

When Small Cell Lung Cancer Hides from Immune Cells, Blood Vessels May Hold the Key

Tumor blood vessels can act like a gatekeeper, preventing natural killer cells from leaving the bloodstream and attacking tumors.

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BOSTON — Researchers at [Dana-Farber Cancer Institute](#) have uncovered why small cell lung cancer (SCLC) can stay largely out of reach of the immune system, even when the cancer cells themselves are vulnerable to immune attack. In the most common form of neuroendocrine SCLC, investigators found that tumor blood vessels can act like a gatekeeper, preventing natural killer (NK) cells from leaving the bloodstream and entering the tumor. When the researchers activated an immune “alarm” pathway called STING in the tumor’s vascular environment, NK cells were able to get into the tumor and kill cancer cells, with an even stronger effect when STING activation was combined with a DLL3-targeted CAR-NK cell therapy in preclinical models.

The study was published in [Cancer Cell](#).

Small cell lung cancer is one of the most aggressive lung cancers and often does not trigger a strong immune response, so many tumors contain very few immune cells. The study focused on the neuroendocrine form of SCLC, where tumor cells commonly reduce a signal called MHC class I that helps T cells recognize abnormal cells. Losing MHC class I can help tumors hide from T cells, but it should make them easier targets for NK cells, which are built to detect cells with low MHC class I. That set up the puzzle the researchers investigated: NK cells can kill these tumor cells in the lab, yet in patient tumors NK cells are often scarce in the very areas where the cancer cells appear most vulnerable.

To understand why NK cells were missing from those regions, the team used high-resolution spatial profiling and spatial transcriptomics to map immune cells and tumor features in patient samples. They then paired those findings with a microphysiological “tumor-on-a-chip” model that recreates SCLC tumors surrounded by functional blood vessels, enabling them to watch how immune cells behave as they circulate, interact with the vessel wall, and attempt to enter tumor tissue. Using a dynamic single-cell RNA sequencing approach called DynaMITE-seq, the researchers captured how tumor, vascular, and immune cells respond to one another over time

and identified the microvasculature as a major checkpoint that restricts NK cell trafficking and entry.

“Small cell lung cancer has been notoriously difficult to treat with immunotherapy, in part because the immune system often can’t access the tumor,” said senior author [Dr. David Barbie](#), Director of the Lowe Center for Thoracic Oncology at Dana-Farber, co-lead this study with Navin R. Mahadevan, MD, PhD, former member of Barbie’s laboratory and currently assistant professor at University of Michigan. “Our study shows that the blood vessels around these tumors can act as a barrier that keeps natural killer cells out, and that activating STING can help unlock that barrier. This points to a promising combination strategy that could make NK-based and potentially other immunotherapies more effective for the patients who need new options most.”

The researchers found that the tumor vasculature was not simply a passive conduit, but an active “gatekeeper” that limited NK cells’ ability to exit the bloodstream and enter tumor regions. This helps explain how a tumor can be NK-sensitive but still NK-invisible in patients, because the immune cells are capable of killing but are physically and biologically blocked from reaching their target. The data also suggested that the immune-suppressive environment surrounding these tumors contributes to this exclusion, reinforcing the importance of strategies that improve immune cell access as well as immune cell function.

The findings also highlight a potential strategy to help NK cells reach these tumors. The researchers used a STING agonist, which turns on an early “alarm” response in the immune system and can change signals in the tumor environment. When they activated STING in and around the tumor’s blood vessels, NK cells were better able to exit the bloodstream, enter the tumor, and attack neuroendocrine SCLC cells. The response was even stronger when STING activation was paired with DLL3-targeted CAR-NK cell therapy, suggesting that priming the tumor’s vasculature may help engineered NK cells get to the cancer and work more effectively.

“In this form of small cell lung cancer, the immune cells aren’t failing because they can’t kill—the problem is they can’t get in,” said first author [Marco Campisi](#), PhD. “By activating STING in the tumor’s vascular neighborhood, we found a way to open the vascular gate so NK cells can enter and attack, and that access appears to make targeted CAR-NK therapy work better.”

Future research will focus on improving the durability and persistence of NK-cell therapies, so they continue to function effectively over time. The team is working with the Rizwan Romee lab, which provided DLL3 CAR-NK cell, to engineer CAR-NK cells that produce IL-12 to enhance proliferation and anti-tumor activity, supported in part by a Claudia Adams Barr Program for Cancer Research award to Campisi.

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