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Study may widen patient pool that benefits from EPZ-5676 against acute myeloid leukemia

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A University of Colorado Cancer Center study published today in the *Journal of Clinical Investigation* shows a weak link in the chain of events that causes an aggressive subtype of acute myeloid leukemia (AML). The study also suggests a possible tool to break this link.

"There's a gene called meningioma-1 or MN1. When it's overexpressed in AML, the prognosis is poor. And when you take this gene and put it in mouse bone marrow, it causes aggressive leukemia. However, it hasn't been clear quite what this gene does," says Kathrin Bernt, MD, investigator at the CU Cancer Center and assistant professor in the Molecular Biology Program at the CU School of Medicine.

In other words, the field has a known cause (MN1) and a known effect (aggressive leukemia), but between these two has been a black box in which the mechanism of oncogenesis takes place.

"Unfortunately, it is currently impossible to use a medicine to directly target a gene. We can't simply switch off MN1. Instead, we must look for essential steps between the existence of gene alteration and the advent of cancer in which to intervene. We can't target MN1, but we can target the program that has to be there for MN1 to do its job," Bernt says.

Discovering this program required opening the black box of oncogenesis

between MN1 alteration and aggressive AML. Bernt and colleagues did this by inducing the overexpression of MN1 in mouse models and noticing the genes that changed in response. These genes looked familiar - MN1 overexpression resulted in the activation of genes previously known to predispose cells to develop AML, namely HoxA9 and Meis1.

"Interestingly, these genes also depend on chromatin regulators," Bernt says. Chromatin regulators help to control the structure of DNA as it is packed for storage or unpacked to be "read". The Bernt lab identified two chromatin regulators essential for creating the environment that MN1 needs to cause leukemia: Mll1 and Dot1l. While MN1 can currently not be "drugged", these molecules that remodel chromatin can. One obvious question is whether it would do any good.

"In mice, we put MN1 in first, leading to AML. Then we knocked out these chromatic regulating molecules, Mll1 or Dot1l. When we did that, the leukemia collapsed," Bernt says.

With promising results in mouse models, the group gathered samples of human AML defined by the over-abundance of MN1, as well as two additional genes, HOXA9 and MEIS1, which are key targets of DOT1L and MLL1. When Bernt and colleagues used the same mouse-model strategy of Dot1l inhibition, these samples of human AML were killed.

Anti-cancer agents targeting Dot1l are already in clinical trials. For example, the experimental anti-cancer agent EPZ-5676 inhibits Dot1l and is currently being tested in a phase I clinical trial in pediatric patients with aggressive leukemias (NCT02141828) marked by a different gene rearrangement, namely aberrations in the MLL1 gene.

"The existing trial targets patients with rearrangements in the gene MLL1. Our study shows another subset of patients that may benefit from this or other therapies aimed at DOT1L inhibition, namely patients

with MN1 overexpression," Bernt says.

Challenges exist before the group hopes to collaborate in a clinical trial of EPZ-5676 against AML marked by MN1 overexpression. For example, "Overexpression exists along a spectrum. At what degree of MN1 overexpression does it become clinically significant?" Bernt asks. Defining the cutoff of MN1 overexpression at which the disease is susceptible to Dot1l inhibition will require further work with AML samples. However, the group remains optimistic that further study could lead to targeted treatment for this subsample of patients with especially aggressive AML.

More information: Simone S. Riedel et al. MLL1 and DOT1L cooperate with meningioma-1 to induce acute myeloid leukemia, *Journal of Clinical Investigation* (2016). DOI: 10.1172/JCI80825

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