

# Researchers identify genetic signature of deadly brain cancer

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A multi-institutional team of researchers have pinpointed the genetic traits of the cells that give rise to gliomas – the most common form of malignant brain cancer. The findings, which appear in the journal *Cell Reports*, provide scientists with rich new potential set of targets to treat the disease.

"This study identifies a core set of genes and pathways that are dysregulated during both the early and late stages of [tumor progression](#)," said University of Rochester Medical Center (URMC) neurologist Steven Goldman, M.D., Ph.D., the senior author of the study and co-director of the Center for Translational Neuromedicine. "By virtue of their marked difference from normal [cells](#), these genes appear to comprise a promising set of targets for [therapeutic intervention](#)."

As its name implies, gliomas arise from a cell type found in the [central nervous system](#) called the glial cell. Gliomas progress in severity over time and ultimately become highly invasive tumors known as [glioblastomas](#), which are difficult to treat and almost invariably fatal. Current treatments, which include surgery, [radiation therapy](#), and chemotherapy, can delay disease progression, but ultimately prove ineffective.

[Cancer research](#) has been transformed over the past several years by new concepts arising from [stem cell biology](#). Scientists now appreciate that many cancers are the result of rogue [stem cells](#) or their offspring, known as [progenitor cells](#). Traditional cancer therapies often do not prevent a

recurrence of the disease since they may not effectively target and destroy the cancer-causing stem cells that lie at the heart of the tumors.

Gliomas are one such example. The source of the cancer is a cell found in the brain called the glial progenitor cell. The cells, which arise from and maintain characteristics of stem cells, comprise about three percent of the [cell population](#) of the [human brain](#). When these cells become cancerous they are transformed into glioma stem cells, essentially glial progenitor cells whose molecular machinery has gone awry, resulting in uncontrolled cell division.

Goldman and his team have long studied normal glial progenitor cells. These cells produce glia, a category that includes both astrocytes – cells that support the function of neurons – and oligodendrocytes – cells that produces myelin, the fatty insulation that allows the long-distance conduction of neural impulses.

While Goldman's group's work has primarily focused on ways to use glial progenitor cells to treat neurological disorders such as multiple sclerosis, their understanding of the biology of these cells and mastery of the techniques required to sort, identify, and isolate these cells has also enabled them to explore the molecular and genetic changes that transform these cells into cancers.

Using human tissue samples representing the three principal stages of the cancer, the researchers were able to identify and isolate the cancer-inducing stem cells. Working with Goldman, lead authors Romane Auvergne, Ph.D. and Fraser Sim, Ph.D. then compared the gene expression profiles of these cancer stem cells to those of normal glial progenitor cells. The objective was to both pinpoint the earliest genetic changes associated with cancer formation and identify those genes that were unique to the cancer stem cells and were expressed at every stage of disease progression.

Out of a pool over 44,000 tested genes and sequences, the scientists identified a small set of genes in the cancerous glioma progenitor cells that were over-expressed at all stages of malignancy. These genes formed a unique "signature" that identified the tumor progenitor cells and enabled the scientists to define a corresponding set of potential therapeutic targets present throughout all stages of the cancer.

"One of the key things you are looking for in drug development in cancer is a protein or gene that is over-expressed, so that you can attempt to achieve therapeutic benefit by inhibiting it," said Goldman.

The researchers chose to test this hypothesis by targeting one such gene, called SIX1, which was highly overexpressed in the glioma progenitor cells. While this particular gene is active in the early development of the nervous system, it had not been observed in the adult brain before. However, SIX1 signaling has been associated with breast and ovarian cancer, raising the possibility of its contribution to brain cancer as well. This turned out to indeed be the case. When the researchers blocked – or knocked down – the expression of this gene, the tumor cells ceased growing, and implanted tumors shrank.

"This study gives us a blueprint to develop new therapies," said Goldman. "We can now devise a strategy to systematically and rationally analyze – and eliminate – glioma stem and progenitor cells using compounds that may selectively target these cells, relative to the normal glial progenitors from which they derive. By targeting genes like SIX1 that are expressed at all stages of glioma progression, we hope to be able to effectively treat gliomas regardless of their stage of malignancy. And by targeting the glioma-initiating cells in particular, we hope to lessen the likelihood of recurrence of these tumors, regardless of the stage at which we initiate treatment."

Provided by University of Rochester Medical Center

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