Common anti-inflammatory coaxes liver cancer cells to commit suicide

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The anti-inflammatory drug celecoxib, known by the brand name Celebrex, triggers liver cancer cell death by reacting with a protein in a way that makes those cells commit suicide, according to a new study.

Researchers also found that the combination of celecoxib with each of two chemotherapy drugs killed more liver cancer cells in culture, making those combinations more effective than either drug on its own.

"Each chemotherapy drug alone will reduce the growth of cancer cells, but when each single drug is combined with Celebrex, a greater growth suppression effect was observed," said Jiayuh Lin, senior author of the study and an associate professor of pediatrics at Ohio State University. "For clinicians, this research suggests the possibility of a new therapeutic strategy."

Celecoxib has this effect by acting on STAT3, a gene inside liver cancer cells that, when activated, allows those cancer cells to resist the effects of chemotherapy drugs. The researchers determined that the celecoxib molecule binds to STAT3 on so-called "hot spots," effectively blocking its ability to function.

Powerful computing techniques were employed before the researchers ever considered celecoxib as a potential treatment for cancer. Celebrex is a nonsteroidal anti-inflammatory drug, or NSAID, and a Cox-2 inhibitor, meaning it helps control inflammation by inhibiting an enzyme known as cyclooxygenase-2. It is most commonly prescribed to treat the

pain of arthritis.

Chenglong Li, an assistant professor of medicinal chemistry and pharmacognosy at Ohio State, has developed computer simulations to identify optimal drug fragment combinations that attach simultaneously to proteins in ways that block the proteins' functions. By searching a database of existing federally approved drugs, he found that celecoxib was structurally similar to a template molecule that he had determined would most effectively bind to STAT3 and inhibit its function.

"Normally, STAT3 is persistently activated in cancer cells. If you have a good molecule that sticks to STAT3, it will prevent its activation," Li said. And when STAT3 is inhibited, cellular survival pathways are blocked that cause the cancer cell to chop itself up and die.

The research appears online and is scheduled for later print publication in the journal *Cancer Prevention Research*.

The biological portion of the study further defined the role of a pro-inflammatory protein in liver cancer's development. The protein, called interleukin-6, or IL-6, is a cytokine, a chemical messenger that causes inflammation, which can have both beneficial and damaging effects in the body. Previous research by other scientists has shown that high levels of IL-6 in the blood are associated with hepatocellular carcinoma, the most common type of liver cancer.

Lin and colleagues determined that IL-6 initiates a chemical reaction called phosphorylation of STAT3. That reaction activates STAT3 inside liver cancer cells, where STAT3 in turn activates at least three other known genes that allow the cells to resist the effects of chemotherapy.

The scientists treated five different types of hepatocellular carcinoma cells with two different doses of celecoxib for two hours, and followed

by giving them IL-6 for 30 minutes. The pre-treatment with the lower dose of celecoxib inhibited IL-6's ability to start the reaction that activates STAT3. The higher dose blocked STAT3 altogether.

The researchers then treated a line of liver cancer cells with celecoxib in combination with two chemotherapy drugs: doxorubicin, which is used to treat breast, ovarian, gastric, thyroid and several other cancers, and sorafenib, which is the only chemotherapy medication approved by the Food and Drug Administration for liver cancer treatment. Its brand name is Nexavar.

With both drugs, the addition of celecoxib treatment reduced the number of viable liver cancer cells by anywhere from approximately 50 percent to more than 90 percent, depending on the doses. The combination of celecoxib and sorafenib also significantly limited the cancer cells' ability to form colonies, a key element of tumor growth and survival after the drug treatment.

"Because liver cancer has a very low five-year survival rate, it is most likely that even sorafenib alone may not be effective to cure the cancer," said Lin, also an investigator in Ohio State's Comprehensive Cancer Center and the Center for Childhood Cancer at Nationwide Children's Hospital. "We hope that using both drugs together could be more effective. Both celecoxib and sorafenib are already approved by the FDA, so we think this combined treatment should be able to be used in the clinic pretty quickly."

The fifth most common cancer in humans, liver cancer remains one of the most difficult to successfully treat. Patients' overall five-year survival rate is about 10 percent, according to the American Cancer Society.

These experiments were conducted in cell cultures. Further testing would be needed to determine celecoxib's effectiveness in human cancers, Lin

noted.

And the powerful computational work led by Li, also an investigator in Ohio State's Comprehensive Cancer Center, is likely to lead to the development of new molecules with even more precise structural relationships with the proteins they are designed to block.

Li's method is called Multiple Ligand Simultaneous Docking. In this work, he used computer simulations to identify "hot spots" on the STAT3 protein – tiny pockets to which molecules could most successfully attach to inhibit the protein's activity. He then searched through drug banks containing more than 7,500 existing and experimental medications to find the most suitable molecular fragments that could be pieced together to produce a new molecule shaped in such a way that it would fit into those pockets.

After designing a template molecule that would most effectively bind to STAT3, he compared that template to the 1,400 federally approved drugs already on the market.

"Celecoxib is almost identical to the molecule template. It attaches to STAT3 in three places. We can optimize celecoxib, and that is expected to come soon. But applying our technique to find those pieces and determining that they come from an existing drug makes the discovery process much faster," said Li, a key co-author of the paper and frequent research collaborator with Lin.

Li has termed this approach as in silico (computer-driven) drug repositioning or repurposing.

The discovery that celecoxib can bind to STAT3 also appears to apply to other cancers. Both Lin and Li were key authors on a recent paper that suggested that celecoxib's ability to block STAT3's function might also

make it effective as a treatment for rhabdomyosarcoma, the most common soft tissue cancer in children and adolescents. This research was published in the April 15 issue of the journal Biochemical and Biophysical Research Communications.

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