A vaccine may cause pancreatic cancer to respond to immunotherapy

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(Medical Xpress)—Pancreatic ductal adenocarcinomas (PDAC) do not typically respond to immunotherapy, which limits treatment options for this cancer. By priming with a therapeutic vaccine and a low-dose chemotherapy combination prior to surgery, researchers converted PDACs into immunogenic cancers that may respond to immunotherapy, according to a study published in *Cancer Immunology Research*, a journal of the American Association for Cancer Research (produced in collaboration with the Cancer Research Institute).

"The only curative treatment for pancreatic cancer is complete surgical resection, and approximately 80 percent of patients who undergo surgery relapse and die from the disease within five years, suggesting a need for effective strategies," said Lei Zheng, MD, PhD, assistant professor of oncology and surgery at the Sidney Kimmel Comprehensive Cancer Center and the Skip Viragh Center for Pancreatic Cancer Research and Clinical Care at the Johns Hopkins University School of Medicine in Baltimore.

In this clinical trial, pretreatment of PDAC patients with the vaccine GVAX and low doses of the chemotherapy cyclophosphamide caused the aggregation of immune cells inside the patients' tumors, and many of these immune cells expressed proteins that may make these cancers amenable to immunotherapies such as PD-1 inhibitors.

"Pancreatic cancer is one of a number of malignancies that typically lack tumor-infiltrating effector lymphocytes and have been considered

'nonimmunogenic' neoplasms," added Zheng. "This situation has drastically slowed the development and application of immune-based therapies for these cancers.

"Our study shows for the first time that treatment with a vaccine-based therapy directly reprograms the pancreatic cancer microenvironment, allowing the formation of lymphoid aggregates, which are organized, lymph node-like, functional immune structures, and which convert an immunologically quiescent tumor into an immunologically active tumor," Zheng said.

Between 2008 and 2012, Zheng and colleagues enrolled 59 patients with PDAC to this study and randomized them among three arms: Patients in arm A received GVAX alone, patients in arm B received GVAX plus a single intravenous dose of cyclophosphamide at 200 mg/m2, and patients in arm C received GVAX plus 100 mg oral doses of cyclophosphamide once daily, on alternate weeks.

About two weeks after vaccination, all patients underwent surgery to remove their pancreatic tumors. Of the 59 patients, 39 remained grossly free of disease after surgery and underwent further treatment with chemotherapy and radiotherapy, and their tumors were analyzed in this study.

In addition to tumor samples from the 39 patients, the researchers used, for the comparative analyses, tumor samples from 58 patients from other studies: Four were unvaccinated patients and 54 were patients whose tumor samples were collected prior to vaccination.

They found that the vaccine-chemotherapy combination resulted in the formation of lymphoid aggregates within the tumors in 33 of the 39 patients within two weeks of vaccination.

Extensive analysis of the various immune cell types found in the tumors after vaccination revealed an increase in the ratio of effector T cells to regulatory T cells. According to Zheng, this meant that the tumors had become immunogenic and the immune cells in the tumor area were capable of fighting the cancer cells. An increase in the ratio was associated with better survival.

The researchers also found that the tumors from patients who survived for more than three years after vaccine therapy had enhanced signaling pathways that promote immune responses, compared with those who survived for less than 1.5 years following vaccination.

"We are further dissecting the immune signatures within the lymphoid aggregates to study the TGF-beta and Th17 signaling pathways. TGF-beta and Th17 pathways may also be key targets, in addition to PD-1/PD-L1, for treatments that enhance vaccine-induced antitumor immune responses in pancreatic cancer," said Zheng.

"Our study has suggested a new model for developing more effective immunotherapy for traditionally nonimmunogenic tumors like pancreatic cancer," Zheng added. "We will next investigate immunotherapies that include both cancer vaccines and treatments that boost the 'good' immune-regulatory signals or block the 'bad' immune-regulatory signals."

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