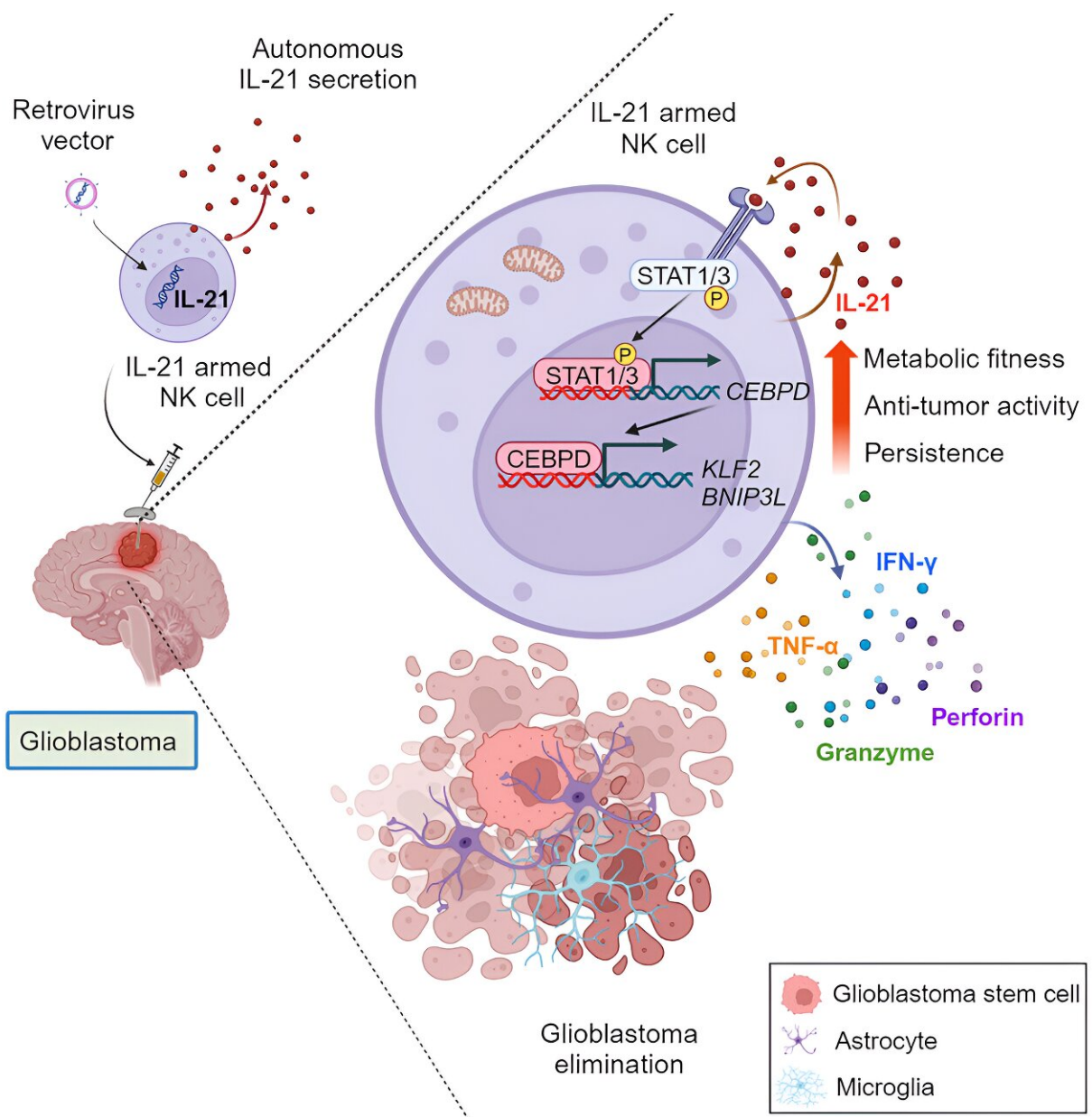


Natural killer cells expressing interleukin-21 show promising antitumor activity in glioblastoma cells

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Graphical Abstract. Credit: *Cancer Cell* (2024). DOI: 10.1016/j.ccell.2024.07.007

Natural killer (NK) cells engineered to express interleukin-21 (IL-21) demonstrated sustained antitumor activity against glioblastoma stem cell-like cells (GSCs) both in vitro and in vivo, according to new research from The University of Texas MD Anderson Cancer Center.

The preclinical findings, published today in [Cancer Cell](#), represent the first evidence that engineering NK cells, a type of innate immune cell, to secrete IL-21 resulted in strong activity against [glioblastoma](#), a cancer type in need of more effective treatment options.

"Our research uncovered a previously unknown mechanism that plays an important role in NK cell memory against glioblastoma, highlighting the potential of NK cells engineered to express IL-21 in treating this disease," said Katy Rezvani, M.D., Ph.D., professor of Stem Cell Transplantation & Cellular Therapy. "The ability of these IL-21 engineered [natural killer cells](#) to recognize and kill glioblastoma stem cell-like cells offers a highly promising therapeutic approach."

Glioblastoma is an aggressive brain cancer with limited therapeutic options. Current treatment options for glioblastoma include surgery, [radiation therapy](#) and chemotherapy, but these options offer limited efficacy and patients have a median survival of just 18 to 21 months. According to the National Brain Tumor Society, the five-year survival rate for patients with glioblastoma is only 6.9%, with an average estimated length of survival of only eight months.

As part of the innate immune system, NK cells have a natural ability to recognize and eliminate GSCs. Engineering these cells can boost their fitness and antitumor activity. IL-21 is an immune signaling protein, or cytokine, shown to promote better metabolic fitness in NK cells.

In this study, first author Mayra Shanley, Ph.D., principal research scientist at MD Anderson, and her co-authors used multiple in vitro and in vivo models to treat GSCs with NK cells engineered to express either IL-21 or IL-15, another cytokine used to boost NK cell activity.

While both groups of engineered NK cells displayed strong activity against GSCs in vitro, the IL-21 NK cells exhibited a stronger metabolic fitness than those expressing IL-15. [Previous research](#) by MD Anderson researchers identified lost metabolic fitness as a key mechanism in tumor resistance.

In vivo, the IL-21 NK cells showed limited toxicity and excellent tumor control in murine models of patient-derived GSC, compared to high toxicity and ineffective tumor control with IL-15 NK cells, which became exhausted over time.

Researchers also identified the CCAAT/Enhancer-Binding Protein (C/EBP), particularly CEBPD, as a critical transcription factor that plays an important role in regulating the sustained anti-GSC cytotoxicity of IL-21 NK cells.

When CEBPD was deleted, the potency of IL-21 NK cells decreased, while overexpression of CEBPD in NK cells increased their long-term cytotoxicity, metabolic fitness and anti-GSC potency in vivo. This enhanced activity was linked to distinct transcriptional and epigenetic signatures compared to IL-15 NK cells.

Based on these findings, researchers at MD Anderson will begin

investigating the clinical application of IL-21 engineered NK cells in patients with glioblastoma, with a trial anticipated to begin later this year.

More information: Interleukin-21 engineering enhances NK cell activity against glioblastoma via CEBPD, *Cancer Cell* (2024). DOI: [10.1016/j.ccell.2024.07.007](https://doi.org/10.1016/j.ccell.2024.07.007). [www.cell.com/cancer-cell/fullt ... 1535-6108\(24\)00272-1](https://www.cell.com/cancer-cell/fulltext/S1535-6108(24)00272-1)

Provided by University of Texas M. D. Anderson Cancer Center

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