. This in turn enables pre-leukemia stem cells to develop into leukemia stem cells and expand their numbers, leading to progression to the more dangerous “blast crisis” stage of CML. This errant off-switch is a potential therapeutic target, Jamieson explained.

“This paper further underscores the importance of the cell type and specific context of molecular events in the evolution of leukemia,” Jamieson said. “It also highlights the malignant consequences of GSK 3 beta deregulation.”

“This knowledge may enable us to design and develop more effective, personalized therapies for these patients,” said staff research associate and co-first author Annelie Abrahamsson.

In CML, an enzyme called ABL goes into overdrive because of a chromosomal mix-up that occurs during blood cell development. The genes ABL and BCR fuse and produce a hybrid BCR-ABL enzyme that drives the excessive proliferation of white blood cells. CML progresses from a chronic stage in hematopoietic stem cells that carry BCR-ABL to the blast crisis stage. This stage is characterized by the over-production of beta-catenin in white blood cells called granulocyte macrophage progenitors (GMP) - in effect, leukemia stem cells.

According to Jamieson, a major roadblock in predicting and stopping the conversion of chronic CML to blast crisis stage was the failure to understand what turned on beta-catenin. The team showed that by injecting blast crisis CML progenitor cells - GMP - into mice lacking working immune systems, they could “transplant” leukemia into the animals. When they did this, they discovered that GSK 3 beta levels dropped. Looking more closely, they found an aberrant “misspliced” form of GSK 3 beta that was unable to turn off beta-catenin, suggesting a potential mechanism behind the change to blast crisis stage.

The scientists also showed that the mice that had received the cells with the bad form of GSK 3 beta developed granulocytic sarcomas, tumors that are seen in patients with the most advanced form of

CML.

“Many investigators have questioned the usefulness of finding and purifying leukemia and cancer stem cells,” said Weissman. “This paper shows why. The damage to the enzyme GSK 3 beta that prevents beta-catenin activation of cell proliferation occurs only in the GMP leukemia stem cells, which are only about 1 in 20 bone marrow cells. Trying to analyze the missplicing of GSK in the whole leukemia would not have worked.

“These kinds of changes in gene expression, which are not mutations, need pure cells to find them. The final proof of the cancer stem cell hypothesis will be to show whether a treatment specific for the changed gene expression eliminates the cancer in the patient.”

“Downregulating beta-catenin and GSK deregulation may have other implications in many cancers,” Jamieson said. “By studying CML, we can understand the molecular evolution of disease and the stepwise progression to cancer. It becomes a useful paradigm for understanding how cancers evolve and the pathways that are essential to escape the normal control mechanisms.”

Provided by UC San Diego

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