Adding oxidative stress to FLT3 inhibition proves promising combination against AML

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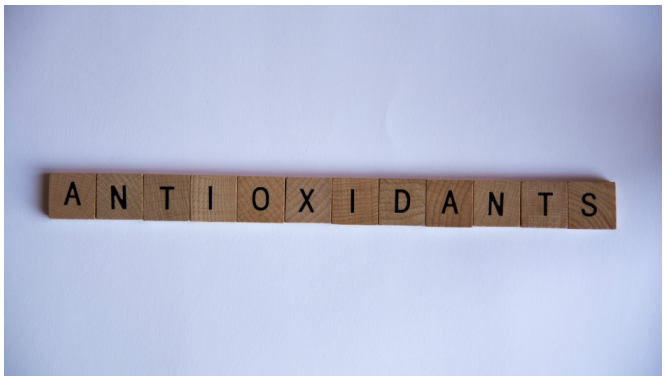

Credit: CU Anschutz Medical Campus

FLT3 inhibitors are a promising new class of drugs targeting acute myeloid leukemia (AML). However, these inhibitors alone tend not to result in long-term control of the disease. A University of Colorado Cancer Center study published today in the *Proceedings of the National Academy of Sciences* demonstrates the promise of adding drugs that increase oxidative stress to FLT3 inhibition, potentially paving the way for combination therapy directed at the disease.

"Essentially, we turned off every single gene in the genome, one by one, and asked which genes, when we turn them off, make AML cells more sensitive to these FLT3 inhibitors," says Mark Gregory, PhD, research instructor in the CU School of Medicine Department of Biochemistry and Molecular Genetics, who works in the lab of CU Cancer Center Associate Director, James DeGregori, PhD.

The group found that many of these genes that were "synthetic lethal" with FLT3 inhibitors were involved in controlling a cell's antioxidant response - basically, the genes discovered in this screen helped cells clear themselves of or protect against reactive oxygen species (ROS), the abrasive and potentially toxic byproducts of oxygen metabolism.

"At first we weren't really clear why genes that control antioxidant response would be protecting these cells," Gregory says. "Later we discovered that FLT3 inhibitors were inducing a great deal of oxidative stress. When you knock out a cell's ability to deal with this oxidative stress, it becomes overwhelming and you kill a lot more of the leukemia cells."

As a trip to the health food store's supplement aisle implies, antioxidants may protect healthy cells. Unfortunately, this study shows that the body's natural antioxidants may also protect the cells of acute myeloid leukemia from therapy.

Specifically, the group found that when they silenced the gene ATM, cells with this silenced gene were more susceptible to FLT3 inhibition. In fact, this gene works through another "downstream" gene, G6PD, and the group found that inhibiting G6PD had a similar sensitizing effect. Turning off ATM or G6PD impairs a cell's ability to make glutathione, an important antioxidant that prevents damage from free radicals and peroxides associated with oxidative stress.

"When you turn off these genes, the AML cells are no longer able to make glutathione and you get a buildup of oxidative stress in the mitochondria, which triggers cell death," Gregory says.

Because drugs to inhibit ATM and/or G6PD are not yet available, the group explored a creative alternative.

"Rather than inhibiting these genes that protect against oxidative stress, we wondered what would happen if we combined FLT3 inhibition with drugs that induce even more oxidative stress," Gregory says.

In both cell-based and mouse models of AML, adding a drug designed to induce oxidative stress resulted in far improved efficacy of FLT3 inhibition.

"We think this approach is very promising," Gregory says. "There are many different pro-oxidative drugs in the clinic. Getting the right combination of one of these drugs with an FLT3 inhibitor could be very promising for AML."

More information: Mark A. Gregory et al, ATM/G6PD-driven redox metabolism promotes FLT3 inhibitor resistance in acute myeloid leukemia, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1603876113