Cellular origin of deadly brain cancer is identified

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Using a mouse genetic system co-developed by researchers at the University of Oregon and Stanford University, a research team led by UO biologist Hui Zong has isolated the cellular origin for malignant glioma, a deadly human brain cancer.

The discovery that oligodendrocyte precursor cells (OPCs) are the point of origin is reported online July 7 ahead of regular print publication in the July 22 issue of the journal *Cell*. These OPCs, the researchers said, were the first cells to display "significant overexpansion and aberrant growth."

Malignant glioma is diagnosed in 10,000 Americans annually, with most patients dying within two years. Victims have included U.S. Sen. Ted Kennedy (2009), pianist George Gershwin (1937), marine biologist Thor Heyerdahl (2002) and film critic Gene Siskel (1999).

"The cure for this devastating disease lies in our ability to unequivocally identify the cell-of-origin for gliomagenesis, which would then allow researchers and doctors to harness the intrinsic properties of such cell types to thwart the attack," said Zong, a member of the UO Institute of Molecular Biology.

Zong, also a fan of the UO's football Ducks, likened the search for tumor-igniting cells to setting up a defense designed to stop a quarterback's distribution of the ball to a receiver or running back. "To study cancer, you have to understand the route of attack," he said. "With

conventional research methods, we saw a snapshot when the ball goes to the quarterback, and then suddenly we see the touchdown: Cancer, six points. That is obviously not enough for us to understand cancer's attacking strategies."

The technique Zong and his team used -- Mosaic Analysis with Double Markers (MADM), developed for studying developmental biology and modeling diseases in mice -- was first described by Zong, co-author Liqun Luo of Stanford University and other colleagues in a paper in Cell in 2005, when Zong was a postdoctoral researcher studying under Luo.

The essence of MADM is its unambiguous labeling of mutant cells with green fluorescent protein, which allowed Zong's team to probe into pre-clinical, tumor-initiating stages that are inaccessible to researchers using conventional tools. "Our system lets us watch the action from the beginning, to watch every direction, every hand off or pass, before a tumor forms," Zong said.

"Another key feature is the concurrent creation of a normal red cell whenever a mutant green cell is generated. In effect, we can compare every player's movement with or without the ball -- the mutations," he said. "If they are doing the same thing, we know they are not attacking. If they are doing different things, we know something is wrong, and should focus our attention to tackle the particular player, the cell type, to prevent a tumor from advancing down the field."

In the current research, funded primarily by the National Institutes of Health, two prevalent mutations found in human glioma patients, p53 and NF1, were introduced into neural stem cells (NSCs) "just like snapping the ball to the quarterback," Zong said. "And to our surprise, the quarterback didn't run, although NSCs have been implicated in gliomagenesis by other research groups using conventional genetic methods."

Further analyses of all cell lineages derived from neural stem cells clearly demonstrated that OPCs are the cell of origin since mutant green OPCs over-populate their normal red counterparts by 130-fold before any visible signs of tumor can be detected. "Therefore," Zong said, "the quarterback role of the NSCs seems to be merely passing the ball to the running back -- the OPCs -- which will then score the touchdown.

To convincingly show that OPCs have intrinsic scoring ability independent of the mutation-passing process from NSCs, researchers in the Zong lab also introduced p53 and NF1 mutations directly into OPCs.

"This time the snap from center actually goes straight to the running back -- a la the wildcat used to perfection since 2008 by the National Football League's Miami Dolphins," Zong said, "and lo-and-behold, gliomas consistently arise in these mice. Now we are convinced that OPC is the cell type that scores for glioma and should become the focus of our defense team."

From a big picture, in addition to the potential to translate this new discovery into clinical diagnosis and treatment, the breakthrough technology should be able to determine the point of ignition in many other cancers, he said.

"It is now obvious that we really need to understand these OPCs," Zong said. "Why do they respond so drastically to these mutations? Which route do they take to become fully malignant tumor cells?"

Data provided by the project inspired a three-year, $1 million grant, awarded to the UO earlier this year, from the W.M. Keck Foundation to study glioma as an evolutionary process.

"Studying cancer in this way should not only lead to molecular diagnostics to detect the earliest emergence of any cancers, but also

allow us to understand the molecular mechanisms by which initial mutant cells progressively gain advantages over normal cells," Zong said. "This type of knowledge should eventually enable us to set up multi-point tackling plan to increase the efficacy of cancer treatment."

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