Study uncovers at least one cause of roadblocks to cancer immunotherapy

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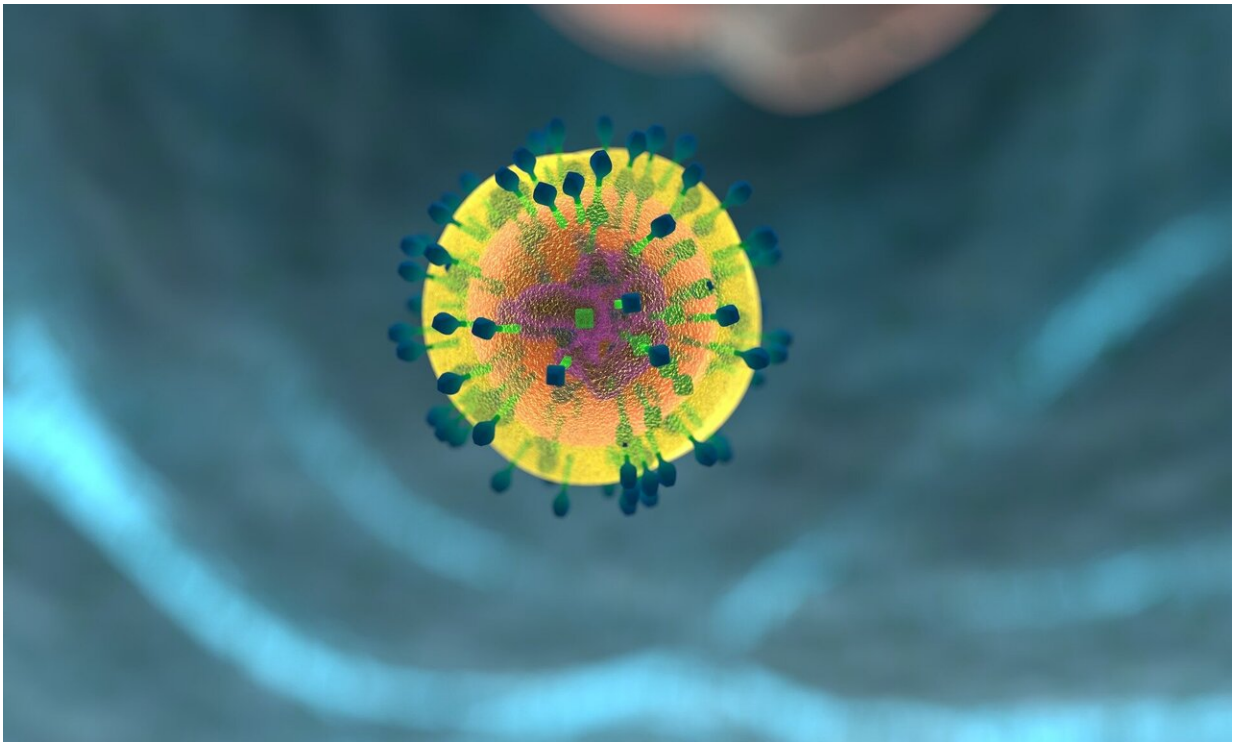

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T cells—the body's foot soldiers against invaders, ranging from everyday infections to cancers—are integral to many successful immunotherapies. However, a frustrating factor is that immunotherapies do not always work.

More than half of human cancers, called "non-inflamed" or "cold" tumors, are not being effectively infiltrated by the cancer-fighting T cells. Essentially, the soldiers are excluded from the battlefield. Researchers want to know why.

A study led by Yale scientists, published in the journal *Science Immunology*, investigated the potential causes associated with T cell exclusion using a genome-wide screen of more than 1,000 human proteins. Of particular interest were signaling proteins that influence T-cell behavior within tissues as they migrate toward inflammation or infection.

The findings identified the protein Phospholipase A2 group 10 (PLA2G10) was highly expressed, or had a strong presence, in cancerous tissue compared with normal tissue. This was true in various human cancers such as lung cancer, pancreatic cancer, and prostate cancer, making it a potential target to be addressed.

Further, in mouse tumor models, the investigators found that a monoclonal antibody—a lab-developed protein that can recognize specific targets—can efficiently disable PLA2G10's function and restore cancer-fighting T-cell infiltration into cancer.

"These findings uncover new tactics that are employed by cancer to escape from immune cell attack and explain why some cancer immunotherapy strategies do not work well in the clinic," said Lieping Chen, MD, Ph.D., a member of Yale Cancer Center, the United Technologies Corporation Professor in Cancer Research, and a professor of immunobiology, of medicine (medical oncology), and of dermatology at Yale School of Medicine.

The authors suspect that PLA2G10 prevents chemokines, secreted proteins that are responsible for attracting cancer-fighting T cells, from

working effectively, slowing down T cell movement. That, in turn, could be why an insufficient amount of T cells are infiltrating cancerous tissues. Further work may reveal whether this sense of the mechanisms involved is accurate.

More information: Tianxiang Zhang et al, Up-regulated PLA2G10 in cancer impairs T cell infiltration to dampen immunity, *Science Immunology* (2024). DOI: 10.1126/sciimmunol.adh2334

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