

Study could help explain why certain brain tumors don't respond well to immunotherapy

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A study led by researchers at the UCLA Jonsson Comprehensive Cancer Center sheds new light on why tumors that have spread to the brain from other parts of the body respond to immunotherapy while glioblastoma,

an aggressive cancer that originates in the brain, does not.

In people with tumors that originated in other parts of the body but spread to the [brain](#), treatment with a type of immunotherapy called [immune checkpoint blockade](#) appears to elicit a significant increase in both active and exhausted T cells—signs that the T cells have been triggered to fight the cancer. The reason the same thing doesn't occur in people with glioblastoma is that anti-tumor immune responses are best initiated in draining lymph nodes outside of the brain, and that process does not occur very effectively in glioblastoma cases.

To date, immunotherapy has not been effective in treating glioblastoma, but it has been shown to slow or even eradicate other types of cancer, such as melanoma, which frequently metastasizes to the brain.

The research, published in the *Journal of Clinical Investigation*, could help improve the effectiveness of immunotherapy for people with [brain tumors](#) and it could suggest new paths in the effort to help develop more effective therapies.

"If we're going to try to develop new therapies for [solid tumors](#), like glioblastoma, which are not typically responsive, we need to understand the tumor types that are responsive, and learn the mechanisms by which that happens," said the study's senior author, Robert Prins, a professor of molecular and medical pharmacology and of neurosurgery at the David Geffen School of Medicine at UCLA.

The researchers studied the immune cells obtained from nine people with metastatic brain tumors who had been treated with immune checkpoint blockade—which works by harnessing the body's immune system to destroy [cancer cells](#)—and compared their observations with immune cells taken from 19 patients with brain metastases that not been treated with immunotherapy.

They used a technique called single-cell RNA sequencing to examine the [genetic material](#) in both sets of samples, and then compared the data to previously published analyses of 25 recurrent glioblastoma tumors to better understand the effect the immunotherapy had on T cells.

"We really were trying to figure out which immune cells are changing in the more responsive tumors in order to better explain the higher response rate to the treatment," said the study's co-first author, Lu Sun, a project scientist in the Geffen School of Medicine's neurosurgery department. "No study has comprehensively examined the differential effect of immune checkpoint blockade treatment on these two types of brain tumors before."

In the tumors that had spread to the brain, the researchers saw that the T cells had specific characteristics associated with fighting tumors entering the brain, most likely due to a more effective priming step that occurs outside of the brain.

Before traveling to the brain, T cells are first activated in the [lymph nodes](#). During this process, a type of [immune cells](#) called [dendritic cells](#) share information about the tumor to T cells so they can better attack the [tumor](#). This priming process, however, doesn't work very effectively when doctors attempt to use immune checkpoint blockade for treating glioblastoma.

The researchers also found that a specific subgroup of those exhausted T cells was associated with longer overall survival in people whose cancer had metastasized to the brain.

"We found quite a significant difference between the two types of brain tumors and how they respond to immunotherapies," said study author Dr. Won Kim, surgical director of UCLA Health's brain metastasis program and a member of the Jonsson Cancer Center.

"There was a tremendous number of T cell lymphocytes that were found within brain metastases following immunotherapy, and while the number of T cell lymphocytes also increased in glioblastoma patients, it wasn't anywhere near the same extent."

Prins, who is also a researcher at the Jonsson Cancer Center, said that finding "suggests that enhancing the activation and presentation of T cells by dendritic cells could be a potential treatment strategy."

In future studies, the researchers plan to analyze data from a larger, more uniform group of people who were diagnosed with melanoma that had spread to the brain.

The study's other co-first author is Jenny Kienzler, who was a UCLA fellow in neurosurgery when the research was conducted.

More information: Lu Sun et al, Immune checkpoint blockade induces distinct alterations in the microenvironments of primary and metastatic brain tumors, *Journal of Clinical Investigation* (2023). [DOI: 10.1172/JCI169314](https://doi.org/10.1172/JCI169314)

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