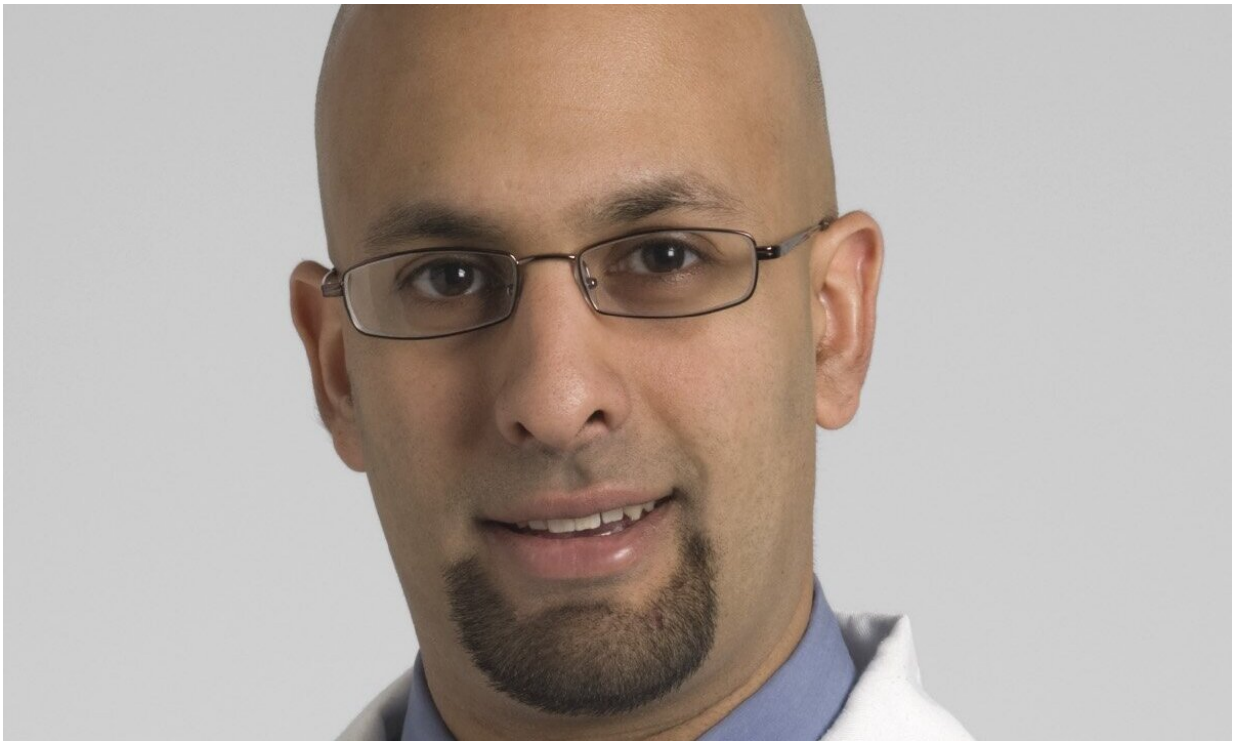
New research published in cancer discovery identifies new drug target for glioblastoma

August 21 2019



Justin Lathia, PhD, Cleveland Clinic Lerner Research Institute. Credit: Cleveland Clinic

A new international study co-led by Cleveland Clinic has identified a new drug target for treating glioblastoma. This target is part of a never-before defined cellular pathway found to contribute to the spread and proliferation of a dangerous subset of cancer cells, called glioma stem

cells.

While previous research has shown that a protein called FGF2 (fibroblast growth factor 2), when activated ("turned on"), contributes to glioma stem cell self-renewal and tumor growth, it was not understood how. This study, co-led by Justin Lathia, Ph.D., Cleveland Clinic Lerner Research Institute, identifies FGF2 as an important intermediary in a multi-step, pro-cancer signaling loop and suggests that "turning off" FGF2 may halt the growth and spread of glioblastoma.

Published in the August 21 issue of *Cancer Discovery*, this study is the first to identify FGF2 as a novel druggable target for glioblastoma, the most common primary malignant brain tumor. With standard treatment, the median survival for adults with glioblastoma is only between 11 and 15 months, and recurrence is very common. New therapies are greatly needed.

Extracellular matrix (ECM) is a network of molecules that—like brick and mortar—help to hold and anchor nearby cells together. The research team found that a protein called ADAMDEC1 (a disintegrin and metalloproteinase domain-like protein decysin 1), which is secreted by glioma stem cells, breaks down ECM. In its absence, cancer cells are able to access key nutrients for their growth that otherwise would not be available.

One of these nutrients is FGF2. The team of researchers showed that ADAMDEC1 activates FGF2, which is found within the tumor microenvironment. Like a lock and key, the "turned on" FGF2 selectively binds to and activates a receptor found on the surface of glioma stem cells, called FGFR1 (FGF receptor 1).

FGFR1, mediated through a few additional signaling cascades, plays two important roles in driving glioblastoma. It helps to mediate the hallmark

pro-cancer characteristics of glioma stem cells, including their ability to self-renew and spread. Additionally, FGFR1 signaling ultimately induces the expression of ADAMDEC1, which sends this whole cellular feedback loop into motion again.

"These findings are exciting because they put forth a new paradigm for glioma stem cell regulation," said Dr. Lathia. "This pathway shows that glioma stem cells' ability to access key nutrients in their surrounding microenvironment, by way of ADAMDEC1, is integral for their maintenance and spread. Finding a way to interrupt this feedback loop will be important for treating glioblastoma."

While additional research is necessary, this study suggests that therapeutically targeting FGF2 may be the key to interrupting this cancer-driving loop.

Provided by Cleveland Clinic