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Scientists break through pancreas cancer treatment barrier

March 19 2012

Pancreas cancer tumors spread quickly and are notoriously resistant to treatment, making them among the deadliest of malignancies. Their resistance to chemotherapy stems in part from a unique biological barrier the tumor builds around itself. Now scientists at Fred Hutchinson Cancer Research Center have found a way to break through that defense, and their research represents a potential breakthrough in the treatment of pancreas cancer.

In a paper to be published in the March 20 issue of *Cancer Cell*, senior author Sunil Hingorani, M.D., Ph.D., an associate member of the Hutchinson Center's Clinical Research and Public Health Sciences divisions, and colleagues describe the biological mechanisms of how the tumor barrier is formed and detail a newly discovered way to break it down. Their research significantly increased the length of survival in a genetically engineered mouse model of the disease. Early clinical trials in humans are under way at a few sites in the U.S. and Europe, including Seattle Cancer Care Alliance, the Hutchinson Center's patient treatment arm.

Using a mouse model developed by Hingorani, the scientists combined gemcitabine, the current standard chemotherapy used to treat pancreatic ductal adenocarcinomas, with an enzyme called PEGPH20. When they infused the combination into specially engineered mice whose pancreas tumors mimic those of human pancreas cancer, the combination broke down the matrix barrier within the tumors and allowed the chemotherapy to permeate freely and spread throughout the cancerous tissue. The result

was a 70 percent increase in survival time of the mice after the start of treatment, from 55 to 92 days.

"This represents the largest survival increase we've seen in any of the studies done in a preclinical model, and it rivals the very best results reported in humans," Hingorani said.

Unlike most solid tumors, pancreas tumors use a two-pronged defense to keep small molecules, such as those contained in chemotherapy, from entering: a vastly reduced blood supply and the creation of a strong fibroinflammatory response. The latter includes the production of fibroblasts, immune cells and endothelial cells that become embedded within a dense and complex extracellular matrix throughout the tumor. One major component of this matrix is a substance called hyaluronan, or hyaluronic acid (HA). HA is a glycosaminoglycan, a complex sugar that occurs naturally in the body and is secreted at extremely high levels by pancreas cancer cells.

Hingorani and colleagues discovered that the fibroinflammatory response creates unusually high interstitial fluid pressures that collapse the tumor's blood vessels. This in turn prevents chemotherapy agents from entering the tumors. The researchers found that HA is the main biological cause of the elevated pressures that leads to blood vessel collapse.

"That's the primary reason pancreas cancers are resistant to everything we've thrown at them: because none of the drugs get into the tumor. It's physics first, before we even get to the intrinsic biology," Hingorani said.

Administering the enzyme/gemcitabine combination degrades HA in the tumor barrier and results in rapid reduction of the interstitial fluid pressure. This in turn opens the blood vessels and permits high concentrations of chemotherapy to reach the tumor.

"Being able to deliver the drugs effectively into the tumor resulted in improved survival as well as the realization that pancreas cancer may be more sensitive to conventional chemotherapy than we previously thought," Hingorani said.

Pancreatic ductal adenocarcinoma is the fourth leading cause of cancer-related death in the United States. Overall five-year survival is less than 5 percent with a median survival of four to six months.

More information: Details about the open clinical trial can be found here: http://clinicaltrials.gov/show/NCT01453153

Cancer Cell paper: "Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma."

Provided by Fred Hutchinson Cancer Research Center