A lethal brain tumor's strength may be a weakness as well

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Malignant gliomas are the most common subtype of primary brain tumor - and one of the deadliest. Even as doctors make steady progress treating other types of solid tumor cancers, from breast to prostate, the most aggressive form of malignant glioma, called a glioblastoma multiforme or GBM, has steadfastly defied advances in neurosurgery, radiation therapy and various conventional or novel drugs.

But an international team of scientists, headed by researchers at the Ludwig Institute for Cancer Research (LICR) at the University of California, San Diego School of Medicine, reports in the August 15 issue of Genes *& Development* that they have discovered a new signaling pathway between GBM cells - one that, if ultimately blocked or disrupted, could significantly slow or reduce tumor growth and malignancy.

More than other types of cancer, GBMs are diverse assemblages of cell subtypes featuring great genetic variation. Anti-cancer therapies that target a specific mutation or cellular pathway tend to be less effective against such tumor heterogeneity.

"These myriad genetic alterations may be one of the primary reasons why GBMs are so lethal," said Frank Furnari, PhD, associate professor of medicine at the UCSD School of Medicine and an associate investigator at the San Diego branch of the LICR.

Even with maximum treatment effort, the median patient survival rate

for a diagnosed GBM is nine to 12 months - a statistic that has not changed substantially in decades.

However, Furnari, along with postdoctoral fellows Maria-del-Mar Inda and Rudy Bonavia, and Webster Cavenee, PhD, professor of medicine and director of the San Diego LICR branch, and others noted that in GBMs only a minority of tumor cells possess a mutant form of the epidermal growth factor receptor (EGFR) gene. These cells drive the tumor's rapid, deadly growth. "Most GBM tumor cells express wild-type or normal EGFR," said Furnari. "Yet when expressed by itself, wild-type EGFR is a poor oncogene."

The scientists discovered that tumor cells with mutant EGFR secrete molecules that cause neighboring cells with wild-type EGFR to accelerate their tumorigenic growth. "The mutant cells are instructing other less malignant tumor cells to become more malignant," said Furnari.

This signaling pathway between GBM tumor cells was not known and presents a new and potentially promising chink in the armor of glioblastomas. "If we can inhibit or block this cellular communication, the tumor does not grow as quickly and may be more treatable," Furnari said. Researchers have already identified two molecules that appear to trigger EGFR activity on non-mutant tumor cells.

The findings may also provide clues in the bigger picture of how GBMs and other cancers survive and thrive. "There are other types of mutations and growth factor receptors in tumors," Furnari said. "We need to look at how they communicate. Historically, brain tumor research has focused upon the most abundantly expressed mutations, but this research suggests minority mutations play very important roles as well."

The researchers' next step will be to create a mouse model with mixed

cell glioblastoma that can be used to test different therapeutics, inhibitors and blocking agents.

Provided by University of California - San Diego