Vitamin C may encourage blood cancer stem cells to die

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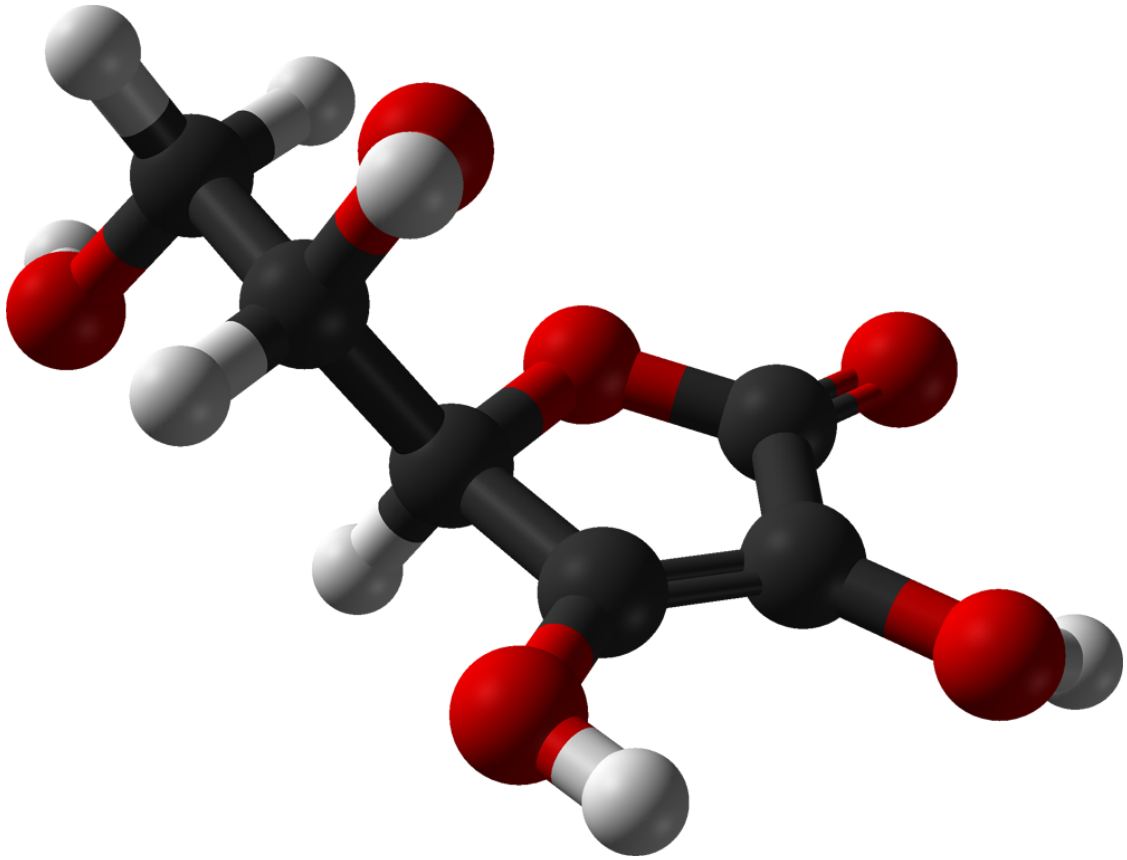

Ball-and-stick model of the L-ascorbic acid (vitamin C) molecule, $C_6H_8O_6$, as found in the crystal structure. Credit: public domain

Vitamin C may "tell" faulty stem cells in the bone marrow to mature and die normally, instead of multiplying to cause blood cancers. This is the finding of a study led by researchers from Perlmutter Cancer Center at NYU Langone Health, and published online August 17 in the journal *Cell*.

Certain genetic changes are known to reduce the ability of an enzyme called TET2 to encourage stem cells to become mature blood cells, which eventually die, in many patients with certain kinds of leukemia, say the authors. The new study found that vitamin C activated TET2 function in mice engineered to be deficient in the enzyme.

"We're excited by the prospect that high-dose vitamin C might become a safe treatment for blood diseases caused by TET2-deficient leukemia stem cells, most likely in combination with other targeted therapies," says corresponding study author Benjamin G. Neel, MD, PhD, professor in the Department of Medicine and director of the Perlmutter Cancer Center.

Changes in the genetic code (mutations) that reduce TET2 function are found in 10 percent of patients with acute myeloid leukemia (AML), 30 percent of those with a form of pre-leukemia called myelodysplastic syndrome, and in nearly 50 percent of patients with chronic myelomonocytic leukemia. Such cancers cause anemia, infection risk, and bleeding as abnormal stem cells multiply in the bone marrow until they interfere with blood cell production, with the number of cases increasing as the population ages.

Along with these diseases, new tests suggest that about 2.5 percent of all U.S. cancer patients - or about 42,500 new patients each year - may develop TET2 mutations, including some with lymphomas and solid tumors, say the authors.

Cell Death Switch

The study results revolve around the relationship between TET2 and cytosine, one of the four nucleic acid "letters" that comprise the DNA code in genes. Every cell type has the same genes, but each gets different instructions to turn on only those needed in a given cellular context.

These "epigenetic" regulatory mechanisms include DNA methylation, the attachment of a small molecule termed a methyl group to cytosine bases that shuts down the action of a gene containing them.

The back- and-forth attachment and removal of methyl groups also fine-tunes gene expression in stem cells, which can mature, specialize and multiply to become muscle, bone, nerve, or other cell types. This happens as the body first forms, but the bone marrow also keeps pools of stem cells on hand into adulthood, ready to become replacement cells as needed. In leukemia, signals that normally tell a blood stem cell to mature malfunction, leaving it to endlessly multiply and "self-renew" instead of producing normal white blood cells needed to fight infection.

The enzyme studied in this report, Tet methylcytosine dioxygenase 2 (TET2), enables a change in the molecular structure (oxidation) of methyl groups that is needed for them to be removed from cytosines. This "demethylation" turns on genes that direct stem cells to mature, and to start a count-down toward self-destruction as part of normal turnover. This serves as an anti-cancer safety mechanism, one that is disrupted in blood cancer patients with TET2 mutations, says Neel.

To determine the effect of mutations that reduce TET2 function in abnormal stem cells, the research team genetically engineered mice such that the scientists could switch the TET2 gene on or off.

Similar to the naturally occurring effects of TET2 mutations in mice or

humans, using molecular biology techniques to turn off TET2 in mice caused abnormal stem cell behavior. Remarkably, these changes were reversed when TET2 expression was restored by a genetic trick. Previous work had shown that vitamin C could stimulate the activity of TET2 and its relatives TET1 and TET3. Because only one of the two copies of the TET2 gene in each stem cell is usually affected in TET2-mutant blood diseases, the authors hypothesized that high doses of vitamin C, which can only be given intravenously, might reverse the effects of TET2 deficiency by turning up the action of the remaining functional gene.

Indeed, they found that vitamin C did the same thing as restoring TET2 function genetically. By promoting DNA demethylation, high-dose vitamin C treatment induced stem cells to mature, and also suppressed the growth of leukemia cancer stem cells from human patients implanted in mice.

"Interestingly, we also found that vitamin C treatment had an effect on leukemic stem cells that resembled damage to their DNA," says first study author Luisa Cimmino, PhD, an assistant professor in the Department of Pathology at NYU Langone Health. "For this reason, we decided to combine vitamin C with a PARP inhibitor, a drug type known to cause cancer cell death by blocking the repair of DNA damage, and already approved for treating certain patients with ovarian cancer."

Researchers found that the combination had an enhanced effect on leukemia stem cells, further shifting them from self-renewal back toward maturity and cell death. The results also suggest that vitamin C might drive leukemic stem cells without TET2 mutations toward death, says Cimmino, given that it turns up any TET2 activity normally in place.

"Our team is working to systematically identify genetic changes that contribute to risk for leukemia in significant groups of patients," says

corresponding author Iannis Aifantis, PhD, professor and chair of the Department of Pathology at NYU Langone Health. "This study adds the targeting of abnormal TET2-driven DNA demethylation to our list of potential new treatment approaches."

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