Anti-inflammatory Drugs May Defeat a Treatment-Resistant Type of Cancer

June 24, 2009

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Irene Pedersen's translational research has revealed a potential new treatment for a form of lymphoma. Photo courtesy Irene Pedersen.

Effective drugs for treating a chemotherapy-resistant form of lymphoma might already be on the market according to a study that has pieced together a chemical pathway involved in the disease.

By following the trail of several molecular flags that mark this type of cancer, a team from the University of California, San Diego, the Burnham Institute for Medical Research and the University of Copenhagen Hospital have discovered that anti-inflammatory drugs used to treat arthritis will shrink lymphoma tumors in mice.

Their report, published in the July issue of the journal EMBO Molecular Medicine, also strengthens evidence for a link between inflammation and cancer.

"If this shows promise with early clinical experiments, the treatment would be immediately available," said Michael David, a professor of biology who leads the group at UC San Diego.

The research focused on a type of non-Hodgkin lymphoma called diffuse large B-cell lymphoma. In some patients with the disease, chemotherapy works well. In a recent study of 40 patients more than 75 percent of patients with one form of this type of lymphoma survived five years or longer.

But that study also identified a group of patients whose cancer proved difficult to treat. Their tumors failed to respond to chemotherapy, and only 16 percent of patients with this form of lymphoma survived more than five years after they were diagnosed.

Several molecular flags mark this treatment-resistant lymphoma, but the links between them were unknown until now. The new paper reports that tumor cells isolated from these patients have depressed levels of a protein called SHIP1, which was known to suppress tumors. In fact, patients with the lowest levels of SHIP1 are the least likely to survive.

The resistant type of lymphoma cells also have elevated levels of miR-155, a specific example of a type of genetic material called microRNA, the team found. They demonstrated that miR-155 suppresses SHIP1 by sticking to the template for the protein, preventing its manufacture.

This raised the possibility that these patients might respond favorably to a treatment that interrupted that pathway. "It makes sense to block that loop," said Irene Pedersen, a research scientist in the Division of Biological Sciences at UC San Diego and lead author of the paper.

The final clue came from earlier reports that an inflammatory molecule called TNFa could boost levels of miR-155. Additional laboratory work confirmed the observation for this type of lymphoma cell.

"Our study strengthens the scientific link between inflammation and tumor progression," David said. "The prevailing thought is that you need two mutations to get cancer. But it might take just one mutation plus inflammation."

The anti-inflammatory drugs etanercept and infliximab, which are currently used to treat arthritis and inflammatory bowel disease, work by suppressing TNFa, suggesting a new way to curb the malignancy of this type of lymphoma.

The team tested the idea in mice that had been injected with aggressive lymphoma cells and found that nascent tumors shrank in six days.

"It's a promising result of this whole translational path," said Pedersen, whose initial training was in cancers of the blood. "To get somewhere we had to study the mouse models and the molecular profiles. I hope it will be beneficial to patients."

Patients with lymphoma that has not responded to chemotherapy and who are ineligible for a bone-marrow transplant will be the first to receive the new treatment. The team in Copenhagen has begun recruiting patients for an initial clinical study.

Grants from the National Cancer Institute and the Novo Nordisk Foundation supported this research program.

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