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**RESEARCHERS TARGET CELLS THAT CAUSE BRAIN CANCER**

Building on previous research linking a common childhood brain cancer called medulloblastoma with high levels of the Notch2 gene, a team led by Charles Eberhart, M.D., Ph.D., is exploiting Notch2 gene products known to regulate brain stem-cell growth and survival. The new studies provide the first hint that a class of drugs, called gamma secretase inhibitors, which block Notch proteins and currently are being developed for Alzheimer's disease, specifically kills stem cells responsible for creating and sustaining a brain tumor.

"Drugs that we typically use to treat cancer don't seem to kill tumor stem cells," says Eberhart, associate professor of pathology and oncology, and after the stem cells survive an onslaught of chemotherapy and radiation, they are left to regrow new tumors.   Gamma secretase inhibitors appear to overcome this barrier.

Eberhart and postdoctoral fellow Xing Fan, M.D., Ph.D., treated medulloblastoma cell cultures for 48 hours with a gamma secretase inhibitor and found that tumor growth slowed.  Closer inspection of the types of cells in the culture revealed that the cancer's stem cells were almost completely eliminated by the drug, but remained in drugless cultures.

Intrigued, the researchers injected the drugged and drug-free cultured cells into mice.  All 24 control mice with cells not treated with the Notch-blocking drug grew large tumors.  Mice that received cells previously treated with the drug fared much better. Only two of eight mice in this group grew very small tumors - less than one-tenth the size of control tumors.

"Medulloblastoma stem cells have much higher Notch gene activity than other cells in the tumor, which may be why the stem cells die first. They are more dependent on the Notch pathway, and blocking it causes severe problems," Eberhart explains.

Although the stem cells are a very small percentage of the entire tumor - approximately 1 percent - other researchers have identified heavy-duty transporters on their cell surfaces that may pump out chemotherapy drugs and cause cancers to become treatment-resistant.

Eberhart and Fan are continuing laboratory studies to select an appropriate gamma secretase inhibitor for clinical trials.

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