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Candidate drug may be effective against broader class of brain cancers

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A Ludwig Cancer Research study explains why a particular mutation in the epidermal growth factor receptor (EGFR), a cell surface protein, results in more aggressive tumors and poorer overall survival of patients diagnosed with the brain cancer glioblastoma multiforme (GBM).

It also suggests that this deadlier form of GBM may be susceptible to a Ludwig-developed antibody drug currently being tested in clinical trials against a different subtype of GBM tumors. GBM is the most common and deadliest type of adult brain cancer.

"This is a perfect example of patient data directing molecular analysis," says study co-leader Frank Furnari, who is a member of the San Diego Branch of the Ludwig Institute for Cancer Research. The study, also led by Zev Binder and Donald O'Rourke of the University of Pennsylvania (UPenn), appears in the July 9 issue of the journal *Cancer Cell*.

Oncologists have long known that EGFR is altered in at least half of GBM tumors. A team led by Binder recently identified a "missense" mutation at alanine 289 (A289) in EGFR that drives a more aggressive and deadlier subtype of the cancer. (A missense mutation causes one amino acid to be substituted with another in the protein encoded by the gene.) Patients with this mutation survived only 6 months on average after diagnosis, compared to 14 to 17 months for those with other EGFR mutations.

Ludwig investigators collaborated with Laura Orellana, a biophysicist

and structural biologist at Stockholm University in Sweden who had hypothesized that mutations such as EGFR^{A289} could respond to mAb806, a monoclonal antibody developed by Ludwig researchers to target EGFRvIII mutations. (EGFRvIII is a well-known mutant of the receptor implicated in glioblastoma.) The antibody has since been "armed" with a drug by the pharmaceutical company AbbVie and is currently in Phase III clinical trials in the U.S. for cancers that exhibit EGFRvIII mutations.

A serendipitous meeting at a conference between Binder and Amy Haseley Thorne, a postdoc in Furnari's lab, started a collaboration between the two groups that would test the therapeutic potential of Orellana's hypothesis.

Leveraging their expertise in molecular analysis, the Ludwig team pinpointed precisely how the EGFR^{A289} mutation can cause more malignant tumors and poorer overall survival in glioblastoma patients. "We showed using mouse models that the mechanism of this mutation was to increase invasion through elevated expression of the protease MMP1," Furnari said.

Short for matrix metalloproteinase-1, MMP1 is secreted by cells to break down the extracellular matrix, the complex network of proteins and molecules that helps bind cells to one another in tissues and aids in cellular communications.

MMP1 is normally expressed during periods when cells need to rearrange themselves, such as embryonic development and cell division. But the Ludwig team showed that the brain tumors of mice with EGFR^{A289V} mutations also express MMP1, making them more invasive and leading to significantly worse survival rates.

The Ludwig and UPenn groups confirmed that, as hypothesized by

Orellana, tumors in mice bearing the $EGFR^{A289}$ mutation are also susceptible to mAb806. When mice with the $EGFR^{A289V}$ mutation were treated with mAb806, their brain tumors shrank and the animals lived significantly longer.

Furnari says that as a follow-up to this study, his team is investigating whether $EGFR^{A289}$ might also be present in other cancer types. "If so," Furnari says, "it would suggest our Ludwig antibody will have some utility for those cancers as well."

More information: Zev A. Binder et al, Epidermal Growth Factor Receptor Extracellular Domain Mutations in Glioblastoma Present Opportunities for Clinical Imaging and Therapeutic Development, *Cancer Cell* (2018). DOI: 10.1016/j.ccell.2018.06.006

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