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Study suggests a way to re-energize tired T cells when treating cancer, viral infections

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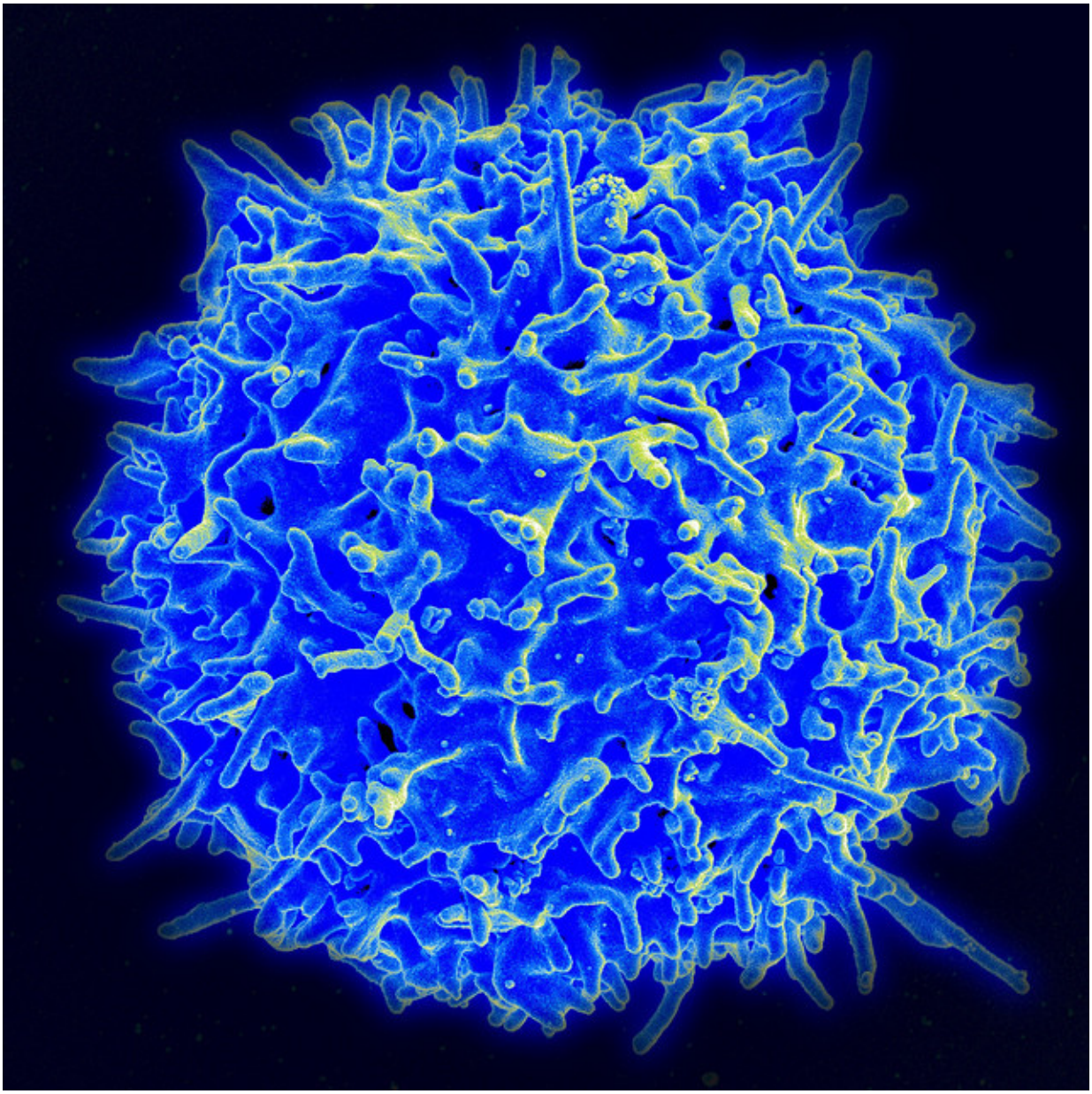

Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. Credit: NIAID

A new study by researchers at The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC—James) suggests a way to re-energize critical killer immune cells that have become exhausted when fighting cancer or chronic viral infections.

Immune cells called CD8 T cells are critically important in the immune system's efforts to eliminate cancer cells and viral infected cells from the body. These cells are also key players in immune therapies called immune checkpoint blockade and CAR T-cell therapy.

For this animal and cell study, researchers first developed a new model system to study human CD8 T-cell dysfunction and whether the dysfunction can be reversed.

The work revealed that chronic signaling by transforming growth factor beta 1 (TGFβ1) accelerates the killer cells' loss of function. It also showed that boosting the activity of a cytokine called bone morphogenetic protein 4 (BMP4) while blocking TGFβ1 could preserve the function of chronically stimulated human CD8 T cells. This also improved responses in animal models to tumors and to a chronic viral infection.

The researchers report their findings in the journal *Nature Immunology*.

"When killer T cells become severely dysfunctional, they are unable to effectively clear cancer or viral infections from the body, and they do not respond well to immunotherapies," said principal investigator Hazem

Ghoneim, assistant professor in the Department of Microbial Infection and Immunity.

"We found that rebalancing TGFβ1 and BMP signaling can unleash these dysfunctional T cells and enhance their response to T cell-based immunotherapies and other immune checkpoint therapies," said Ghoneim, who is also a member of OSUCCC-James Cancer Biology Research Program.

"This novel strategy could potentially improve the effectiveness of these therapies and help to clear chronic infections or tumors more effectively," he added.

Ghoneim and his colleagues reasoned that cues in the tumor microenvironment likely triggered the shift of T cells to a pathway leading to dysfunction. They also reasoned that identifying the key signals involved in that shift would reveal new targets that could improve the effectiveness of T-cell immune therapies.

Constant exposure to cancer-cell antigens in the tumor microenvironment causes killer T cells to show signs of mild burnout and to become mildly dysfunctional. The researchers found that these mildly dysfunctional T cells are driven to a state of profound dysfunction by chronic exposure to TGFβ1 that remain stable even after resting the cells.

They also found that the cytokine BMP4 limits the exhaustion and improves the survival of chronically stimulated CD8 T cells.

The researchers then used animal models to show that adjusting the balance of TGFβ1 and BMP signaling could:

- Maintain the tumor-killing ability of human CD8 T cells;

- Boost exhausted T-cell responses to an immune checkpoint blockage therapy; and
- Control a lifelong chronic lymphocytic choriomeningitis viral infection.

"Our findings," Ghoneim said, "indicate that relative levels of TGF beta and bone morphogenetic protein in a tumor microenvironment strongly influence the function of chronically stimulated CD8 T cells, revealing a potential new strategy to epigenetically reprogram dysfunctional T cells during immune checkpoint blockade therapy."

Other Ohio State researchers involved in this study were Abbey A. Saadey, Amir Yousif, Nicole Osborne, Roya Shahinfar, Yu-Lin Chen, Brooke Laster, Meera Rajeev, Parker Bauman and Amy Webb.

More information: Abbey A. Saadey et al, Rebalancing TGFβ1/BMP signals in exhausted T cells unlocks responsiveness to immune checkpoint blockade therapy, *Nature Immunology* (2022). DOI: 10.1038/s41590-022-01384-y

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