Cancer cells mediate immune suppression in the brain

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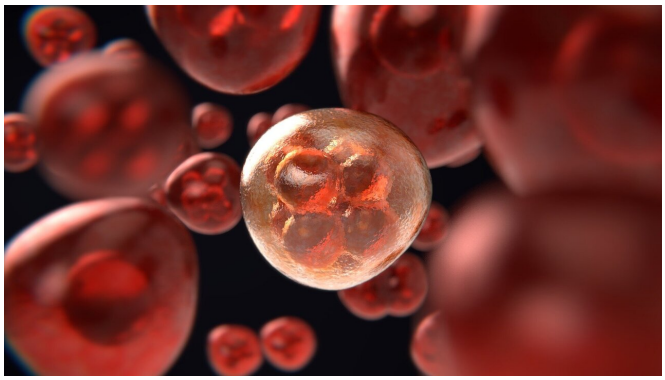

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Scientists have long believed that the brain protects itself from an aggressive immune response to keep down inflammation. However, that evolutionary control may work against it when a cancer cell attempts to spread to the brain, researchers at the University of Notre Dame have discovered.

In newly published research in the journal *Cell*, researchers showed that one type of cell important for immunity, called a myeloid cell, can suppress the immune response—which has the effect of allowing breast cancer cells to metastasize to the brain to form secondary tumor cells there.

"We wanted to understand how the brain immune environment responds to the tumor, and there are so many different cells, and so many changes," said Siyuan Zhang, the Dee Associate Professor in the Department of Biological Sciences, a researcher for Harper Cancer Research Institute and a co-author on the paper. "The traditional belief was that the process described in this paper would be anti-tumor, but in our case, after a lot of experimenting, we discovered it is a proponent of metastasis."

Through single-cell sequencing—not powerful enough even a few years ago for this type of work—and an imaging technique, the researchers discovered that a myeloid cell type called microglia promoted the outgrowth of breast cancer that has spread to the brain by the expression of several proteins. The microglia release one protein—an immune cell-attracting protein called CXCL10—to recruit more microglia to the metastasis. All these microglia express a protein named VISTA, which serves as protection against brain inflammation. But when faced with a cancer cell, this two-part process suppressed important T-cells. T-cells, which heighten the body's immune response, would usually prevent the spread of cancer throughout the body.

The activation of the VISTA checkpoint had not previously been known as a potential promoter of brain metastasis, said the paper's lead author, Ian Guldner, a graduate student in Zhang's lab. In addition to using a mouse model for the research, the team used data mining techniques to validate how humans' brains would respond.

Clinically, the discovery is relevant, because antibodies have been developed that blocked VISTA in humans, Guldner said. However, significant additional work needs to be performed to ensure the safe and effective use of VISTA-blocking antibodies in people with brain metastases.

Learning about the structures within cells in the brain will help researchers not only understand cancer, but also degenerative diseases such as Parkinson's, multiple sclerosis and Alzheimer's, Zhang said.

"The brain immune system is a very active field, since brain cells are dysregulated during the aging process," Zhang said. "There is so much to learn."

More information: Ian H. Guldner et al, CNS-

Native Myeloid Cells Drive Immune Suppression in the Brain Metastatic Niche through Cxcl10, *Cell* (2020). DOI: 10.1016/j.cell.2020.09.064