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Mucin found as barrier to pancreatic cancer drug

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(PhysOrg.com) -- Current treatments for pancreatic cancer have failed to effectively manage the disease and improve the grim survival rate. A Northeastern University study found that the thick layer of mucin covering the tumor cells acts as a barrier to chemotherapy drugs, thus it is responsible for the diminished anti-tumor effect of popular treatment drugs such as 5-FU (fluorouracil).

Professor Robert B. Campbell and his Ph.D. student Ashish V. Kalra have found not only that reducing the mucin on the tumor cell's surface increases the effect of 5-FU significantly, it may also contribute to a decrease in the amount of drug needed to get the same therapeutic result.

"We are beating down the barrier that stands in the way of effective cancer treatment," said Campbell, Assistant Professor of Pharmaceutical Sciences at Northeastern's Bouvé College of Health Sciences. "Our goal is to help improve the efficacy of drugs and limit the amount of these toxic drugs needed for treatment."

This is the second phase of Campbell's and Kalra's study of the biological attributes of pancreatic tumor cells and the role cellular barriers play in limiting the effectiveness of drugs. During Phase I, the researchers found that extracellular-bound mucin was impeding the cytotoxic effect of 5-FU against the growth of pancreatic cancer cells in vitro.

In Phase II, they confirmed that the mucin glycation mesh produced

during the normal development of pancreatic tumors limits the overall effectiveness of 5-FU in vivo. They also showed that the concentration of 5-FU taken up by the target cell was 7~fold greater when the formation of the glycation mesh was inhibited, further supporting the barrier effect of mucin.

“We knew from the first study that the ability of pancreatic cancer cells to respond to 5-FU treatment in vitro can be enhanced by inhibiting mucin o-glycosylation,” said Campbell. “This time, we found that the overall tumor response to 5-FU in mice that received intratumoral injections of the mucin O-glycosylation inhibitor was greater than the saline control group.”

In addition to the enhanced cell killing effect of 5-FU in a reduced extracellular mucin environment, Campbell and Kalra also confirmed that the exposure to mucin inhibitors did not harm the viability and morphology of the pancreatic cancer cells.

“Improving efficacy of chemotherapeutic drugs plus reducing toxicity in pancreatic cancer patients by limiting the amount of drugs needed to get the same results are hugely important steps toward effective treatment of pancreatic cancer,” added Campbell. “These findings also have the potential to improve the effectiveness of other conventional chemotherapeutic drugs.”

Campbell’s and Kalra’s findings are discussed in an article titled “Mucin overexpression limits the effectiveness of 5-FU by reducing intracellular drug uptake and antineoplastic drug effects in pancreatic tumors” published in this month’s issue of the European Journal of Cancer.

The article discussing Phase I of the study appeared in the October ’07 issue of the *British Journal of Cancer*.