Cancer that spreads to the lung maneuvers to avoid being attacked by 'killer' T cells

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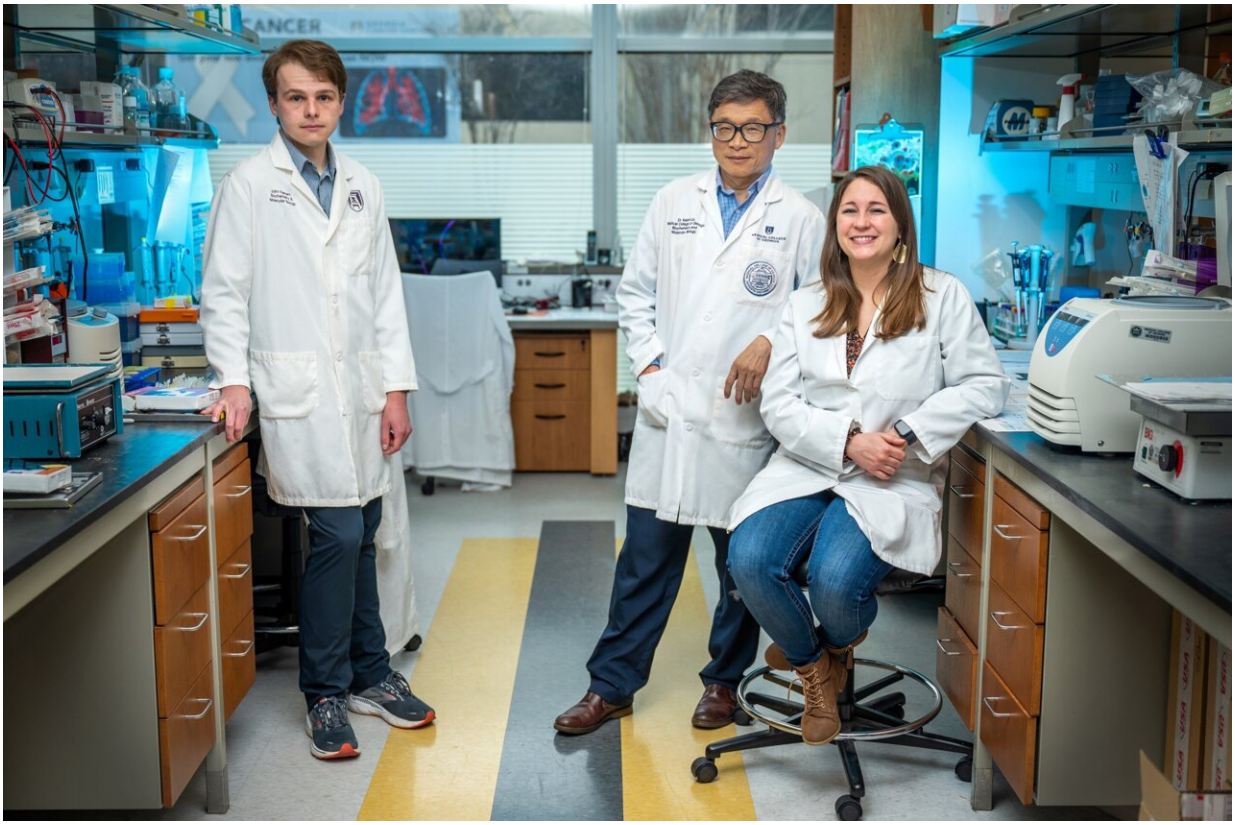

(from left) First author John Klement, a 2022 graduate of MCG's MD/PhD program who is now an internal medicine resident at Stanford University; Kebin Liu, PhD; and co-first author and former AU graduate student Priscilla Redd, PhD. Credit: Michael Holahan, Augusta University

Cancer that has spread to areas like the lungs can apply the brakes to a

natural pathway that should recruit killer T cells directly to where it has metastasized, scientists report.

That newly found strategy used by tumors that have spread—and are consequently more deadly—may help explain why sometimes promising immunotherapies designed to help the immune system kill cancer don't, says Kebin Liu, Ph.D., cancer immunologist in the Department of Biochemistry and Molecular Biology at the Medical College of Georgia.

It also may mean an additional therapeutic maneuver is needed to stop some tumors, which often are diagnosed after they have spread, says Liu, corresponding author of the study in the journal *Cancer Cell*.

T cells are drivers of the immune response which cancer tries to waylay, and drugs like Keytruda (pembrolizumab) and OPDIVO (nivolumab), also known as immune checkpoint inhibitors, try to set these "killer" T cells free.

The mutual target of cancer and these drugs is PD-1, a protein and natural checkpoint that enables T cells to be turned on or off.

The protein PD-L1 naturally binds to PD-1 to effectively turn the T cells off, which is a good thing, when helping avoid, for example, an overzealous immune response to your own body tissue which results in conditions like lupus.

But cancer usurps this natural switch to protect itself in a move dubbed "immunoescape."

"PD-L1 is the brake," say Liu. "The PD-L1 cancer cells express is in direct response to the PD-1 that T cells express. One of the reasons people may not have the success you would expect with immunotherapy is the smartness of the tumor in using PD-L1."

Cancer binds to the PD-1 on T cells, effectively turning them off. Drugs like Keytruda bind to and block the receptor for PD-1 on T cells to keep them free to attack.

But Liu and his colleagues have found that there is more to the story, particularly when it comes to the spread of cancer, which is responsible for more than 90% of cancer mortality.

Immune cells called myeloid cells talk to T cells and can also both activate and prevent these frontline responders from attacking an invader like cancer or a virus. Myeloid cells also express PD-1.

Liu and his colleagues found that metastatic tumor cells also directly engage with the PD-1 on these myeloid cells, where they suppress a natural pathway that produces type 1 interferon, which they found is essential to bringing "killer" T cells right to the spreading cancer's doorstep.

Interferon is a natural protein made by our cells that is known to help the body fight invaders like a virus or cancer. It's also synthetically produced to treat a variety of conditions from skin cancer to hepatitis.

"The tumor uses PD-L1 to bind to the PD-1 on the myeloid cells therefore the myeloid cells cannot produce interferon to help the T cells infiltrate the tumor," Liu says of their findings in cancer metastasis.

They found that the signaling pathway for this interferon is essential to the recruitment of killer T cells to, in this case, the site of cancer that has spread to the lungs. They found in this scenario the PD-L1 from cancer cells interacts directly with the PD-1 on myeloid cells to suppress interferon's production.

They already are working to see if this happens at other common sites

for cancer spread like the liver. The lung and liver are usual sites of metastasis for a variety of cancers, Liu notes. Breast cancer, for example, is known to spread to the bone, brain, liver and lung, according to the National Cancer Institute. The liver and lung are also major sites of metastasis for cancer of the kidney, melanoma, as well as ovarian, prostate and pancreatic cancer. Primary lung cancer can spread to a number of sites including the adrenal gland and liver but also to the other lobe of the lung.

Liu is also pursuing a more direct approach for targeting cancer's metastatic disease maneuver, working with biomedical engineers at Boston University on a molecule that will force the tumor cells themselves to express interferon so they cannot escape being invaded by T cells. "We want to put a bomb inside the tumor's house," he says.

Type 1 interferon alpha was the first immunotherapy approved by the Food and Drug Administration and there is emerging evidence that type 1 interferon enables conversations between immune cells that are in the tumor's supportive microenvironment, they write. They and others have shown that type 1 interferon induces both PD-1 and PD-L1 in myeloid cells. And type 1 interferon has been shown to be silenced in areas of cancer spread.

More information: John D. Klement et al, Tumor PD-L1 engages myeloid PD-1 to suppress type I interferon to impair cytotoxic T lymphocyte recruitment, *Cancer Cell* (2023). DOI: 10.1016/j.ccell.2023.02.005

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