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Team reveals novel way to treat drug-resistant brain tumor cells

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New research from the University of Wisconsin-Madison explains why the incurable brain cancer, glioblastoma multiforme (GBM), is highly resistant to current chemotherapies.

The study, from the brain-tumor research lab of Dr. John Kuo, assistant professor of neurological surgery and human oncology at UW School of Medicine and Public Health, also reports success for a combination therapy that knocks out signaling of multiple members of the epidermal growth factor receptor (EGFR) family in brain-cancer cells.

The late U.S. Sen. Edward M. Kennedy died of GBM in 2009. People diagnosed with GBM live on average for only 15 months after diagnosis, even after undergoing aggressive surgery, radiation and chemotherapy. Earlier research from Dr. Kuo and other scientists showed that GBM cancer stem cells escape current treatments and proliferate rapidly to cause tumor recurrence.

Several years ago, research suggested that a drug engineered to target EGFR signaling might work against GBM because many brain cancers carried EGFR mutations. Excessive and abnormal EGFR signaling spurs the growth of cancer cells. Although cetuximab, a monoclonal-antibody drug, was successful in clinical trials for patients with lung, colorectal, and head and neck cancers, it failed against GBM.

Research by Dr. Paul Clark, a scientist in Kuo's lab and the study's lead author, shows why. When cetuximab treatment switches off EGFR

activity and should inhibit cancer-cell growth, cancer stem cells compensate by turning on two other EGFR family receptors (ERBB2 and ERBB3) and continue to grow. One of these receptors, ERBB2, is implicated in certain types of chemotherapy-resistant breast cancer. Fortunately, another novel drug already approved by the FDA, lapatinib, inhibits ERBB2 activity and signaling by multiple EGFR members.

This study shows that cancer stem-cell growth was markedly inhibited by lapatinib treatment, which results in combined knockout of multiple EGFR family members.

"This is good news, because these drugs target an important mechanism for the (GBM) cancer cells to grow so quickly and evade current therapies, and these molecularly targeted drugs are also well-tolerated by patients and have minimal side effects," Dr. Clark said.

Kuo, director of the Comprehensive Brain Tumor Program at UW Health and chair of the Carbone Cancer Center brain tumor group, said that results of several brain cancer clinical trials with these novel drugs and other new strategies are pending or underway.

Provided by University of Wisconsin-Madison