VISTA checkpoint implicated in pancreatic cancer immunotherapy resistance

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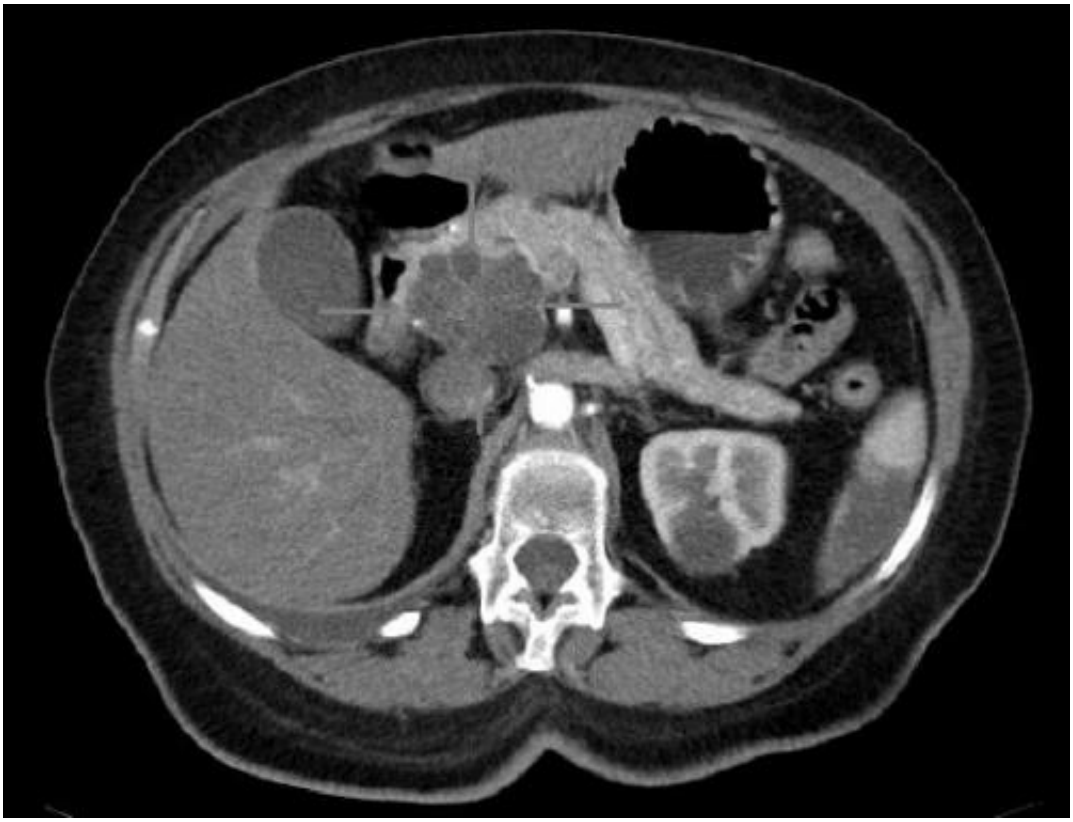

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Researchers have identified a new potential immunotherapy target in pancreatic cancer, which so far has been notoriously resistant to treatment with immune checkpoint blockade drugs effective against a

variety of other cancers.

The University of Texas MD Anderson Cancer Center research team found overexpression of the immune checkpoint VISTA on immune cells, especially macrophages, that infiltrated pancreatic tumors. Their paper will be published online Friday at the *Proceedings of the National Academy of Sciences*.

"VISTA is a potential therapeutic target in pancreatic cancer, and there are several antibodies to block VISTA under clinical development," said co-senior author Padmanee Sharma, M.D., Ph.D., professor of Genitourinary Medical Oncology and Immunology. "Additional research also needs to be done to see if we can come up with other targets for these VISTA-positive cells as well."

Present immune checkpoint inhibitors that unleash an immune attack on cancer by blocking PD-1 and CTLA-4 brakes on T cells have been ineffective against pancreatic cancer, one of the most lethal cancers. The five-year survival rate for patients with pancreatic cancer is 7 percent or less.

The team, led by Sharma and 2018 Nobel Laureate Jim Allison, Ph.D., professor and chair of Immunology, set out to shed light on infiltration of immune cells and expression of immunity-inhibiting checkpoints in pancreatic cancer by comparing those tumors to melanoma, the cancer that is most vulnerable to immune checkpoint blockade.

They first analyzed expression of nine immune inhibitory genes in 23 untreated, surgically removed pancreatic cancer tumors and found the results separated the patients into two groups, 11 with high-expression of inhibitory genes and 12 with low expression.

Those with low-expression of immune inhibitors had a median survival

of 37 months versus 20 months for the high-expression group, indicating potential immune impact on overall survival.

Tumor architecture: Stroma and malignant cells

Pancreatic cancer tumors include a high density of stroma, non-malignant supportive cells, while melanoma is at the other end of the spectrum with minimal stroma. These differences came into play in the team's analyses. The pancreatic tumors were composed of 30 percent malignant cells and 70 percent stroma, while those proportions were flipped in melanoma tumors.

In addition to the vastly different ratio of stromal cells, the architecture of the tumor types also diverges, Sharma notes. "In melanoma, you have a large area of malignant cells surrounded by a thin layer of stroma. With pancreatic cancer, it's more like cancer cells, stroma, cancer cells, stroma ? blended."

Analysis of 29 untreated pancreatic cancer tumors and 44 untreated melanomas found heavier penetration of attacking immune T cells in melanoma as well as higher levels of cells expressing the inhibitory checkpoint molecules PD-1 and its activating ligand PD-L1, which are successfully targeted by inhibitors to treat melanoma. However, pancreatic tumors had much higher expression of VISTA.

About a third of the pancreatic tumors had T cell penetration roughly equal to that found in melanoma, but the T cells were concentrated mainly in the stroma of the tumors, rather than the malignant cells, while they were evenly distributed between cancer cells and stroma in melanoma.

To the researchers, that makes sense. "In pancreatic cancer, you have much more stroma than malignant cells in the tumor. Why is that? I

think it's how the tumor is growing," Sharma said.

Allison noted the stromal cells might be keeping the T cells out of the cancer cells.

VISTA and macrophages

VISTA is predominantly expressed on macrophages—big eater" immune cells that engulf and digest microbes, cellular debris, and tumor cells as part of immune response. VISTA is known to deactivate T cells.

While the researchers found roughly equal density of CD68-positive macrophages in both tumor types, in pancreatic cancer they were again concentrated in the stroma. Macrophages in the pancreatic tumors had much higher expression of VISTA.

A separate comparison of three types of pancreatic tumor—untreated primary, treated metastatic and primary tumors pretreated before surgery—found low penetration of T cells in the metastatic tumors and elevated levels of VISTA in the untreated primary and metastatic tumors.

Analysis of seven pancreatic samples found that CD68-positive macrophages had distinct PD-L1 and VISTA pathways that inhibit immune response separately. Experiments with T cells taken from tumors of three patients with metastatic pancreatic cancer showed that an active VISTA pathway decreased active T cell responses in the tumor to a greater degree than PD-L1 inhibition. This suggests treatment with PD-1/PD-L1 inhibition might fail because an untreated VISTA pathway still suppresses immune response.

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