Researchers identify immune cell that helps kill bladder cancer tumors

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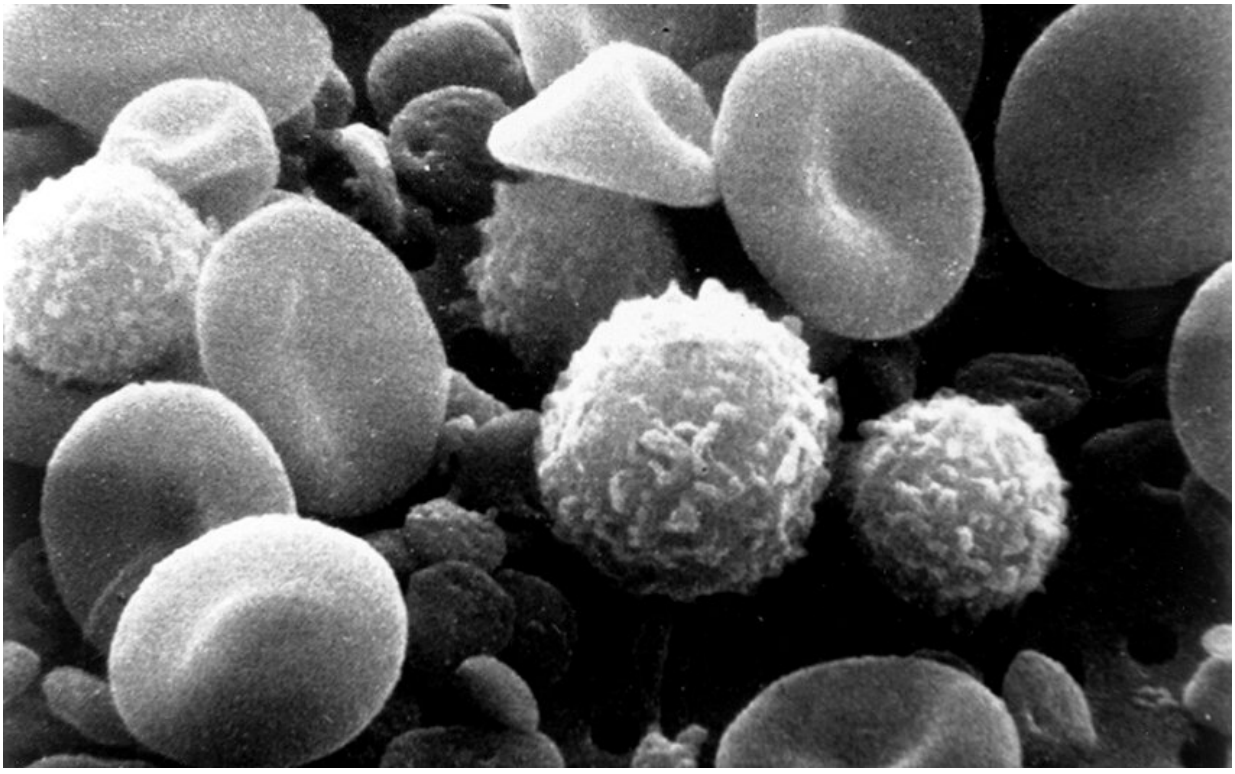

Myeloid immune cells alongside red blood cells in an electron micrograph of human blood. Credit: National Cancer Institute

Mount Sinai researchers have made two important discoveries about the mechanism by which bladder cancer cells foil attacks from the immune system. The research, published in *Cancer Cell* in September, could lead

to a new therapeutic option for patients with these types of tumors.

Advanced bladder cancer is aggressive and patients generally have poor prognoses. Several immune checkpoint inhibitors have been approved by the Food and Drug Administration for bladder cancer, but they only sustain good responses in about 20 percent of patients.

When people get cancer, a type of immune cell called a "natural killer cell" swings into action to try to kill off the tumor cells. However, the tumor cells are often able to foil the attacks from the natural killer cells. The Mount Sinai researchers reported that they had found a subset of CD8 T cells that adapts to tumor evasion strategies by appropriating innate-like properties traditionally ascribed to natural killer cells, offering a strategy to reduce the tumor cells' ability to fight them off.

To create additional killer cells, the researchers showed that they could induce CD8+ T cells to express a molecule known as NKG2A on their surface, allowing them to behave more like natural killer cells. This study showed that NKG2A is associated with improved survival and with responsiveness to a cancer-fighting immunotherapy known as PD-L1 checkpoint blockade.

The second discovery concerns cancer cells' ability to resist PD-L1 checkpoint blockade therapy. The researchers noted that tumors can maintain expression of a protein called HLA-E on their surface that can resist the T cells because HLA-E binds to the NKG2A molecule and disables the T cells' ability to fight. An immunotherapy that specifically targets the HLA-E/NKG2A axis could be an effective way to attack cancers in these patients, the researchers said.

"These findings suggest that antibodies that block both NKG2A and PD-L1 could be a more effective treatment strategy for patients whose bladder cancer tumors have both high levels of HLA-E and NKG2A-

positive CD8+ T cells," said lead and co-corresponding author Amir Horowitz, Ph.D., Assistant Professor of Oncological Sciences at The Tisch Cancer Institute at Mount Sinai and member of the Precision Immunology Institute at the Icahn School of Medicine at Mount Sinai. "These findings provide a framework for future clinical trials that combine a therapy that blocks NKG2A with other immunotherapies in these tumors."

"Immune checkpoint blockade is a leading type of cancer immunotherapy that targets the PD1-PDL1 pathway in order to re-engage 'exhausted' CD8+ T cells in the fight against tumors," said co-corresponding author Nina Bhardwaj, MD, Ph.D., Director of Immunotherapy, Co-Director of the Cancer Immunology Program and Professor of Medicine (Hematology and Medical Oncology) at The Tisch Cancer Institute at Mount Sinai. "In this paper, we show that responses to PD-L1 blockade in patients with bladder cancer are influenced by an additional immune checkpoint axis identified recently in other cancers: NKG2A-HLA-E."

To conduct the study, the researchers profiled tumors and blood of bladder cancer patients across various stages of the disease, and studied all specimens immediately after surgical removal from patients to ensure they could capture live immune cells and examine their functioning. The study integrated several cutting-edge single-cell technologies and leveraged publicly available datasets through The Cancer Genome Atlas (TCGA) and the ImVigor210 trial of atezolumab, an anti-PDL1 immunotherapy.

Several collaborators contributed to this study, including Columbia University, Karolinska Institutet, Frederick National Laboratory for Cancer Research at the National Institutes of Health, Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, Harvard University, University of Genoa, University of Lausanne, Oslo

University, Sema4, Genentech and Astra Zeneca. Funding from the U.S. Department of Defense, Parker Institute for Cancer Immunotherapy, the National Cancer Institute and the National Institute of Allergy and Infectious Diseases supported this work.

More information: Bérengère Salomé et al, NKG2A and HLA-E define an alternative immune checkpoint axis in bladder cancer, *Cancer Cell* (2022). DOI: 10.1016/j.ccell.2022.08.005 , dx.doi.org/10.1016/j.ccell.2022.08.005

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