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Targeted agent shows promise for chronic lymphoid leukemia

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Researchers at the Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James) have identified an experimental agent that targets chronic lymphocytic leukemia and perhaps other proliferative disorders of lymphocytes.

Their study shows that the small-molecule inhibitor CAL-101 directly promotes cell death by apoptosis in chronic lymphocytic leukemia (CLL) cells and disrupts several external survival pathways needed for CLL cell viability and proliferation.

The agent blocks a molecule called PI3K-delta, an isomer of the PI3K (phosphatidylinositol-3 kinase) pathway, which is activated mainly in blood-forming, or hematopoietic, cells.

The research used cells from patient tumors and was posted recently in the journal *Blood*.

"Overall, our findings provide a rationale for the development of CAL-101 as the first in a new class of targeted therapies for CLL," says principal investigator Amy J. Johnson, assistant professor of hematology and medicinal chemistry, and a CLL researcher in the OSUCCC-James.

"A PI3K inhibitor hasn't been developed yet because this pathway is required for many essential cellular functions, but the identification of PI3K-delta, which is hematopoietic-selective, unlocks a potential new

therapy for B-cell malignancies," Johnson says.

CLL is the most common from of adult leukemia in the United States, with about 15,000 new cases and 4,500 deaths annually. An estimated 100,760 people in the United States are living with or are in remission from CLL.

People with the asymptomatic phase of CLL can live many years, even without treatment. But once the disease progresses to its symptomatic phase, treatment is required. This is usually a chemotherapy-based regimen that often induces remission. But current therapies are not curative and nearly all patients relapse.

The PI3K pathway is essential for survival of cells generally. This made it an unsuitable target for small molecule inhibitors until recently when research showed that PI3K-delta expression occurs mainly in hematopoietic cell types. Preclinical studies suggest that blocking this molecule may kill B cells with little toxicity to other hematopoietic cells.

The present study, which used CLL cells from patients, found the following:

- CLL cells show high PI3K pathway activity and PI3K-delta expression;
- CAL-101 preferentially kills CLL cells compared to normal B-cells;
- CAL-101 selectively inhibits PI3K-delta and directly promotes apoptosis in primary CLL cells, and it disrupts multiple external survival pathways;

- CAL-101 cell killing is caspase dependent and not diminished by the presence of stromal cells;

- CAL-101 does not kill normal T-cells or NK cells or reduce antibody-dependent cellular cytotoxicity, but it does lower production of inflammatory and anti-apoptotic cytokines by activated T-cells.

Provided by The Ohio State University