Molecule treats leukemia by preventing cancer cell repair, scientists report

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Kevin Mills, Ph.D. (JPG)

(Medical Xpress)—Researchers at The Jackson Laboratory have identified a molecule that prevents repair of some cancer cells, providing a potential new "genetic chemotherapy" approach to cancer treatment that could significantly reduce side effects and the development of treatment resistance compared with traditional chemotherapy.

In healthy people, white blood cells called B cells (or B lymphocytes) are a kind of sophisticated tool kit, making antibodies against pathogens or other invaders. In the process of antibody production, B cells turn on the gene known as activation-induced cytidine deaminase (AID), which acts as a sort of molecular scissors that cut the chromosomes within the B cell. This is needed to rearrange pieces of the B-cell chromosomes and produce different "flavors" of antibodies that do different jobs.

But in some cancers this process goes wrong, with AID acting out of control and creating mutations and chromosome rearrangements that make the tumor more aggressive.

Those AID-induced cancers proliferate with help from the cell-repair mechanism known as homologous recombination (HR). Researchers in the laboratory of Associate Professor Kevin Mills, Ph.D., identified a molecule called DIDS (for 4,4'-diisothiocyanatostilbene-2-2'-disulfonic acid) that blocks the DNA repair action in chronic lymphocytic leukemia (CLL), causing the cancer cells to die.

"This treatment affects every cell in the body," Mills says. "But by its mode of action it kills only tumor cells that are expressing AID, yet it is almost entirely harmless to normal, healthy cells."

The research, published in *The Journal of Experimental Medicine*, is the latest proof of principle for what Mills calls "genetic chemotherapy": using the mechanisms involved in genetic instability in cancer, to cause tumor cell self-destruction.

For the new paper, authors Kristin Lamont, Ph.D., a postdoctoral associate, and Muneer Hasham, Ph.D. an associate research scientist, both in the Mills laboratory, tested DIDS in normal mouse cells, mouse cancer cells, human cancer cell lines and human primary cancers. "We collected 74 different primary patient CLL samples," Lamont says, "and measured AID expression in those samples. We found that about 40 percent of them express AID, and if we treated those with DIDS in vitro, the AID-expressing ones had significantly higher levels of DNA damage and died."

Mills adds, "Demonstrating that this works on primary cancer cells moves us one step closer to eventually testing this in patients." The DIDS treatment approach, Mills adds, also addresses the issues of side effects, a major problem with standard chemotherapy.

"By its selectivity for cancer cells, DIDS reduces the issue of the really nasty side effects associated with chemotherapy treatments," Mills explains.

Moreover, the list of cancers associated with aberrant AID expression is growing, so the treatment approach could apply not only to leukemia but also a range of other cancer types.

Mills' collaborators at Memorial Sloan-Kettering Cancer Center in New York shared their expertise in DNA repair to understand the action of the DIDS molecule. "We hypothesized that the molecule would work as it did," Mills says, "but they helped us to determine exactly why and how it works."

Since the researchers submitted the paper for publication, they have developed a new and better potential treatment molecule. "One of our goals is to design an even better molecule," Mills says. "And we've done that. We now have a new molecule in that same class, that delivers

significantly more potency, with just as much selectivity as the original molecule."

Cyteir Therapeutics, Inc. a startup biotechnology company founded by Mills in 2012, continues to pursue development of the new molecule for cancer therapy, while Dr. Mills and his team at Jackson will keep studying the cellular mechanisms, in the hope of finding yet more potential new cancer drugs. Cyteir Therapeutics is now ramping up the R&D efforts necessary to take the genetic chemotherapy treatment to clinical trials, possibly in 2014.

More information: Lamont et al.: Attenuating homologous recombination stimulates an AID-induced antileukemic effect. The *Journal of Experimental Medicine*, The Rockefeller University Press, April 15, 2013. jem.rupress.org/content/early/ … 3/04/09/jem.20121258

Provided by Jackson Laboratory