Notch-blocking drugs kill brain cancer stem cells, yet multiple therapies may be needed

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Working with mice, Johns Hopkins scientists who tested drugs intended to halt growth of brain cancer stem cells - a small population of cells within tumors that perpetuate cancer growth - conclude that blocking these cells may be somewhat effective, but more than one targeted drug attack may be needed to get the job done.

One focus of attack is a chemical pathway within stem cells known as Notch, which scientists have shown is important for cancer stem cell growth. A new study published in the January 28 issue of *Stem Cells* by Charles Eberhart, M.D., Ph.D., associate professor of pathology, ophthalmology, and oncology at Johns Hopkins, now extends these findings to glioblastoma, the most common malignant brain tumor, and ultimately suggests other pathways and treatment with two or more drugs may need to be involved.

Eberhart based his conclusion on experiments in which he coaxed a glioblastoma cell line to form embryolike balls called neurospheres. Unlike most cells that will clump together in a culture dish, neurospheres - more organized groups of neural cells - can only form from stem cells. When Eberhart treated the neurospheres with a drug called GSI-18, which blocks the Notch pathway, the spheres were reduced by 70 percent or more. Eberhart also found that molecular markers typically found on the surface of brain cancer stem cells also plunged.

"This told us that the Notch pathway is a good target for drug development," says Eberhart, but further experiments suggested this

approach may not be thorough enough.

In a second set of experiments, Eberhart collected the neurospheres that remained after treatment with the Notch-blocking drug and injected them into the brains of mice. The neurosphere transplants eventually grew into tumors and reignited the Notch pathway.

"This result suggested we didn't get rid of all the stem cells," says Eberhart, "so it's likely we may need to add more therapies or increase the dosage of Notch-blocking drugs."

The study by Eberhart identified additional molecular pathways, including Stat 3 and AKT, which are connected to Notch. He says that a combination of therapies blocking Notch and other pathways such as these could target brain cancer stem cells at several levels and possibly avoid drug resistance.

To test how a Notch-blocking drug worked in an animal model, Eberhart injected tumors into the brains of mice and let the cancer grow for two weeks. Then, at the tumor site, he implanted a polymer bead that was soaked in GSI-18. Five of six mice that received the drug-laden bead survived while all 12 that received a bead with no drug died.

Eberhart notes that Notch-targeting drugs can prove problematic in therapy because the Notch pathway is critically important for cells in the gut, helping cells there alternate between secreting mucus and absorbing nutrients. "A dosing regimen that preserves gut function has been developed, and forthcoming studies in humans will test whether it can kill the cancer stem cells."

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