Blocking an oncogene in liver cancer could be potential therapy option

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Scientists have found that a synthetic molecule they designed can block activation of a gene in liver cancer cells, halting a process that allows some of those cancer cells to survive chemotherapy.

Without the interference of this gene's function, certain liver cancer cells appear to be protected from the toxic effects of chemotherapy drugs.

Blocking the oncogene, called STAT3, prevents a protein from protecting the cells, the research suggests. As a result, more liver cancer cells succumb to treatment.

Researchers hope an anti-cancer drug based on the molecule's design eventually will be developed for use in patients, after the required animal and clinical testing is completed.

The scientists have seen similar results in studies using this experimental molecule, called LLL12, to block STAT3 as a way to induce cell death in breast and pancreatic cancer cells.

"For patients, it would be easy to use an intravenous drug based on this small molecule, which is relatively cheap and easy to manufacture," said Jiayuh Lin, senior author of the study and an associate professor of pediatrics at Ohio State University.

"We also have seen signs that blocking STAT3 could block other downstream targets, and could affect other STAT3-regulated genes that

can turn normal cells into cancer cells. We believe this molecule has a lot of potential for cancer therapy."

Lin led the team of scientists who designed LLL12 using powerful computers and a computational method called structure-based design. The group reported on its creation earlier this year.

This new study is published in a recent issue of the Journal of Biological Chemistry.

The protein in this process is called interleukin-6, or IL-6. It is a cytokine, a chemical messenger that causes inflammation, and 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.

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.

In this study, the researchers observed that liver cancer cells known to be resistant to a common chemotherapy drug, doxorubicin, had higher levels of IL-6 than did other liver cancer cells – an indication that the protein likely fosters the drug resistance. Subsequent tests showed that these resistant cells with high IL-6 also had higher levels of STAT3 phosphorylation than did other cells.

To further demonstrate this relationship between the protein and cell survival, Lin and colleagues pretreated liver cancer cells with the chemotherapy drug and then followed with different doses of IL-6. The addition of IL-6 rescued these cells from chemo-induced death.

Alternately, when the scientists introduced an antibody to inhibit IL-6 in drug-resistant cancer cells and then followed with doses of doxorubicin, 70 percent more of the cells treated with the IL-6 inhibitor died compared to cells treated with the chemo drug alone – a sign that the loss of IL-6 lowers survival in these particular cancer cells.

After determining in cell cultures that IL-6 activates STAT3 to help perform this cell survival function, the researchers focused on testing the effects of blocking the gene alone.

They first used silencing RNA, or siRNA, to prevent activation of the STAT3. More of the siRNA-treated cells died than did cells in which the STAT3 was not blocked.

"At this point, we know that STAT3 plays an important role, and that IL-6 depends on STAT3 to protect cells from dying," said Lin, also an investigator in Ohio State's Comprehensive Cancer Center and the Center for Childhood Cancer at Nationwide Children's Hospital.

The scientists then turned to the synthetic molecule, LLL12, which was designed specifically to tuck itself into a gap in STAT3's two-part structure and disable its activation.

The researchers introduced LLL12 to four types of liver cancer cells and followed with a dose of IL-6. The IL-6 protein had no protective effect on cells treated with the molecule, meaning it could not turn on STAT3, a required step in protecting the cells from death.

To be sure, they also tested how cells with and without LLL12 treatment responded to chemotherapy. The small molecule treatment completely blocked resistance to the drug, Lin said, even in the types of liver cancer cells that express the highest IL-6 levels and are most resistant to doxorubicin.

Importantly, the researchers were able to determine that inhibiting STAT3 activation did not affect other proteins that are induced by IL-6 for potentially beneficial reasons. The small molecule also did not exacerbate the effects of chemotherapy on normal liver cells.

Lin and colleagues are currently testing the effects of LLL12 in multiple myeloma, breast and colon cancer cells, in which the IL-6/STAT3 pathway also plays an important role.

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