Targeting cell pathway may prevent relapse of leukemia

March 25 2010

About 40 percent of children and up to 70 percent of adults in remission from acute myelogenous leukemia (AML) will have a relapse. In recent years, doctors have come to believe that this is due to leukemia stem cells, endlessly replicating cancer cells that generate the immature blood cells characteristic of leukemia and are resistant to typical cancer treatments. Now, researchers at Children's Hospital Boston have found a possible way to kill off these cells, and prevent them from initiating a relapse.

The study, published online March 26th in the journal *Science,* shows that leukemia stem cells cannot thrive without a particular cell pathway, known as the Wnt/beta-catenin pathway, suggesting that targeting this pathway may prevent the growth and development of AML.

"The biggest potential for this study is in suppression of leukemia recurrence by a drug that inhibits beta-catenin," says Scott Armstrong, MD, PhD, of Children's Division of Pediatric Hematology/Oncology and senior author of the study.

Yingzi Wang, PhD, of Children's Division of Pediatric Hematology/Oncology, a member of Armstrong's team and lead author of the study, zeroed in on beta-catenin as an important player in leukemia stem cells by working with two different types of early blood cells - blood stem cells, which generate all the different types of blood cells, and granulocyte/macrophage-restricted progenitors, more mature, differentiated cells that only generate certain white blood cells. They did

this by activating two genes previously found to induce AML, Hoxa9 and Meis1, then injecting the cells into mice.

Activation of the two genes induced AML in mice injected with the blood stem cells, but not in mice injected with the progenitors. Genetic analyses revealed the progenitors lacked an active beta-catenin pathway. Though this pathway is still active in blood stem cells after a person is born, it plays a vital role only during fetal development, and is completely inactive in more differentiated progenitor cells. This led the team to think beta-catenin was needed for leukemia stem cells to develop, thrive and induce leukemia.

To test this idea, the researchers introduced an active form of beta-catenin into the progenitor cells after activating Hoxa9 and Meis1. Once injected into mice, these progenitor cells later induced leukemia.

The researchers further confirmed the role of beta-catenin by treating mice they had injected with leukemia stem cells with the drug indomethacin, which blocks the beta-catenin pathway. Tests showed the number of leukemia stem cells dwindled in the mice that received the drug. Indomethacin also reduced the number of stem cells in mice with fully-developed leukemia.

Most young children with AML develop the disease as a result of what researchers call mixed lineage leukemia fusion proteins, which can activate the Hoxa9 and Meis1 genes. To see if one of these proteins also affected the beta-catenin pathway, the team treated progenitor cells with the mixed lineage leukemia fusion protein MLL-AF9. MLL-AF9 activated Hoxa9 and Meis1, as well as the beta-catenin pathway, and the mice injected with these progenitor cells developed leukemia. But when the mice were treated with an agent to deactivate the beta-catenin pathway in vivo, the leukemia stem cells could not thrive.

This research suggests that leukemia stem cells need the beta-catenin pathway to survive, and treatments that block this pathway may eradicate the leukemia stem cells and prevent AML patients from having a relapse .

Before these findings can be applied in the clinic, better beta-catenin inhibitors are needed, since it's not known if indomethacin can be given to people with leukemia in high enough doses to wipe out leukemia stem cells without having toxic effects, Armstrong says. The next step for researchers is to determine the reason why leukemia stem cells need the beta-catenin pathway to survive.

"Any step along the pathway is a potential therapeutic opportunity," Armstrong says.

More information: Yingzi Wang, Andrei V. Krivtsov, Amit U. Sinha, Trista E. North, Wolfram Goessling, Zhaohui Feng, Leonard I. Zon, Scott A. Armstrong. "The Wnt/b-catenin Pathway Is Required for the Development of Leukemia Stem Cells in AML." *Science* March 26, 2010.

Provided by Children's Hospital Boston