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Researchers find coupling of proteins promotes glioblastoma development

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Two previously unassociated proteins known to be overly active in a variety of cancers bind together to ignite and sustain malignant brain tumors, a research team led by scientists at The University of Texas MD Anderson Cancer Center reports this week in the journal *Cancer Cell*.

This research is the first to connect FoxM1 to a molecular signaling cascade that regulates normal neural stem cells, said senior author, Suyun Huang, M.D., Ph.D., associate professor in MD Anderson's Department of Neurosurgery.

"When FoxM1 binds to beta-catenin, we found that it also supports the self-renewal and differentiation of glioma- initiating cells, cancer stem cells thought to drive glioblastoma multiforme," Huang said.

Glioblastoma multiforme is the most common and lethal form of brain tumor. Glioma- initiating cells are prime suspects in the disease's resistance to treatment and ability to reoccur.

Protein's connection could be drug target

The scientists established the relationship between FoxM1 and beta-catenin in a series of cell line experiments and then confirmed their findings in mouse models of human glioblastoma and in an analysis of human tumors.

FoxM1 and beta-catenin separately so far have largely evaded targeting by drugs. Huang and her team are focusing on the details of the connection between the two proteins in search of small molecules that might block their binding.

"Our study might lead to the development of a new class of small-molecule anti-cancer drugs, including but not necessarily limited to glioblastoma multiforme," Huang said. Much preclinical work remains before such a drug can be identified and brought to clinical trial.

Blocking FoxM1 reduces glioblastoma in mice 100 percent

FoxM1 previously was known solely as a transcription factor – a protein that binds to the DNA in a gene's promoter region to prompt the gene's expression of messenger RNA that is processed into a protein.

Structural analysis led Huang and her team to suspect FoxM1 might be a binding match for beta-catenin, a crucial protein in the Wnt signaling pathway, which regulates self-renewal and differentiation of neural stem cells. When a normal cell divides, it produces two copies of itself. A neural stem cell produces one copy of itself (self-renewal) and a copy of a functional brain cell, such as a neuron or an astrocyte (differentiation). Mutations occur in the Wnt pathway in other types of cancer, but are largely absent in glioblastoma.

Blocking either FoxM1 or beta-catenin function strongly influenced whether mice injected with glioblastoma cells developed brain tumors. Most dramatically, blocking FoxM1 with short hairpin RNA completely prevented development of brain tumors in 38 mice, while all 20 with unimpeded FoxM1 developed tumors.

In a series of cell line experiments leading to the mouse model research, the group found:

- FoxM1 is expressed at high levels in glioma and in glioma-initiating cells.
- FoxM1 and beta-catenin bind to each other in tumor cells.
- Wnt promotes the movement of both FoxM1 and beta-catenin to the cell nucleus.
- FoxM1 is required for beta-catenin to move to the cell nucleus in both neural stem cells and in tumor cells.
- The FoxM1 and beta-catenin connection is required for transcription and expression of beta-catenin Wnt- targeted genes in the nucleus.
- Interaction between the two proteins is critical to both cell renewal and differentiation in glioma stem cells.

The team analyzed 40 glioblastoma samples and found FoxM1 moderately expressed in 14 and highly expressed in 18. Levels of FoxM1 in the cell nucleus correlated directly with levels of beta-catenin expression and the expression of two Wnt target genes.

Additional analysis of eight tumors found the two proteins present together in the cell nuclei and a direct correlation with the presence of one protein marker for glioma-initiating cells.

Provided by University of Texas M. D. Anderson Cancer Center