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New leukemia signal could point way to better treatment

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Cancer researchers at the Stanford University School of Medicine have discovered a promising new chemotherapy target for a deadly form of leukemia. Their discovery hinges on a novel "double agent" role for a molecular signal that regulates cell growth.

The rogue signal, glycogen synthase kinase 3, was previously found to halt uncontrolled cell growth, preventing several forms of cancer. It also keeps growth of healthy cells in check. But new data show that GSK3 fuels a deadly form of white blood cell cancer, which accounts for five to 10 percent of child and adult leukemias and more than three-quarters of leukemias diagnosed in infants.

"This finding was quite unexpected," said Michael Cleary, MD, senior author of a paper describing the discovery. "GSK3 has never been implicated in promoting cancer." Cleary is a professor of pathology and of pediatrics and a member of the Stanford Cancer Center. The research will appear online in *Nature* on Sept. 17.

Cleary's team discovered that inhibiting GSK3 combats leukemias caused by mutated MLL genes. MLL, an acronym for "mixed-lineage leukemia," refers to an unusual feature of these deadly cancers. Most leukemias begin in just one of the body's two white blood cell factories, either the lymph nodes or the bone marrow. But in mixed-lineage leukemias, the bad cells can show markers from both kinds of tissue.

Newly diagnosed leukemia patients have their cancer cells tested to see

which genes are driving the cancer. Mutated MLL genes are viewed as a bad prognostic marker, Cleary said.

"There is intense interest in coming up with better ways to treat these patients," he said. Cleary's findings indicate GSK3 may be an effective target for future leukemia drugs.

The first hint of GSK3's role came from petri-dish tests on cancer cells. Postdoctoral scholar Zhong Wang, PhD, treated dishes of different kinds of cancer cells with a battery of chemicals that inhibit various cell signals. When a GSK3 inhibitor clobbered cells with mutant MLL genes, Wang realized his work was cut out for him.

"I was excited, but I knew I'd have to do lots of work to confirm the finding," he said. "Most people say GSK3 cannot be a cancer target." That's because of earlier discoveries that showed GSK3 slowed malignancies such as colon cancer.

But Wang's extensive follow-up experiments confirmed GSK3 drove leukemia. For instance, he gave the psychiatric drug lithium, a weak GSK3 inhibitor, to mice with MLL-gene leukemia. Mice that got lithium lived longer than those that did not.

Now that the team knows GSK3 is a potential anti-leukemia target, they're studying how the signal revs up cancer.

They're also starting the hunt for high-potency GSK3 inhibitors that could safely be given to humans. The signal is an especially promising leukemia drug target, the researchers said, because GSK3 normally slows the growth of healthy bone marrow stem cells. Thus, it's possible that giving GSK3 inhibitors will have a double-whammy effect on leukemia, killing the cancerous white blood cells and promoting growth of healthy stem cells, such as those given in a bone marrow transplant.

"Most current cancer drugs target both the normal and the aberrant cells," Cleary said. It would be a big advantage in cancer treatment if a drug were developed that could selectively kill cancer but help healthy cells grow. Of course, the danger with GSK3 inhibitors would be that they might also cause other cancers if given long-term. Cleary said it's too early to tell if or how a new drug might skirt that problem.

"There will be a lot of hard work required to get better anti-GSK3 compounds, test them in preclinical models and translate them to human trials," he said.

Source: Stanford University