

# Animal model demonstrates role for metabolic enzyme in acute myeloid leukemia

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In recent years, mutations in two metabolic enzymes, isocitrate dehydrogenase-1 and 2 (IDH1 and IDH2), have been identified in approximately 20 percent of all acute myeloid leukemias (AML). As a result, mutant IDH proteins have been proposed as attractive drug targets for this common form of adult leukemia.

Now a scientific team at Beth Israel Deaconess Medical Center (BIDMC) has generated a [transgenic mouse model](#) of the most common IDH2 mutation in human AML, and, in the process, answered a central question of whether these mutant IDH proteins are required for leukemia initiation and maintenance in a living organism.

Currently published on-line in the journal *Cell Stem Cell* and scheduled to appear in print in March, these new findings confirm a potent oncogenic role for IDH2, and support its relevance as a therapeutic target for the treatment of this widespread blood cancer. Equally important, this transgenic model provides an important new tool for evaluating the pharmacological efficacy of potential mutant IDH2 inhibitors, either alone or in combination with other compounds.

"The real hope is that we would one day be able to treat IDH2-mutant leukemia patients with a drug that targets this genetic abnormality," explains senior author Pier Paolo Pandolfi, MD, PhD, Director of the Cancer Center and the Cancer Research Institute at BIDMC and the George C. Reisman Professor of Medicine at Harvard Medical School. "Our transgenic animal model has now demonstrated that the IDH

mutation contributes to the initiation of acute leukemia in vivo and that mutant IDH is essential for the maintenance of leukemic cells even in a genetic setting where mutant IDH is not required for cancer initiation."

IDH1 and IDH2 proteins are critical enzymes in the TCA cycle, which is centrally important to many biochemical pathways. Mutated forms of these proteins gain a novel ability to produce 2-hydroxyglutarate (2HG), a metabolite that has been shown to accumulate at high levels in cancer patients and is therefore described as an "oncometabolite."

"Our goal was to generate an animal model of mutant IDH that was both inducible and reversible," explains co-lead author Markus Reschke, PhD, an investigator in BIDMC's Cancer Research Institute and Research Fellow in the Pandolfi laboratory. "This enabled us to address an important unanswered question: Does inhibition of mutant IDH proteins in active disease have an effect on tumor maintenance or progression in a living organism?"

Reschke and co-lead author Lev Kats, PhD, also a Research Fellow in the Pandolfi lab, studied two different models: a retroviral transduction model and a genetically engineered model in which IDH mice were crossed to mice harboring other leukemia-relevant mutations.

In the first model, the IDH mutation was combined with the oncogenes HoxA9 and Meis1a, two downstream targets of numerous pathways that are deregulated in AML. The results showed evidence of differentiation within two weeks of genetic deinduction of mutant IDH, and two weeks later, six of eight animals showed complete remission with elimination of any detectable leukemic cells.

These results, say the authors, were both surprising and encouraging, demonstrating a situation in which IDH mutation occurs as an early event and leukemic transformation occurs as a result of subsequent

genetic "hits."

"The retroviral model enabled us to observe that mutant IDH2 is essential for the maintenance of HoxA9/Meis1a-induced AML," explains Kats. "But this was still a surrogate model – this isn't what happens in human patients, per se."

The investigators, therefore, went on to develop a transgenic model that more closely recapitulates the genetics of human AML.

"By crossing the mutant IDH2 animals with other leukemia-relevant mutations, including mutations in the FMS-like tyrosine kinase 3 [FLT3], we observed that compound mutant animals developed acute leukemias," explains Reschke. "This exciting finding told us that mutant IDH2 contributes to leukemia initiation in vivo." As with the retroviral transduction model, genetic deinduction of mutant IDH2 in the context of a cooperating Flt3 mutation resulted in reduced proliferation and/or differentiation of [leukemic cells](#), further demonstrating that mutant IDH2 expression is required for leukemia maintenance.

"This model has validated [mutant](#) IDH proteins as very strong candidates for continued development of targeted anticancer therapeutics," says Pandolfi. "The [model](#) will also be of paramount importance to study mechanisms of resistance to treatment that may occur."

Provided by Beth Israel Deaconess Medical Center

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