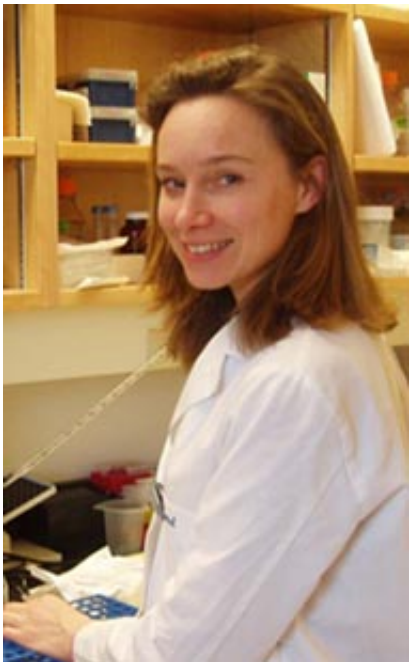


Researchers discover normal molecular pathway affected in poor-prognosis childhood leukemia

June 6 2013



Patricia Ernst, Ph.D., is co-director of Cancer Mechanisms, at Dartmouth-Hitchcock Norris Cotton Cancer Center. Credit: Dartmouth-Hitchcock

Through genetic engineering of laboratory models, researchers at Dartmouth-Hitchcock Norris Cotton Cancer Center have uncovered a vulnerability in the way cancer cells diverge from normal regenerating cells that may help treat children with leukemia as reported in the journal *PNAS* on June 3, 2013. Dartmouth researchers are trying to

understand the key pathways that distinguish how a normal blood cell grows and divides compared to the altered growth that occurs in leukemia. In addition to the treatment of leukemia, the work has relevance for expanding umbilical cord blood or bone marrow stem cells for transplantation.

Leukemia often occurs due to chromosomal translocations, which are broken chromosomes that cause [blood cells](#) to grow uncontrollably. One gene that is involved in chromosomal translocations found at high frequency in [childhood leukemia](#) is the MLL1 (Mixed Lineage Leukemia 1) gene. Conventional chemotherapy is very ineffective at curing patients with this translocation, in contrast to other types of childhood leukemia, which are relatively curable.

Using [genetic engineering](#), the researchers generated a [mouse model](#) to discover genes that are regulated by MLL1 in hematopoietic stem cells, the cells that give rise to all white and [red blood cell](#) types. In the course of these studies, they identified several [unique properties](#) of the normal MLL1 pathway in hematopoietic stem cells that may be exploited to better treat leukemia harboring MLL1 translocations.

"We discovered that many genes that depend upon the normal MLL1 protein are involved in maintaining hematopoietic stem cells, thus manipulating this pathway could be a way to expand cells from normal bone marrow or umbilical cord blood donors to improve transplantation of these cell types, which is a procedure used to treat certain chemotherapy-resistant cancers," said Patricia Ernst, PhD, co-director Cancer Mechanisms, Dartmouth-Hitchcock Norris Cotton Cancer Center, associate professor of Genetics and of Microbiology and Immunology at the Geisel School of Medicine at Dartmouth, Hanover, NH.

As principle investigator, Ernst and her team set out to discover the

genetic pathways controlled by the normal form of the MLL1 protein and leukemogenic MLL1 fusion proteins specifically in [hematopoietic stem cells](#) (HSCs). Delineation of these pathways will facilitate research by her group and others aimed at developing strategies to kill leukemia cells without harming HSCs, which are often profoundly affected by current chemotherapeutic regimens. In performing this research, they also discovered a new molecular pathway that controls normal HSC biology.

"We demonstrate in this study, that some direct MLL1 target genes in HSCs are affected by Menin loss (a protein involved in the inherited disorder, Multiple Endocrine Neoplasia), and some are not," said Ernst. "This is a fundamentally important observation that demonstrates this category of chromatin modifiers utilizes different protein complexes/mechanisms to target different classes of genes in different cell types."

Ernst points out that this highly desirable outcome that would not have been predicted for this targeted therapy and may illustrate that drugs blocking the interaction of these two proteins (currently under development by other groups) leave normal hematopoiesis intact. She is working on follow-up studies of this finding.

Provided by Dartmouth-Hitchcock Medical Center

Citation: Researchers discover normal molecular pathway affected in poor-prognosis childhood leukemia (2013, June 6) retrieved 27 April 2024 from <https://medicalxpress.com/news/2013-06-molecular-pathway-affected-poor-prognosis-childhood.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.
