

Penn researchers identify new combination therapy that promotes cancer cell death

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Philadelphia -- Researchers at the University of Pennsylvania School of Medicine identified a combination therapy as a way to sensitize resistant human cancer cells to a treatment currently being tested in clinical trials. They propose that the therapy may help to selectively eliminate cancer cells while leaving healthy cells intact, providing a cancer treatment with fewer side effects. The Penn team reports their findings in the July issue of *Cancer Cell*.

To test the ability of the combined therapy in treating cancerous tumors, senior author Wafik S. El-Deiry, MD, PhD, and colleagues administered TRAIL, a tumor necrosis factor, and sorafenib, an inhibitor currently used to treat renal cancer, to mice with colon carcinomas. The sorafenib and TRAIL therapy reduced the size of tumors in mice with few side effects, demonstrating the potential effectiveness of the combined treatment on human colon cancers.

"Cancer cells will do whatever it takes to survive in harsh environments," explains El-Deiry, Professor of Medicine, Genetics, and Pharmacology. To kill hearty cancer cells, El-Deiry and other scientists are working on ways to alter them so they become more susceptible to cell death.

In ongoing clinical trials, doctors are giving cancer patients extra doses of TRAIL (TNF- α -related apoptosis-inducing ligand), a molecule naturally produced by the body's immune system that promotes cell death, to help kill off cancer cells. While TRAIL-based therapy is promising, over 50 percent of all cancer cells show resistance to TRAIL.

To create a more potent form of targeted cancer therapy, El-Deiry's research team began searching for ways to reverse TRAIL resistance in cancer cells.

Recently, El-Deiry's research group found that TRAIL-resistant cells avoid death by producing 'survival' proteins called cIAP2 and Mcl-1. The oncogene c-Myc in part hampers a cancer cell's survival strategy by blocking the function of an intermediate protein that oversees cIAP2 and Mcl-1 production. Without these survival proteins, cancer cells are unable to resist the death initiated by TRAIL.

In search of drugs that perform a similar cancer-cell death function to c-Myc, El-Deiry's lab turned to sorafenib, which is also being considered for the treatment of a variety of cancers. Like c-Myc, the researchers found that sorafenib blocked the intermediate and survival proteins when combined with TRAIL, causing TRAIL-resistant colon and lung cancer cell lines to die.

"Our findings are exciting because TRAIL in combination with sorafenib appears to be much less toxic than current chemotherapy drugs," explains El-Deiry. "Plus, sorafenib is already available in a pill form."

While enthusiastic about his recent findings, El-Deiry notes sorafenib may be working to increase cell sensitivity to TRAIL through more biochemical pathways than the intermediate alone.

"The ability of sorafenib to work through multiple pathways may be beneficial to cancer treatments because cancer may be altering multiple targets," says El-Deiry.

In the future, El-Deiry plans to explore additional pathways sorafenib may be working through to increase TRAIL sensitivity and to compare

the effectiveness of other drugs.

"In addition to proposing a combination therapy that's rational, non-toxic, and effective in preclinical trials, our findings open up new avenues of molecular exploration for designing targeted anti-cancer therapies," said El-Deiry.

Source: University of Pennsylvania School of Medicine

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