To combat deadly brain cancer, target the stem cells

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Researchers have uncovered a new target that could stop the growth of glioblastoma, a deadly form of brain cancer. In the July 8th issue of the journal *Cell*, a Cell Press publication, a new study identifies an enzyme found in glioma stem cells that allows them to grow and seed tumors. Importantly, normal stem cells, including those in the brain, don't appear to share that same dependency.

"When thinking about therapeutics [targeting cancer stem cells], you have to be careful that you aren't interfering with normal stem cells," said Christine Eyler of the Cleveland Clinic. "Glioma stem cells are not derived from normal stem cells but they do share many features with them. The trick to therapy is to find pathways exhibited only by cancer stem cells."

The goal of Eyler's team, led by Cleveland Clinic scientist Jeremy Rich, was to identify just such a pathway in glioma stem cells, a particularly devastating form of brain cancer. Despite modern surgical and medical therapies, those diagnosed with a glioblastoma have a median survival of just over a year.

Previous work identifying glioma cells with stem-cell like behavior and demonstrating the propagation of gliomas in animals offered hope for the development of anti-glioma therapeutics. The challenge, however, has been finding pathways that differ between glioma and normal stem cells in spite of evidence that the glioma stem cells closely resemble embryonic and neural stem cells.

Earlier studies led the researchers to investigate the pathway that produces nitric oxide (NO), a molecule thought to support tumors' growth and resistance to treatment. Those experiments showed that glioma cells express varying levels of nitric oxide synthases, critical enzymes in that pathway.

"It's important to note that there are different forms of nitric oxide synthases," said Anita Hjelmeland, also at the Cleveland Clinic. "We focused on one that is well restricted to glioma stem cells."

In the current study, the authors use mouse models of glioma to show that glioma stem cells have elevated levels of nitric oxide synthase-2 (NOS2). This leads to exess production of NO, which, in turn, endows stem cells with the ability to growand seed tumors.

These findings have real clinical relevance, the researchers say. They found that high NOS2 levels correlate with decreased survival in patients with glioma. Moreover, treatments designed to block NOS2 in the brain slow the growth of brain tumors in mice.

Notably, NOS2 inhibitors have already been tested in clinical trials for other treatments. "The exciting part is the drugs have already been given to people," Eyler said, and it appears they have little toxicity.

NOS2 inhibitors could be a welcome addition to therapies in use for gliomas today. "If you target the tumor as a whole, you may get rid of most cells but leave the stem cells behind," Hjelmeland said. But if you only target cancer stem cells and leave the rest intact, tumors may continue to grow. By combining approaches, "you'll have a better therapy."

Eyler said she wouldn't be surprised if the nitric oxide pathway uncovered in glioma stem cells might also prove to be important in other

forms of cancer. The researchers also continue to look for other pathways unique to cancer stem cells.

Provided by Cell Press