MedicalXpress

Pancreatic tumors are marked for immunotherapy

November 30 2009

Pancreatic tumors can be identified by a readily detectable marker that shows promise as a basis for immune therapy against the disease, according to research at Washington University School of Medicine in St. Louis.

The marker is mesothelin, a protein normally found on mesothelial cells that line the body cavities. Several types of cancer cells make large amounts of mesothelin, which then circulates in the blood.

Mesothelin levels in the blood were shown in earlier studies to predict survival in patients with ovarian cancer and mesothelioma (a cancer of mesothelial cells). The researchers wanted to know if elevated blood levels of mesothelin could be used as a biological indicator for pancreatic disease. The study, published this month in *Clinical Cancer Research,* also examined whether the protein could be useful for immune-based cancer treatments.

"All pancreatic tumor specimens we tested displayed mesothelin on them, and the protein could be detected in the blood of 99 percent of our study patients with pancreatic cancer," says co-senior author Peter Goedegebuure, Ph.D., research associate professor of surgery. "Other studies suggest that mesothelin plays an essential role in the development and growth of cancer, making it an ideal target for therapy."

Pancreatic adenocarcinoma, the most common type of pancreatic cancer, strikes about 40,000 Americans per year. However, it is often

not diagnosed until advanced stages of the disease because symptoms are non-specific or completely absent. Fewer than five percent of patients will survive more than five years after diagnosis.

"If we can turn on the immune system to attack cells that have mesothelin, that might become an important part of pancreatic cancer therapy," says co-senior author William G. Hawkins, M.D., a pancreatic cancer surgeon with the Siteman Cancer Center at Barnes-Jewish Hospital and Washington University. "Because mesothelin aids tumor growth, loss of mesothelin could make cancer cells behave more like normal cells. That means even if immunotherapy only knocked out the mesothelin in pancreatic cancer cells instead of killing the cells, it could still be effective. That's what's so exciting about mesothelin as a therapeutic target."

The study showed that mesothelin in the blood was significantly higher in 73 of 74 patients with pancreatic adenocarcinoma when compared to healthy people. There was no relationship between stage of disease or tumor volume and level of circulating mesothelin. Additionally, five patients with benign pancreatic disease who were tested had high levels of circulating mesothelin.

"A number of benign or inflammatory conditions of the pancreas increase mesothelin levels as much as pancreatic cancers do," says Hawkins, who is also associate professor of surgery at Washington University School of Medicine. "So our study suggests that blood mesothelin levels will not be useful for diagnosing pancreatic cancer or predicting patient outcome."

However, the researchers discovered that immune cells taken from pancreatic cancer patients could be coaxed to target mesothelin.

"Mesothelin-specific immune cells are present in pancreatic cancer

patients and can be activated," Goedegebuure says. "And those results suggest that we could potentially design a vaccine to boost the immune response to mesothelin to target pancreatic cancer cells."

Before that becomes a reality, the team will need to overcome obstacles that have previously limited the success of immune-based strategies targeted at cancer, says Hawkins.

"We need three things to come together," Hawkins says. "We need to identify the correct antigens, and this paper suggests mesothelin is one. We need to introduce the antigen in a way that looks dangerous to the human body to elicit an immune response. And we need to interfere with the ability of cancers to turn down the immune response near them."

Researchers have made progress on these fronts. Hawkins is conducting a clinical trial with pancreatic cancer patients of an agent that may boost activation of tumor-specific immune cells. Other researchers at Washington University are testing vaccines that train the immune system to recognize cancer-specific antigens and methods of reducing cancer's ability to suppress immune responses.

"The real breakthroughs in cancer immunotherapy are going to come when we bring these kinds of independent projects together into combined therapies," Hawkins says.

More information: Johnston FMc, Tan MCB, Tan BR, Porembka MR, Brunt EM, Linehan DC, Simon PO. Plambeck-Suess S, Eberlein TJ, Hellstrom KE, Hellstrom I, Hawkins WG, Goedegebuure P. Circulating mesothelin protein and cellular antimesothelin immunity in patients with pancreatic cancer. Clinical Cancer Research Nov. 1, 2009; 15(21):6511-6518.

Source: Washington University School of Medicine (news : web)