Researchers discover brain tumor's 'grow-or-go' switch

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Cancer cells in rapidly growing brain tumors must adjust to periods of low energy or die. When energy levels are high, tumor cells grow and proliferate. When levels are low, the cells grow less and migrate more.

Researchers at the Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute have discovered the switch responsible for this grow-or-go behavior.

Their study shows that a molecule called miR-451 coordinates the change, and that the change is accompanied by slower cell proliferation and an increase in cell migration.

This behavior was closely linked to the cancer's ability to invade and spread. For this reason the molecule might serve as a biomarker to predict how long patients with the brain tumor glioblastoma multiforme will survive and may serve as a target to develop drugs to fight these tumors.

The researchers found that glioblastoma cells shift from their typical means of metabolizing glucose - a sugar brought by the bloodstream and usually used for energy - to an alternate means that consumes resources within the cell.

The findings are published in the March 12 issue of the journal *Molecular Cell*.

"Our study reveals how brain tumor cells adapt to their surroundings and survive conditions that might fatally starve them of energy," says co-author Dr. E. Antonio Chiocca, professor and chair of Neurological Surgery at Ohio State. "We have discovered that glioblastoma cells use miR451 to sense the availability of a nutrient - glucose.

"Levels of miR-451 directly shut down the engine of the tumor cell if there in no glucose or rev it up if there is lots of glucose. This important insight suggests that this molecule might be useful as a biomarker to predict a glioblastoma patient's prognosis, and that it might be used as a target to develop drugs to fight these tumors."

About 10,000 new cases of glioblastoma multiforme occur annually in the United States. The tumors are highly invasive, which makes them difficult to remove surgically, and respond poorly to radiation therapy and chemotherapy.

Average survival is 14 months after diagnosis.

MiR-451 belongs to a class of molecules called microRNA, which play a key role in regulating the levels of proteins that cells make. Changes in levels of these molecules are a feature of many cancers, the researchers say.

"The change in miR-451 expression enabled the cells to survive periods of stress caused by low glucose, and it causes them to move, perhaps enabling them to find a better glucose supply," says principal investigator Sean Lawler, assistant professor of neurological surgery.

"The migration of cancer cells from the primary tumor, either as single cells or as chains of cells, into the surrounding brain is a real problem with these tumors. By targeting miR-451, we might limit the tumor's spread and extend a patient's life."

For this study, Lawler, Chiocca, Jakub Godlewski, the postdoctoral fellow who was the first author of the study, and their colleagues first compared microRNA levels in migrating and nonmigrating human glioblastoma multiforme cells. The analysis suggested an important role for miR-451.

Experiments with living cells showed that high levels of glucose correlated with high levels of the molecule, and that this promotes a high rate of tumor-cell proliferation. Low glucose levels, on the other hand, slowed cell proliferation and increased cell migration.

Furthermore, when the researchers boosted levels of the molecule in migrating cells, it slowed migration 60 percent, and, after 72 hours, nearly doubled the rate of cell proliferation compared with controls.

Most exciting, when they forced an increase in miR-451 levels, the cells quickly died, suggesting a possible role in therapy.

Analyses of patient tumors showed that three of five had elevated levels of the molecule. Finally, the researchers compared the survival in 16 patients with high miR-451 and 23 patients with low levels. Those with high levels of the molecule had an average survival of about 280 days while those with low levels lived an average of about 480 days.

"This suggests that molecule may be a useful prognostic marker," Chiocca says.

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