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Preclinical study shows potential to increase the effectiveness of leukemia treatments

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Preclinical experiments led by a team of researchers at VCU Massey Cancer Center have shown that blocking the production of a protein known as chromodomain helicase DNA-binding protein 4 (CHD4) may help increase the effectiveness of first-line treatments for acute myeloid leukemia (AML), a particularly lethal blood cancer that is increasing in incidence among older adults.

Recently published in the journal *Blood*, the novel findings demonstrate that depletion of the CHD4 protein makes AML cells more susceptible to standard chemotherapy agents by reducing their ability to repair DNA damage. Importantly, blocking CHD4 did not increase the sensitivity of healthy bone marrow cells to the chemotherapy agent or affect their growth. Additionally, the scientists found that depletion of CHD4 decreased the ability of AML cells to form colonies in preclinical laboratory and animal models. These tumor-forming properties are thought to be a major cause of AML relapse in patients who respond to first-line chemotherapy regimens.

"We are very encouraged by these findings," says the study's lead author Gordon Ginder, M.D., who is director of Massey Cancer Center, Lipman Chair in Oncology, a member of Massey's Cancer Molecular Genetics research program and a professor of internal medicine in the Division of Hematology, Oncology and Palliative Care at the VCU School of Medicine. "Targeting the CHD4 protein could allow us to reduce chemotherapy doses, which could potentially mean more effective first- and second-line treatments with fewer serious side effects."

CHD4 is an enzyme that is involved in silencing tumor suppressor genes in cancer cells. Recently, it has been shown to play a role in repairing DNA damage, which is a major mechanism through which chemotherapy kills cancer cells. In preclinical experiments, the researchers observed that CHD4 depletion severely restricted the ability of AML cells to develop colonies in soft agar models as well as established tumors in mouse models (both types of models provide methods for confirming a hallmark of tumor-initiating cells). In addition, blocking the production of CHD4 rendered AML cells more sensitive to daunorubicin and cytarabine, two chemotherapy agents that are the basis for standard initial AML treatment.

"This study builds on our team's efforts to understand the molecular processes through which epigenetic regulators impact gene expression," says Ginder. "Future studies will attempt to uncover the detailed mechanism through which CHD4 decreases the ability of AML cells to initiate leukemia and will look for potential ways to target this important protein. The fact that it functions as an enzyme suggests it may be druggable."

More information: The full manuscript of this study is available online at: www.bloodjournal.org/content/1 … ong?sso-checked=true

Provided by Virginia Commonwealth University

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