

Most common brain cancer may originate in neural stem cells

June 1 2009

University of Michigan scientists have found that a deficiency in a key tumor suppressor gene in the brain leads to the most common type of adult brain cancer. The study, conducted in mice that mimic human cancer, points the way to more effective future treatments and a way to screen for the disease early.

Appearing June 2 in *Cancer Cell*, the U-M team's findings in mice show for the first time that:

- Glioblastoma, the type of cancer that afflicts U.S. Sen. Edward Kennedy and is diagnosed in about 10,000 Americans each year, may originate in neural stem cells located in a brain region known as the subventricular zone, or SVZ.
- In mice, neural stem cells that normally live in this niche give rise to more specialized [nerve cells](#) that migrate out of the niche. Cancer could begin with a single genetic mutation in the [p53 gene](#), which makes stem cells migrate out of the niche like their specialized progenies.

Much research on cancer has focused on the p53 gene, known as the "guardian of the genome" because it initiates a wave of other gene actions that normally thwart cancer.

The finding of a specific zone of origin could lead to treatments that

may improve the dire median survival rate of 12 months for this type of [brain cancer](#), says Yuan Zhu, Ph.D., the study's senior author and assistant professor in the departments of internal medicine and cell and developmental biology at the U-M Medical School.

"We have to pay more attention to the stem cell niche" in both early detection and treatment, says Zhu. If glioblastoma originates in neural stem cells in the subventricular zone in humans as it does in mice, the study suggests that doctors need to direct treatments there, as well as to the tumor, to eliminate the source of the cancer and keep it from returning, Zhu says.

The findings in mice also may lead in time to effective early screening tests for glioblastoma. The U-M scientists show that the expression of mutant p53 protein is a marker for glioma cells in all stages of the disease.

"Now, if we believe that the SVZ is the location of the cells of origin, with enhanced resolution we could detect tumor cells there," says Zhu. If it's possible to detect the disease early, the chances of treatment success should improve.

The link between neural stem cells and this aggressive type of cancer is a warning sign for scientists to proceed carefully with new treatments for neurodegenerative diseases such as Parkinson's disease, where the hope is to use neural stem cells to help regenerate lost nerve function, says Zhu.

"Our results in mice show that these neural stem cells in the brain have high potential to accumulate genetic lesions and to become a cellular target for cancerous cells," he says. "To some degree, the cancerous cells in early stages are not much different from normal stem cells, but aberrantly combine the key features of neural stem cells (self-renewal)

and specialized progenies (migration). We have to understand these stem cells more extensively before we can harness them to treat disease."

Glioblastoma, also called glioblastoma multiforme, is notoriously hard to treat. It returns in most cases despite virtually all current therapies, which include surgery, radiation and chemotherapy. Survival rates have not improved for two decades, a fact that the new insights into p53 may help explain.

The results found in mice add specific new insights to an unfolding picture of how genes go awry to result in brain cancer. Scientists recently learned that certain genes and pathways of cell action are altered in glioblastoma. One of these key alterations involves mutations in genes that are players in the p53 pathway. But until now, scientists have not known what cell type initiates the cancer, or precisely how a deficiency in p53-mediated pathways works with other mutations to transform brain cells into cancerous ones.

In the last six years, studies have shown that stem cell-like cells are involved in a number of cancers, including glioblastoma. But the new study specifically reveals that glioblastoma begins in neural stem cells that have a p53 mutation. These cells then give rise to mutated, fast-multiplying cells down the line of cell differentiation - a class called transit-amplifying progenitor cells.

"We found that the cells with p53 mutations are highly plastic. If a treatment blocks one path of action, they may learn other ways to grow," Zhu says. That helps explain why glioblastoma multiforme returns in drug-resistant forms.

Zhu's team conducted a series of experiments using mice engineered to have a p53 mutation in the central nervous system. They found that a majority developed malignant brain tumors, and that a mutant form of

p53 was present in the tumor cells, a phenomenon that is commonly found in human glioblastoma.

"Then we asked, does mutant p53 have any role in tumor initiation and progression? If so, we can use this as a marker for brain cancer in brain cells," says Yuan Wang, the study's first author and a U-M Ph.D. student in cell and [developmental biology](#). The team found that mutant p53 was detectable in a minority of highly proliferative neural stem cells of p53-deficient mice two months after birth, and that the expansion of the mutant-p53-expressing cell population with features of transit-amplifying cells underlies the tumor initiation. The evidence supports the idea that mutant p53 can be a useful marker to trace the glioma cells at all stages.

Before any treatments based on these discoveries can benefit people, scientists will need to do more animal studies and verify the animal findings in human studies.

Zhu and his team plan to continue experiments in mice to see if p53 function can be restored in tumor cells. They are also examining whether inhibiting neural stem cells in the SVZ has promise as a potential therapy. Given the plasticity of these cancer-initiating cells, targeting a single signaling pathway may not be sufficient, says Zhu. This trait adds to the complexity of cancer therapy.

More information: *Cancer Cell*, June 2, 2009

Source: University of Michigan Health System ([news](#) : [web](#))

Citation: Most common brain cancer may originate in neural stem cells (2009, June 1) retrieved 24 April 2024 from

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