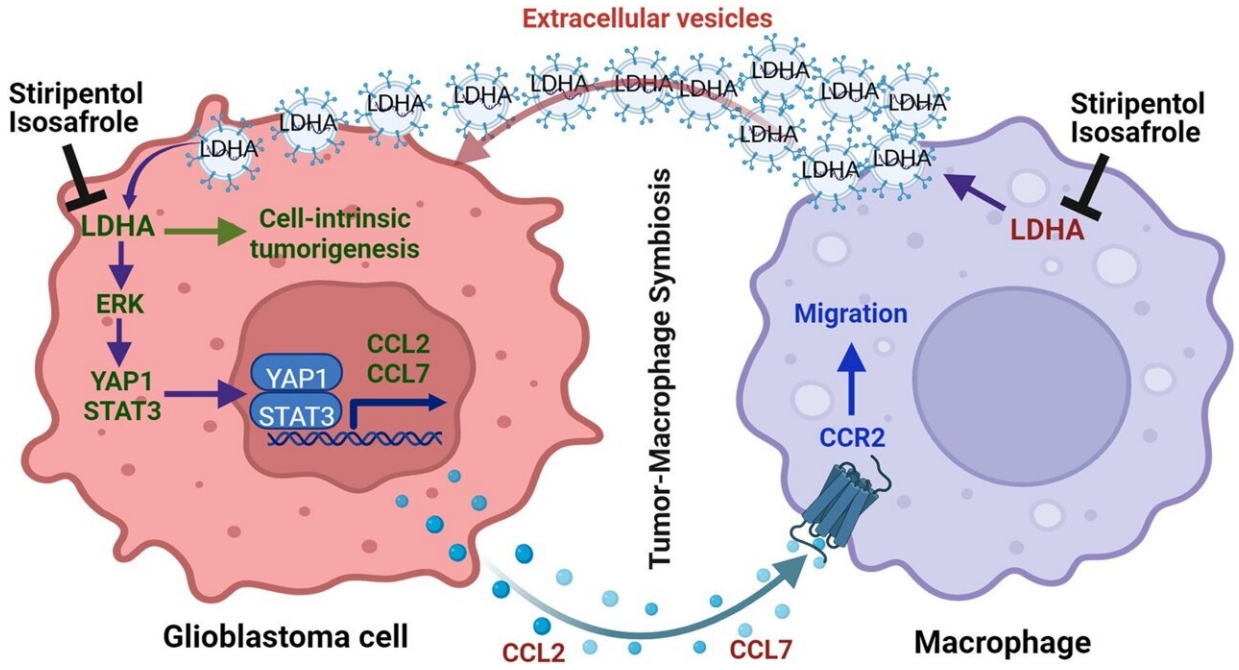
Investigating mechanisms of aggressive glioblastoma tumor growth

March 27 2024, by Olivia Dimmer



Schematic representation of the role of the LDHA–ERK–STAT3/YAP pathway in regulation of CCL2 and CCL7 in glioblastoma cells, which, in turn, promotes macrophage infiltration. These infiltrating macrophages are educated by the TME and promote glioblastoma cell proliferation and survival via transferring LDHA-containing extracellular vesicles. Created with BioRender.com. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-46193-z

Northwestern Medicine investigators have identified a metabolism-related gene that may play a role in recruiting immune cells to support the growth of aggressive brain tumors, according to a study recently published in *Nature Communications*.

Glioblastoma, one of the most complex and treatment-resistant cancers, has a five-year survival rate of just 6.9%, according to the National Brain Tumor Society. The average length of survival is estimated to be about 14–20 months, a figure that has barely improved since glioblastoma was first identified in scientific literature in the 1920s.

Treating glioblastoma is particularly difficult because the tumor recruits immunosuppressive macrophages—white blood cells that defend the body against disease and infections—into the tumor microenvironment to support the tumor's growth and make the tumor more resistant to therapy, said Peiwen Chen, Ph.D., assistant professor of Neurological Surgery and senior author of the study.

"Tumor-associated macrophages are the largest population of cells and can account for about 30% to 50% of the total cells in the glioblastoma tumor," said Chen, who is also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

"The infiltration of macrophages and altered tumor metabolism are two key hallmarks of glioblastoma. However, we don't know much about the mechanism underlying their connection, so that's the question we are trying to answer."

In the study, Chen and his collaborators screened a panel of metabolic small-molecule compounds to identify which ones can inhibit glioblastoma cell-induced macrophage migration. They found that

stiripentol—an FDA-approved antiepileptic drug that inhibits expression of the gene LDHA, a gene partially responsible for glycolysis—emerged as the top hit.

Additionally, investigators observed increased expression of LDHA in glioblastoma cells which was induced by tumor-associated macrophages delivering more proteins to the tumor. This process formed a feedback loop which resulted in more macrophages being recruited to the tumor, according to the study.

The scientists then aimed to inhibit the glioblastoma-macrophage symbiotic interaction with drugs designed to inhibit LDHA and found that the treatment impaired glioblastoma cell proliferation and macrophage migration. The findings were then validated in mouse models, according to the study.

"We identified that LDHA mediates the symbiotic interaction between glioblastoma cells and macrophages. And when we block this interaction by inhibiting LDHA, we find that this interaction was blocked and the tumor progression was significantly inhibited," Chen said.

The findings suggest LDHA could serve as a potential therapeutic target for glioblastoma, Chen said.

"There is already an FDA-approved LDHA inhibitor drug which could be used," Chen said. "For the future, we would like to prove this further in mouse models and then in humans to initiate a clinical trial for the use of LDHA inhibitors in treating glioblastoma patients."

More information: Fatima Khan et al, Lactate dehydrogenase A regulates tumor-macrophage symbiosis to promote glioblastoma progression, *Nature Communications* (2024). DOI: 10.1038/s41467-024-46193-z

Provided by Northwestern University