

Discovery about obesity drug helping scientists develop new cancer treatments

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Based on their surprising discovery that an obesity drug can kill cancer cells, scientists at Wake Forest University School of Medicine have made a new finding about the drug's effects and are working to design more potent cancer treatments.

Published online today in Nature Structural and Molecular Biology, the study is the first to report how the drug orlistat (Xenical® or Alli®) binds and interacts with a protein found in tumor cells. The drug blocks the protein's function and causes cell death.

The project started five years ago when Steven Kridel, Ph.D., an assistant professor in the Department of Cancer Biology, analyzed prostate cancer cells to see which enzymes were expressed at high levels. His hope was that treatments to inhibit those enzymes could also stop tumor growth.

“We found that a protein known as fatty acid synthase is expressed at high levels in prostate tumor cells, and is fairly absent in normal cells,” said Kridel.

Other research has shown that the protein is found in many tumor cells including breast, colon, ovarian, liver, lung and brain.

“High levels of fatty acid synthase correlate with a poor prognosis so it is a great treatment target,” said Kridel. “This makes an exciting treatment target because theoretically you don't have to worry about harming

nearby healthy tissue.”

Unfortunately, orlistat itself cannot be used as a cancer treatment because, while it can kill cancer cells in the laboratory, in humans it is designed to act only in the digestive tract.

“Understanding this drug-protein interaction is essential for designing new drugs,” said W. Todd Lowther, Ph.D., an assistant professor in the Department of Biochemistry. “We’ve used a technique known as X-ray crystallography and now have a three-dimensional snapshot of the drug interacting with the protein.”

“Our goal is to develop an orlistat-like drug that can get into the bloodstream and go to the site of a tumor,” said Lowther.

Once they developed the three-dimensional map of the interaction, Lowther and Kridel began screening hundreds of thousands of compounds to identify those that interact with cancer cells in the same way as orlistat. They have narrowed the list of possibilities down to a dozen and will now work to optimize the compounds in hopes of creating potent cancer treatments. The drugs will first be tested in animals and then in human cancer patients.

Fatty acid synthase is also found in fat cells, which suggests that if the scientists are successful in developing an anti-cancer drug, it could also be an effective obesity drug.

“You might have the same drug for treating a cancer patient as an obese patient,” said Lowther.

Source: Wake Forest University Baptist Medical Center

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