

Mutation in gene IDH a possible target for AML treatment

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Many patients with acute myeloid leukemia (AML) share a mutation in a gene called IDH. A University of Colorado Cancer Center study published this week in the journal *Leukemia & Lymphoma* shows that this IDH mutation may be the first domino in a chain that leads to a more aggressive form of the disease.

"In fact, it's not IDH itself that causes the problem," says Dan Pollyea, MD, MS, investigator at the CU Cancer Center and assistant professor of hematologic oncology at the University of Colorado School of Medicine. Rather, the mutation in IDH leads to exponentially higher blood levels of a protein called 2-hydroxyglutarate. This protein "mucks up," as Pollyea says, other genes that in turn promote cancer or fail to inhibit its growth.

The recent study shows that AML patients in remission who retain high levels of 2-hydroxyglutarate – due universally to IDH mutation – are much more likely to relapse than patients without similarly elevated levels.

The chain of causation includes another couple links.

"2-hydroxyglutarate reduces genes' ability to regulate themselves," says Pollyea. Over time genes accumulate gunk in the form of methylation – these methyl groups attach to silence parts of gene promoters, helping to decide which genes are and are not turned into proteins. Too much methylation is associated with many cancers, including AML. And

2-hydroxyglutarate turns off one of the body's methylation-regulating genes.

So an IDH mutation leads to high 2-hydroxyglutarate, leads to bad gene regulation, leads to hypermethylation, leads to AML.

Pollyea hopes to stop the first domino from falling by targeting IDH [mutations](#). "Imagine screening for patients prospectively and then if they have the mutation, we could use something like an IDH inhibitor," Pollyea says. Turn off this mutation and doctors may be able to turn off the disease, or at least its most aggressive characteristics.

But the genetic testing for IDH mutation is currently costly and time consuming. And so Pollyea hopes to identify patients with the IDH mutation by looking downstream – tests for blood-levels of 2-hydroxyglutarate being developed at the CU [Cancer Center](#) could determine the [patients](#) most likely to benefit from an IDH inhibitor.

Finally, Pollyea and colleagues including molecular biologist James DeGregori, PhD, are exploring novel ways to target the IDH mutation. "I think that even beyond the very real promise of IDH inhibitor drugs, this is a potential weak spot for AML that can be targeted in a number of ways," Pollyea says.

Pollyea also points out that IDH mutations were first discovered in brain tumors and have also been found in other cancers. A technique targeting IDH mutation in AML may have wide-ranging implications for a variety of cancers.

Provided by University of Colorado Denver

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