Drug reprograms immune responses to target glioblastoma

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Investigators from Northwestern University Feinberg School of Medicine and The University of Texas MD Anderson Cancer Center have discovered that using a novel drug to target the STING pathway in glioblastoma reprogrammed previously suppressed immune responses. The findings are published in the Journal of Clinical Investigation.

The study, co-led by Amy Heimberger, MD, Ph.D., the Jean Malnati Miller Professor of Brain Tumor Research, vice chair for Research in the Department of Neurological Surgery, demonstrates the potential of a novel therapeutic strategy for patients with glioblastoma who do not typically respond to current FDA approved immunotherapies.

"It's not so much reinvigoration of a prior failed immune response but rather a nucleation of a new response directed toward the tumor," said Michael Curran, Ph.D., associate professor of Immunology in the Division of Basic Science Research at the University of Texas MD Anderson Cancer Center and co-corresponding author of the study.

Glioblastoma is the most common type of primary brain cancer in adults with an average survival time of just 15 months, according to the Centers for Disease Control and Prevention. For recurrent glioblastoma, there are currently no available treatment options.

Recent work has shown that targeting the STING (stimulator of interferon genes) pathway increased anti-tumor immune responses in other types of tumors, notably pancreatic cancer and melanoma.
"The trigger of the STING pathway turns an otherwise quiescent, calm bed of cells into one that is highly visible to the immune system and is calling out to be investigated and possibly eliminated," Curran said.

In the context of glioblastoma, the tumor will recruit a variety of immunosuppressive cells to support tumor growth and keep the immune system at bay.

In a previous study led by Heimberger, investigators found that activating the STING pathway in dogs with glioblastoma was well tolerated, suggesting that targeting STING may be a promising therapeutic approach in humans.

In the current study, the scientists hypothesized that activating the STING pathway in glioblastoma tumor cells could transform immunosuppressive myeloid cells within the tumor microenvironment into anti-tumor inflammatory cells that can be detected by the body's adaptive immune system.

"We're turning them [myeloid cells] into traitors against the tumor that are instead going to assist your adaptive immune system in eliminating it. It raises this red flag that not only helps activate inflammation and anti-tumor immunity there but also helps call in T-cells from outside the brain lymphatics, like the cervical lymph nodes," Curran said.

Mobilizing T-cells that are capable of directly killing the tumor is crucial in the context of glioblastoma, Heimberger said, because a very limited number of T-cells exist within the tumor microenvironment.

By analyzing RNA sequencing datasets and immunofluorescence multiplex imaging of patient glioblastoma samples, investigators showed that STING pathway activation occurs in subsets of myeloid cells, including microglia, which are immune cells of the nervous system.
Next, using a novel STING agonist developed by the investigators, the team used the drug to evaluate its efficacy in a wide variety of preclinical models of glioblastoma, including those that are immune checkpoint inhibitor-resistant.

Subsequent ex vivo analysis showed that the agonist successfully induced immune responses in T-cells and NK (natural killer) immune cells from surrounding lymphatics, and also mobilized inflammatory myeloid cells.

"We demonstrated that the therapeutic activation of the STING pathway within the glioma microenvironment significantly reprograms the immune populations," said Hinda Najem, MD, MS, a postdoctoral fellow in the Heimberger laboratory and co-first author of the study. "These marked findings merit consideration for human clinical translation."

The scientists are now beginning to evaluate the agonist in glioblastoma mouse models who received radiation to determine if the therapy could be effective when given to patients before cancer recurrence.

"Ultimately, this therapy has to get to patients. Both of us feel very strongly that way," Curran said.

**More information:** Hinda Najem et al, STING agonist 8803 reprograms the immune microenvironment and increases survival in preclinical models of glioblastoma, *Journal of Clinical Investigation* (2024). [DOI: 10.1172/JCI175033](https://doi.org/10.1172/JCI175033)

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