

Developing cancer treatments directed at critical developmental pathway

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Researchers from the University of Pennsylvania School of Medicine and colleagues discovered that the Notch signaling pathway, which determines the development of many cell types, and is also implicated in some cancers, is not universally essential for the maintenance of stem cells. The findings appear this week in *Cell Stem Cell*, and indicate that inhibitors of Notch may not affect bone marrow stem cells.

Notch is one of a select set of proteins that influence the development of a wide variety of types of cells. Prior work has shown that increases in signals generated by Notch are important in certain human tumors, particularly some kinds of childhood leukemia, making Notch an attractive target for new cancer therapies.

However, it has also been suggested that Notch is needed to maintain the stem cells in the bone marrow from which normal blood cells are formed, raising the concern that Notch inhibitors might destroy the normal bone marrow. “This potential risk raised important questions about treating leukemia patients with Notch inhibitors,” notes senior author Warren Pear, MD, PhD, Associate Professor of Pathology and Laboratory Medicine and the Abramson Family Cancer Research Institute.

Previous work from the Pear lab and others has shown that Notch signals are required for the proper development of lymphocytes. More importantly in terms of human disease, work done together with co-author Jon Aster’s lab at Harvard over the last decade has shown that

abnormal increases in Notch signaling cause T-cell acute lymphoblastic leukemias, which make up about 15-20 percent of childhood leukemias. Growth of these leukemias can be stopped in the laboratory by new kinds of Notch pathway inhibitors.

“We have several projects focused on the development of new leukemia therapies that are designed to inhibit Notch,” notes Pear. “But it was important to know if this would have detrimental effects on bone marrow stem cells.”

This new work from the Pear group and colleagues showed definitively that adult bone marrow stem cells do not require Notch signals, indicating that it should be possible to give these inhibitors to patients without fear of causing bone marrow failure.

Source: University of Pennsylvania

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