RLIP76 contributes to pancreatic cancer cell resistance to chemotherapy and radiation

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Researchers at the City of Hope Comprehensive Cancer Center have not only identified a protein that allows pancreatic cancer cells to resist therapy but also developed a way to block it, according to results presented at the American Association for Cancer Research's Pancreatic Cancer: Progress and Challenges conference.

"Cancer of the pancreas is notoriously difficult to treat because it usually presents at late stages due to minimal or nonspecific symptoms in the early stages. Thus, surgical treatment is either not possible or fails to cure most patients, resulting in a dismal prognosis — 90 percent of patients are likely to die within a year," said Sanjay Awasthi, M.D., professor of medical oncology and therapeutics research, and diabetes, endocrinology and metabolism at City of Hope in Duarte, Calif.

One of the reasons that pancreatic cancer is so difficult to treat is that the tumor cells are largely resistant to the cell death caused by radiation and chemotherapy. Awasthi and colleagues have previously shown that the protein RLIP76 plays a key role in defending cells from other types of cancers from death caused by exposure to chemotherapy or radiation.

"RLIP76 works like an exhaust system," said Awasthi. "It pumps out the toxic chemicals that accumulate in the cancer cell as a result of chemo- or radiotherapy before they can cause cell death."

Now, Awasthi and colleagues have found that there is more RLIP76 in human pancreatic cancer cells than there is in normal human pancreatic

cells. Depleting levels of RLIP76 killed human pancreatic cancer cells in culture and shrank established human pancreatic tumors in mice. Moreover, blocking RLIP76 or depleting levels of the protein dramatically enhanced the ability of radiation and the chemotherapeutic agent doxorubicin to destroy human pancreatic cells in culture.

"Pancreatic cancer patients are a special case of the particularly unlucky, and in many ways the most miserable. The drug and radiation resistance of this cancer is legendary," Awasthi said.

"Because we have defined RLIP76 as an essential drug- and radiation-resistance mediating protein, and because blockade of RLIP76 caused regression of less therapy-resistant cancers (lung, colon, breast), as well as equally resistant cancers (kidney, prostate, resistant neuroblastoma), we undertook the present studies to determine whether this treatment could be effective in pancreatic cancer.

"Fortunately, our data show that the seemingly unconquerable pancreatic cancer has an Achilles heel; its toxin exhaust system," he explained. "Moreover, plugging this exhaust caused pancreatic cancer cell death, leaving normal cells relatively unfazed. We hope to translate these studies into clinical trials in the near future."

According to Awasthi, they saw an added benefit to depleting levels of RLIP76 in the mice with established tumors: a decrease in blood sugar, cholesterol and triglycerides. "These findings indicate that it might be possible to develop a single class of medications that have potent antidiabetic and anticancer effects," he said.

Awasthi is the founder of Terapio, which makes the recombinant RLIP76 protein for treatment of radiation poisoning. However, Terapio does not work on the RLIP76-blockading technology that is the crux of the anticancer treatment strategy.