Study ties protein 'reader' ENL to common leukemia

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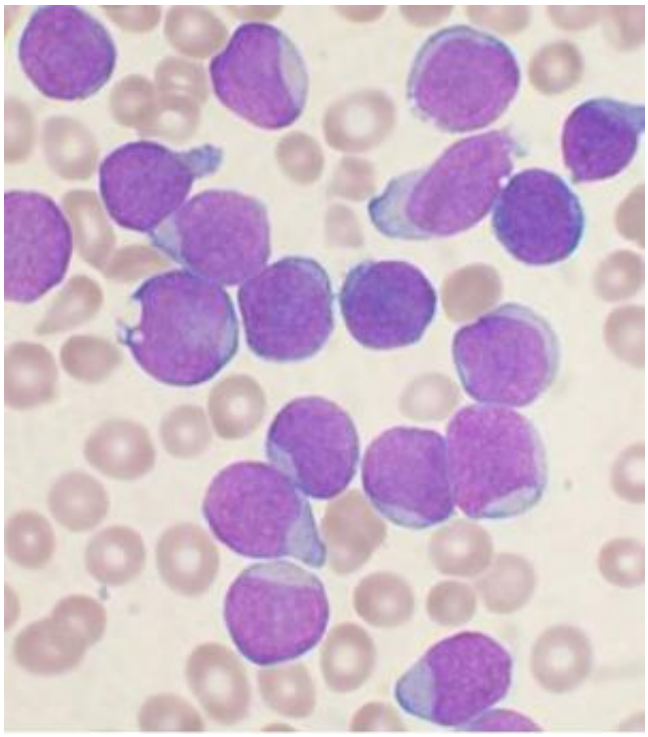

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

Anyone who uses an employee badge to enter a building may understand how a protein called ENL opens new possibilities for treating acute myeloid leukemia (AML), a fast-growing cancer of bone marrow and blood cells and the second most common type of leukemia in children and adults.

Findings from a study at The University of Texas MD Anderson Cancer Center revealed the leukemia-boosting abilities of ENL, which contains a protein component called YEATS that "reads" histone proteins. Histone proteins make up chromatin, large clusters of DNA- and RNA-containing molecules comprising our body's chromosomes. Just as a scanner "reads" data on an identification badge, ENL recognizes a type of histone modification known as acetylation.

Research results, which build upon a previous MD Anderson study of histone-reading proteins, are published in the March 1 online issue of *Nature*. The findings indicated treatment against ENL with a class of experimental drugs called bromodomain and extra-terminal (BET) inhibitors may be effective for treating AML.

"Our study showed that ENL is required for disease maintenance in AML," said Xiaobing Shi, Ph.D., associate professor of Epigenetics and Molecular Carcinogenesis. "Depletion of ENL led to anti-leukemic effects, suppressing growth both in vivo and in vitro. Notably, disrupting ENL further sensitized leukemia cells to BET inhibitors."

Histone modifications like acetylation serve as docking sites for reader proteins which recognize specific modifications, influencing downstream biological outcomes. While many such reader proteins have been identified for histone modifications called methylation, few are known to recognize histone acetylation.

Shi's team employed CRISPR, a gene-editing tool, to deplete ENL and suppress cancer gene expression, which was crucial given that cancer cells often co-opt chromatin regulatory pathways.

"Targeting epigenetic readers represents a class of anti-cancer therapy that we believe holds clinical promise," said Hong Wen, Ph.D., research assistant professor of Epigenetics and Molecular Carcinogenesis and co-first author of the paper. "Our study revealed ENL as a chromatin reader that regulates oncogenic programs, thus establishing ENL as a potential drug target for AML."

More information: ENL links histone acetylation to oncogenic gene expression in acute myeloid leukaemia, *Nature*,

nature.com/articles/doi:10.1038/nature21687