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METABOLIC STATE OF BRAIN CANCER STEM CELLS IS SIGNIFICANTLY DIFFERENT THAN THAT OF DIFFERENTIATED CANCER CELLS

Metabolic Differences May be Helping the Cancer Stem Cells Escape Treatment and lead to Recurrence Later

The metabolic state of glioma stem cells, which give rise to deadly glioblastomas, is significantly different from that of the brain cancer cells to which they give birth, a factor which helps those stem cells avoid treatment and cause recurrence later.

Researchers with the UCLA Department of Radiation Oncology at UCLA's Jonsson Comprehensive Cancer Center also found for the first time that these glioma stem cells can change their metabolic state at will, from glycolysis, which uses glucose, to oxidative phosphorylation, which uses oxygen.

The glioma stem cells' ability to change their metabolic state at will also allow these stem cells that seed new cancer growth to evade treatment and remain alive, said Dr. Frank Pajonk, an associate professor of radiation oncology and senior author of the study.

"We found these cancer stem cells are substantially different in their metabolic states than the differentiated cancer cells they create, and since they act differently, they can't be killed in the same way," Pajonk said. "And as yet, we don't have anything to target these glioma stem cells specifically."

The study is published this week in the early online edition of the peer-reviewed journal Proceedings of the National Academy of Sciences.

Cancer cells take up large amounts of glucose, which fuels their grow and spread and allows them to be differentiated from normal cells under Positron Emission Tomography (PET) scanning, which captures metabolic activity. Pajonk and his team found that the glioma stem cells took up much less glucose, which makes them difficult to detect with PET.

Targeting cancer metabolic pathways as a treatment has gained new interest in recent years. However, these cancer stem cells that take up less glucose could evade those treatments by utilizing glucose more efficiently through oxidative phosphorylation, which would not be targeted by such drugs.

"If glioma stem cells are indeed important for tumor control, knowledge of the metabolic state of glioma stem cells is needed," the study states.

Using a unique imaging system Pajonk and his team developed for glioma stem cells that relies on low enzymatic activity of the proteasome in cancer stem cells, they were able to assess

them for metabolic function, including oxygen consumption rates, glucose uptake and other markers. They also found that the glioma stem cells were resistant to radiation, another roadblock to targeting these cells with conventional treatments.

Pajonk and his team concluded that glioma stem cells rely mainly on oxidative phosphorylation for energy. But they found if the stem cells were challenged, they could switch on additional metabolic pathways.

The study also shows for the first time that low expression of proteasome sub-units, an indicator of large numbers of glioma stem cells in the tumor, predicts unfavorable treatment outcomes for those patients.

“What I think is really exciting is we have here for the first time a novel cancer stem cell marker in glioma, which gives us an additional tool to look for these cells and come up with therapies that target them,” said Pajonk, who also is a researcher with the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA.

This study was funded by the National Cancer Institute.

UCLA's Jonsson Comprehensive Cancer Center has more than 240 researchers and clinicians engaged in disease research, prevention, detection, control, treatment and education. One of the nation's largest comprehensive cancer centers, the Jonsson center is dedicated to promoting research and translating basic science into leading-edge clinical studies. In July 2011, the Jonsson Cancer Center was named among the top 10 cancer centers nationwide by U.S. News & World Report, a ranking it has held for 11 of the last 12 years. For more information on the Jonsson Cancer Center, visit our website at **http://www.cancer.ucla.edu**.

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