Modification of tumor suppressor affects sensitivity to potential GBM treatment

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Despite years of research, glioblastoma, the most common and deadly brain cancer in adults, continues to outsmart treatments targeted to inhibit tumor growth.

Biologists and oncologists have long understood that a protein called the epidermal growth factor receptor or EGFR is altered in at least 50 percent of patients with glioblastoma. Yet patients with glioblastoma either have upfront resistance or quickly develop resistance to inhibitors aimed at stopping the protein's function, suggesting that there is another signalling pathway at play.

Researchers from the Ludwig Institute for Cancer Research, the University of California, San Diego (UCSD) and Los Angeles (UCLA) and the University of São Paulo, Brazil published their findings on a mechanism that defines these types of resistance in the August 13 online issue of *Proceedings of the National Academy of Sciences.*

Previous research suggested that PTEN, a tumor suppressor gene, may be turned off in some cancer patients, disabling its function and potentially causing the resistance to EGFR inhibitors. "We asked ourselves, how is PTEN being modified? What is altering its function?," said Frank Furnari, PhD, corresponding author and Ludwig senior investigator based at UCSD.

The researchers focused on one type of modification called phosphorylation, the process by which some proteins are turned on and

off. They mapped the sites where PTEN was changed or phosphorylated and subsequently developed an antibody that would recognize the PTEN protein when it was phosphorylated.

The team then put the antibody to the test. Together with Suely Marie, MD, at the University of São Paulo, they first evaluated a large series of clinical samples from patients with glioblastoma and found that the presence of phosphorylation was associated with shortened survival. Then with Paul Mischel, MD, at UCLA, they examined samples from a completely different series of patients who were EGFR positive and did not respond to EGFR-inhibitor treatment. The results confirmed that patients with modified PTEN had resistance to EGFR inhibitors.

"We think this modification of PTEN may become a useful marker to determine if a patient will respond or not to a growth factor receptor inhibitor," added Furnari. "If you can prevent phosphorylation, our studies showed that you have created a scenario where EGFR inhibitors will work better."

The team identified two enzymes responsible for turning off the brakes of PTEN - the fibroblast growth receptor and SRC family kinases. By understanding how these enzymes disable the suppressor function of the gene, scientists may be able to target different molecules that can intervene to stop resistance.

"The more we understand, the better we can conceive of ways to restore PTEN function in tumor cells and stop resistance to EGFR inhibitors in patients with glioblastoma," said lead author, Tim Fenton, PhD, who conducted this research while at the Ludwig Institute at UCSD and is currently at the University College London Cancer Institute.

According to Paul Mischel, who has since moved from UCLA to become a Ludwig member based at UCSD, "The study outcomes

provide a potentially clinically targetable pathway. The findings enable us to move forward to identify and develop small molecule inhibitors for eventual use in combination with EGFR inhibitors for the treatment of glioblastoma and other cancers."

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