MedicalXpress

Antipsychotic drug exhibits cancer-fighting properties

January 9 2014

In a prime example of finding new uses for older drugs, studies in zebrafish show that a 50-year-old antipsychotic medication called perphenazine can actively combat the cells of a difficult-to-treat form of acute lymphoblastic leukemia (ALL). The drug works by turning on a cancer-suppressing enzyme called PP2A and causing malignant tumor cells to self-destruct.

The findings suggest that developing medications that activate PP2A, while avoiding perphenazine's psychotropic effects, could help clinicians make much-needed headway against T-cell ALL, and perhaps other tumors as well.

A study team led by Alejandro Gutierrez, MD, and A. Thomas Look, MD, of Dana-Farber/Boston Children's Cancer and Blood Disorders Center, and Jon Aster, MD, PhD, of Dana-Farber Cancer Institute and Brigham and Women's Hospital, reported the results Jan. 9 in the *Journal of Clinical Investigation*.

T-ALL is rarer and more aggressive than the B-cell form of ALL, and it has a relatively poor prognosis. Despite improvements in the treatments available, 20 percent of children and more than 50 percent of adults diagnosed with T-ALL succumb to it.

To identify possible new treatment options, Gutierrez, Look and their collaborators screened a library of 4,880 compounds—including FDA-approved drugs whose patents had expired, small molecules and natural

products—in a model of T-ALL engineered using zebrafish.

Strategies that identify new uses for existing drugs have grown in popularity in recent years as a way of quickly developing new disease therapies. Zebrafish models are cost-effective platforms for rapidly conducting drug screens, as well as basic stem cell, genetic, cancer and developmental research.

"We wanted to see if there were drugs or known bioactive molecules that are active against T-ALL that hadn't been tested yet," Look explained. "There may be drugs available for other indications that could be readily repurposed if we can show activity."

One of the strongest hits in the zebrafish screen was the drug perphenazine. It is a member of the phenothiazines, a family of antipsychotic medications used for 50 years, because they can block dopamine receptors.

The team verified perphenazine's anti-leukemic potential in vitro in several mouse and human T-ALL cell lines. Biochemical studies indicated that perphenazine's anti-tumor activity is independent of its psychotropic activity, and that it attacks T-ALL cells by turning on PP2A.

The fact that perphenazine works by reactivating a protein shut down in cancer cells is itself novel in the drug development field.

"We rarely find potential drug molecules that activate an enzyme," Gutierrez explained. "Most new drugs deactivate some protein or signal that the cancer cell requires to survive. But, here, perphenazine is restoring the activity of PP2A in the T-ALL cell."

Gutierrez and Look, along with their collaborators, are now working to

better understand the interactions between PP2A and perphenazine. They also want to search for or develop molecules that bind to and activate the enzyme more tightly and specifically to avoid perphenazine's psychiatric effects.

"The challenge is to use medicinal chemistry to develop new PP2A inhibitors similar to perphenazine and the other phenothiazines, but to dial down dopamine interactions and accentuate those with PP2A," Look said.

The researchers see future PP2A inhibitors not as magic bullets but as potentially important additions to the oncologist's arsenal when treating patients with T-ALL.

" T-ALL patients are often on the borderline between a long remission and a cure," Look said. "If we can push the leukemia cells a little harder, we may get more patients who are actually cured. In this way, PP2A inhibitors may, in combination with other drugs, make a real difference for patients."

It may be that the benefits of PP2A-activating drugs could extend beyond T-ALL. "The proteins that PP2A suppresses, such as Myc and Akt, are involved in many tumors," Look noted. "We are optimistic that PP2A activators will have quite broad activity against different kinds of cancer, and we're anxious to study the pathway in other malignancies as well."

Provided by Dana-Farber Cancer Institute