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'Gateway' gene discovered for brain cancer

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Researchers have discovered that the same genetic regulator that triggers growth of stem cells during brain development also plays a central role in the development of the lethal brain cancer malignant glioma. In experiments on mice with such gliomas, they showed that knocking out the function of a particular regulatory protein, Olig2, almost completely eliminated tumor formation.

The researchers said their findings suggest that targeting Olig2 could offer a potential avenue for treatment that would kill tumor cells without affecting normal tissue.

Dana-Farber Cancer Institute investigators Charles Stiles and David Rowitch and their colleagues reported their findings in the February 15, 2007 issue of the journal *Neuron*, published by Cell Press.

Olig2 is a "transcription factor"—a protein that regulates the activity of genes. Prior studies had indicated that it plays a central role in enabling neural stem cells to replicate during embryonic brain development. Also, studies have suggested that brain tumors might arise from aberrant neural stem cells or the neural progenitor cells to which they give rise.

Analyzing tissue from human gliomas, Stiles, Rowitch, and their colleagues discovered that Olig2 is activated in the stem and progenitor cells found in the tumors. In a mouse model of malignant glioma, they found that knocking out Olig2 function prevented tumor formation in 91 percent of the animals.

Their analysis of the role of Olig2 in both tumor cells and normal neural stem cells revealed that it plays a key role in enabling cell growth. Specifically, they found that Olig2 represses the gene for a cell-replication "brake" called p21, which normally inhibits cell growth. Thus, they concluded that Olig2 is a "unifying feature of normal cell cells and malignant glioma" and a "gateway" gene for brain tumor development.

"Lineage-restricted pathways that regulate brain tumor behavior may represent more specific therapeutic targets with little potential to affect off-target cell types," commented the researchers.

"Brain tumors remain a major cause of cancer-related death despite advances in surgery, imaging, and conventional treatment modalities," they wrote. "This emphasizes the need to develop novel medical strategies based on a comprehensive understanding of the biological mechanisms underlying gliomagenesis."

They wrote that "our findings identify this core transcriptional regulator as an important candidate for antitumor therapeutics." While transcription factors are not generally considered useful targets for anti-cancer drugs, there are multiple ways that Olig2 could be inhibited, as well as ways to target other components of the regulatory pathway by which it exerts its influence on tumor growth, wrote the researchers.

Source: Cell Press