'Mutation accelerator' identified in gene mutation linked to common adult leukemia

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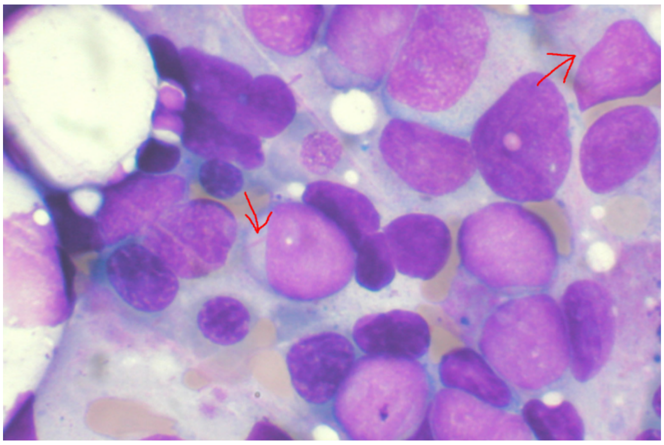

Bone marrow aspirate showing acute myeloid leukemia. Several blasts have Auer rods. Credit: Wikipedia

In preliminary experiments with mice and lab-grown cells, Johns Hopkins Kimmel Cancer Center scientists have found that a protein-signaling process accelerates the work of the gene most frequently mutated in a common form of adult leukemia and is likely necessary to bring about the full-blown disease.

The Kimmel team, in a report published in the June 10 issue of *Science Translational Medicine*, demonstrated the impact of the so-called Hedgehog protein signaling pathway by successfully using a combination of two drugs to both block the activity of the mutated gene, called FLT3, and a part of the Hedgehog pathway. The combination limited the growth of AML cells in mice and bone marrow cell lines.

"From our data, it appears that Hedgehog signaling is like an accelerator," says William Matsui, M.D., professor of oncology at the Johns Hopkins University School of Medicine. "It facilitates the cellular events that lead to cancer, but it itself is not the driver of the whole process."

The findings of the study, Matsui says, may eventually hold implications for the development of new or better combinations of gene-based therapies for AML, which strikes an estimated 20,000 people in the U.S. each year and kills 10,000. An estimated 35 percent of patients have a mutation in FLT3 that signals bone marrow stem cells to divide and replenish themselves at abnormal rates, causing the rapid growth of leukemia cells.

In the experiments, a combination of a FLT3 blocker called sorafenib, and an experimental Hedgehog-pathway blocker called IPI-926 reduced, by up to half, the percentage of leukemic cells in the blood and bone marrow of five mice, compared with two groups of five mice treated with either one of the drugs alone. In addition, three of five mice treated with the drug combination survived past the 16 days of the experiment without any further treatment, compared with none of the mice that received either drug alone.

The human FLT3 gene was first cloned by Kimmel Center scientists led by Donald Small, M.D., who also identified drugs that could block the activity of FLT3. Adult patients with the FLT3 mutation tend to have worse outcomes than those without the mutation, Matsui notes, and historically, drugs that inhibited FLT3's activity can eliminate leukemic cells from the blood, but without lasting effects. The reason, he says, is that tumor cells persist in the bone marrow.

Matsui says the new research, therefore, offers some promise of better outcomes for people with the FLT3 mutation by revealing the Hedgehog protein signaling as a possible second target for treatment in combination with drugs that directly hit the mutation.

"The Hedgehog protein signaling pathway plays a major role in the development of the embryo," says Matsui. "If the pathway stays active later in life, however, it can jumpstart the growth and survival of tumor cells," he explains.

"In the case of AML," he says, "if the FLT3 mutation is like a car that's going 55 miles an hour, then when you add Hedgehog, you put the 'pedal to the metal.'"

In their study, Matsui and his colleagues also found that mice that had both the FLT3 mutation and Hedgehog activity had a significantly shorter lifespan—an average of 12 weeks—compared with an average of 40 weeks for those that had just the FLT3 mutation.

"When we treat mice that have leukemia with both drugs," Matsui says, "they live longer than with either drug alone, and there is a portion of them that don't die at all."

It's likely, Matsui says, that Hedgehog signaling is involved in the progression of a number of cancers, and "this study brings home the idea that in treating these cancers, clinicians may need to inhibit Hedgehog along with specific gene mutations."

Scientists are continuing their search for more protein targets within the Hedgehog pathway, says Matsui, and he and his colleagues have begun work in the laboratory to see how Hedgehog inhibitors work when combined with newer drugs that target FLT3 more precisely than sorafenib.

If these lab tests continue to show signs that the two types of inhibitors can stop AML, "we think this would be a rational combination to try in patients," Matsui says.

Sorafenib, sold under the name Nexavar, is approved by the FDA to treat certain types of liver, kidney and thyroid cancers, and is among a group of costly—up to $10,000 per month—gene-targeting, anti-cancer drugs. The scientists say the expense drives the urgency to find more potent combinations of such anti-cancer drugs with fewer doses needed for patients. IPI-926 is an experimental drug currently being tested in clinical trials for various cancer types.

More information: Integration of Hedgehog and mutant FLT3 signaling in myeloid leukemia, *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/ … scitranslmed.aaa5731

Provided by Johns Hopkins University School of Medicine

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