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Treating deadly brain tumors by combining drugs

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Lab studies show that combining drugs that target a variety of developmental cell signaling pathways may do a better job of killing deadly brain tumors than single drugs that target one pathway at a time, according to a new study by Johns Hopkins Kimmel Cancer Center researchers. The combined therapy approach apparently reduces tumor resistance to chemotherapy, they say.

The new research, described in the Dec. 15 issue of the journal *Clinical Cancer Research*, found that simultaneously blocking the so-called Notch and Hedgehog pathways, both critical in cell development, did more to decrease growth of human glioblastoma cells and tumor cell clusters compared with drugs aimed at just the Notch pathway. Most standard clinical treatments for glioblastoma currently target just one pathway.

“Our study indicates it may be necessary to simultaneously target multiple development signaling pathways to prevent cancers from becoming resistant to therapy,” says Charles Eberhart, M.D., Ph.D., the study’s senior author and associate professor of pathology, ophthalmology and oncology. “A single agent is not likely to work for prolonged periods.”

Glioblastoma is one of the most aggressive brain tumors, killing nearly every patient within two years. Even when the tumors initially seem to respond to medication, they generally develop resistance. This led researchers to speculate that tumors might compensate for therapy directed against one cancer cell development pathway by turning on a

different one.

Eberhart and colleagues studied glioblastoma cell lines to investigate the effects of a gamma-secretase inhibitor, a medication that blocks the Notch receptor, on tumor growth. They also studied how Notch affects other pathways and evaluated the effects of combined therapy with a Hedgehog inhibitor.

They found that blocking just the Notch pathway in glioblastoma cells using the gamma-secretase inhibitor led to increased activity in both the Hedgehog and Wnt pathways, both important in cell development. Further study showed that certain proteins involved in the Notch pathway interacted directly with proteins in the Hedgehog pathway, suggesting that Notch-targeted therapies can disrupt other cell signaling pathways that fuel tumors.

They next treated a group of glioblastoma cell lines with either the gamma-secretase inhibitor, a Hedgehog inhibitor, or both, finding that cell growth decreased slightly with either therapy alone, but by about 90 percent with dual therapy. The combined treatment also increased natural “programmed” cell death and decreased the ability of cells to form clusters, or colonies. In a group of glioblastoma samples taken during surgical removal of the human cancers, the combination therapy decreased by 50 to 80 percent the number of colonies formed and decreased the average size of cell clusters.

Clinical trials evaluating inhibitors of Hedgehog or Notch in a number of cancer types are currently under way at Johns Hopkins and several other sites across the country, Eberhart says. Further studies will examine the relationship among the Notch, Hedgehog and Wnt pathways in glioblastoma and look for other signaling processes that help tumors become resistant to therapy, he says.