Cancer stem cells suppress immune response against brain tumor

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Amy Heimberger, M.D., is an associate professor in M. D. Anderson's Department of Neurosurgery. Credit: M. D. Anderson

Cancer-initiating cells that launch glioblastoma multiforme, the most lethal type of brain tumor, also suppress an immune system attack on the disease, scientists from The University of Texas M. D. Anderson Cancer Center report in a paper featured on the cover of the Jan. 15 issue of *Clinical Cancer Research*.

The researchers demonstrate that this subset of tumor cells, also known as cancer stem cells, stifles the immune response in a variety of ways,

but that the effect can be greatly diminished by encouraging the stem cells to differentiate into other types of brain cell.

"We've known for years that glioblastoma and cancer patients in general have impaired immune responses," said senior author Amy Heimberger, M.D., an associate professor in M. D. Anderson's Department of Neurosurgery. "Our research uncovers an important mechanism that shows how that happens. The cancer stem cells inhibit T cell response, and it is these T cells that recognize and eradicate cancer."

Definitions of cancer stem cells vary. To meet the researchers' definition, the cells had to express a marker called CD133, form neurospheres (little round balls) in culture, and be able to recreate glioblastoma multiforme when injected into the brain of a mouse. They also had to be capable of differentiating into specific types of brain cells - neurons, astrocytes and glial cells.

Glioblastoma stem cells have been implicated in tumor resistance to chemotherapy and radiation, and are the believed to be responsible for the relentless recurrence of the disease, said first author Jun Wei, Ph.D., an instructor in the Department of Neurosurgery.

Wei explained that the glioblastoma stem cells suppress T cell response three different ways by:

- Producing immunosuppressive cytokines that prevent the responses of T cells.
- Inducing some T cells to become regulatory T cells, which act as brakes on the immune response.
- Killing T cells via apoptosis, or programmed cell suicide. This is

accomplished via the immunosuppressive protein B7-H1 in the stem cells directly contacting the T cells or by secretion of Galectin-3.

Wei said this immunosuppressive effect was reversed when the team placed the undifferentiated glioma stem cells in a culture medium that causes them to differentiate into the three types of neural cell.

"There are multiple research groups around the country, including ours, trying to develop vaccines or other immunotherapeutics against glioma stem cells," Heimberger said. "Now we have to be cognizant that the stem cell may deliver a fatal blow back to the immune system, which will help us understand how to design immune-based therapies."

New drugs or combination therapies are needed, because after decades of research, little progress has been made in treating glioblastoma multiforme. With the best of care patients survive an average of 14 months.

STAT3 pathway inhibits T cell response

In a separate paper in the Jan. 15 issue of Molecular Cancer Therapeutics, the research team also reports that the STAT3 signaling pathway is highly active in glioblastoma stem cells and suppresses immune system response.

Heimberger said the STAT3 molecule is known to induce cancer proliferation and survival migration and invasion, growth of new blood vessels, and immunosuppression.

Inhibiting STAT3, either by silencing it with small interfering RNA or by treatment with an experimental drug called WP1066, reactivates the immune response.

"We showed that if you treat the cancer stem cells with an inhibitor of STAT3, you can restore T cell proliferation and the ability of those cells to make pro-inflammatory cytokines," Heimberger said.

While the response is powerful it is not complete, so the researchers conclude there a STAT3-independent pathway is also at work in mediating immune suppression.

Research continues on how the inhibitors work, and whether they cause the stem cell differentiation that the team has shown reverses immune suppression.

The experimental drug WP1066 was developed by Waldemar Priebe, Ph.D., professor in M. D. Anderson's Department of Experimental Therapeutics. The drug has been shown to inhibit STAT3 in mice and reverse the immune suppression caused by cancer stem cells.

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