Small addition to cancer drug may make big difference

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University of Florida researchers have found a way to use just a fraction of the normal dosage of a highly toxic, debilitating chemotherapy drug to achieve even better results against colon cancer cells.

More research is needed before the therapy can be tested in patients, but the discovery in human colon cancer cell lines and mice with established human tumors suggests that the addition of a small molecule to the cancer drug Temozolomide disrupts repair mechanisms in a type of tumor cells that is highly resistant to treatment.

The discovery is featured on the cover of December's *Molecular Cancer Research*, a journal of the American Association for Cancer Research.

"This is very important because aside from aggressive surgery with possibly chemotherapy, there are no specific treatments for colon cancer," said Satya Narayan, a professor of anatomy and cell biology at the College of Medicine and a member of the UF Shands Cancer Center. "The recurrence rate for this type of cancer after surgery is very high, about 30 to 50 percent, and there is an urgent need to develop new approaches to manage this deadly disease."

The National Cancer Institute estimates there will be about 106,000 new cases of colon cancer in the United States in 2009. It is the second most common cause of cancer-related death in both men and women in the Western hemisphere. The disease forms in the large intestine and survival rates vary according to how soon the cancer is diagnosed and the

treatment is started.

Narayan's research team evaluated more than 140,000 small molecules, finally arriving at a tiny molecule that precisely blocks the ability of cancer cells to recognize and repair the DNA damage inflicted by Temozolomide, or TMZ.

"Our idea was if you induce DNA damage (with TMZ), and at the same time block cell repair, you can synergize toxic effects to the cancer cells," Narayan said. "We hope that with this combination treatment we can reduce the tumors drastically and expand the lifetime of patients much longer than is currently possible."

TMZ is commonly used against certain types of brain cancer. It works by damaging the DNA of the cancer. However, the challenge of treating patients is that colon cancer is not a single disease but an array of disorders with distinct molecular mechanisms, with one type being quite proficient at repairing the DNA damage inflicted by the drug.

By combining TMZ with the small molecule, Narayan's team was able to disable the colon cancer's ability to manufacture repair enzymes.

The UF researchers effectively used an amount of TMZ that is about 10 times lower than recommended in its studies of mice with human colon cancer tumors.

If only about one-tenth as much TMZ is needed to kill cancer cells, Narayan said, it will be possible to use lower doses of a drug that creates a great deal of adverse side effects, a partial listing of which includes anxiety, back pain, breast pain, constipation, cough, diarrhea, dizziness, drowsiness, dry skin, hair loss, headache, joint pain, loss of appetite, mouth sores, muscle aches and nausea.

"By using these strategies we can predict that disruption of DNA repair by small molecules can bypass drug resistance factors and dramatically reduce side effects caused by toxic doses of TMZ," Narayan said.

More study is needed before the combination can be tested in patients, but Narayan believes that TMZ can be combined with the small molecule in a single dose in pill or capsule form.

The research demonstrates that it is possible to sensitize colon cancer cells to TMZ more broadly than is now possible — a benefit of particular importance to patients with cancers that are as varied as colon cancer, said Sankar Mitra, Ph.D., a professor in the department of biochemistry and molecular biology at the University of Texas Medical Branch in Galveston, who did not participate in the study.

"This could be the start of other small molecule inhibitors," he said.

Mitra also noted that the researchers selected their therapeutic molecules through sophisticated analysis of the structure of tens of thousands of potential small molecules from the National Cancer Institute database. The computer-based process, which can suggest likely cancer therapeutics within hours, replaces analysis that would normally have taken weeks or months.

"There have been a multitude of studies suggesting that inhibition of DNA polymerase beta would enhance chemotherapeutic response," said Robert W. Sobol, Ph.D., an assistant professor of pharmacology and chemical biology, and human genetics, at the University of Pittsburgh Cancer Institute. "However, potential inhibitors have been challenging to identify and most have proven to be non-specific and/or non-selective. The compound identified by Dr. Narayan appears to be the first in what I expect to be a growing list of DNA polymerase beta inhibitors that have clinical potential."

Source: University of Florida (news : web)