Mushroom compound appears to improve effectiveness of cancer drugs

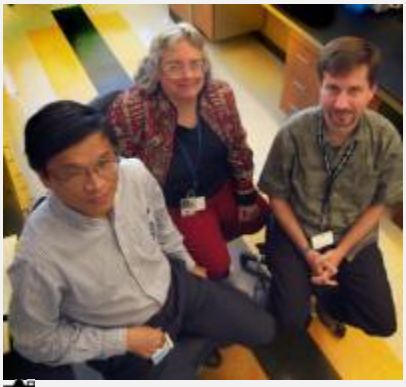

IMAGE: A compound isolated from a wild, poisonous mushroom growing in a Southwest China forest appears to help a cancer killing drug fulfill its promise, researchers report. Pictured (L to R)...

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AUGUSTA, Ga. – A compound isolated from a wild, poisonous mushroom growing in a Southwest China forest appears to help a cancer killing drug fulfill its promise, researchers report.

The compound, verticillin A, sensitizes cancer cells to TRAIL, a drug which induces cancer cells to self destruct, said Dr. Kebin Liu, cancer immunologist at the Georgia Health Sciences University Cancer Center and corresponding author of the study in the journal *Cancer Research*.

The compound appears to keep cancer cells from developing resistance to TRAIL, short for tumor necrosis factor-related apoptosis inducing ligand. Drug resistance, intrinsic or acquired, is a major problem for cancer patients, accounting for greater than 90 percent of treatment failures in patients with metastatic disease.

"If we can make drugs work again, more people will survive," Liu said.

Patient experience has shown cancer's skill at desensitizing itself to the TRAIL. "It looks as though most cancer cells have found a way to become resistant and evade its action," said Dr. Wendy Bollag, cell physiologist at GHSU and a study co-author.

Tenacious cancer cells also are naturally resistant to cell suicide, which is how TRAIL works.

In mice, they found verticillin A alone was adequate to kill cancer cells, but the required dose made the mice sick, a common problem with many cancer therapies. However, when a lower dose was paired with TRAIL, it became a powerful, more tolerable recipe that killed previously resistant cells.

They also found that the compound improved the efficacy of commonly used cancer drugs etoposide and cisplatin, which also work by promoting cancer cell death but are less targeted than TRAIL. "We believe this could be a good companion drug for a lot of cancer therapies," Liu said.

One way verticillin A appears to work is by upregulating BN1P3, a gene that promotes cell death, the researchers said. Cancer cells work to silence BN1P3 through a process called DNA methylation; verticillin A appears to modify the same process to turn the gene on.

All cells use DNA methylation but cancer cells use it differently, said Dr. Keith Robertson, cancer epigeneticist and Georgia Cancer Coalition Scholar. "Verticillin A may

be working by altering methylation in a way that makes the cancer cells sensitive to TRAIL," Robertson said.
Their studies were of metastatic human colon cancer cells, which are highly resistant to treatment, including TRAIL, both in culture as well as transplanted into mice. They did similar studies on sarcoma, lung adenocarcinoma and breast cancer.
Additional toxicity studies are needed before moving forward with clinical trials, Bollag said. The researchers also want to pursue the compound's potential in melanoma and pancreatic cancer.

Verticillin A was isolated from mushrooms in Dr. Ping Wu's laboratory at the Research Centre of Siyuan Natural Pharmacy and Biotoxicology at China's Zhejiang University and brought to GHSU by former postdoctoral fellow, Dr. Feiyan Liu, the study's first author, who studied with Kebin Liu in Augusta for two years. The Chinese university is involved in extensive studies to isolate active compounds from plants to explore their therapeutic potential and both Dr. Lius liked verticillin A's aggressive response against cancer.

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GHSU and Zhejiang University have a joint use patent on verticillin A and Zhejiang University has a synthesis patent.

http://www.eurekalert.org/pub_releases/2011-10/ghsu-mca101111.php