Slow growth of childhood brain tumors explained

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(Medical Xpress) -- Johns Hopkins researchers have found a likely explanation for the slow growth of the most common childhood brain tumor, pilocytic astrocytoma. Using tests on a new cell-based model of the tumor, they concluded that the initial process of tumor formation switches on a growth-braking tumor-suppressor gene, in a process similar to that seen in skin moles.

The findings, published in the June 1 issue of Clinical Cancer Research, could lead to better ways of evaluating and treating pilocytic astrocytomas.

“These tumors are slow-growing to start with, and sometimes stop growing, and now we have a pretty good idea of why that happens,” says Charles G. Eberhart, M.D., Ph.D., associate professor of Pathology, Ophthalmology and Oncology at Johns Hopkins. “These tumors also can suddenly become more aggressive, which we now think represents an inactivation of this tumor-suppressor gene, and this inactivity could be used as a marker to determine which patients need more therapy.”

Pilocytic astrocytoma arises in brain cells known as astrocytes, which, among many functions in the brain, help support neurons. These cancerous astrocytes have DNA mutations that force a growth-related gene, BRAF, into an abnormal, always-on state. Biologists call such cancer-driving genes oncogenes.

Eberhart and his team used a viral gene-transfer technique to deliver an

oncogenic, always-on version of BRAF, to fetal brain cells in a lab dish. The idea was to create a cell model of pilocytic astrocytoma, to enable easier study of its growth patterns. As the researchers expected, the cells quickly formed tumorlike colonies – but the growth of these colonies soon sputtered out.

The same phenomenon, sparked by an oncogene, was first described six years ago in a study of the biology of skin moles. Moles typically begin in skin cells whose inherited or spontaneous mutations – often affecting BRAF – drive the cells' growth beyond normal limits. "The oncogene drives the excessive growth of skin cells, which forms a mole. This overgrowth triggers the downstream activation of tumor-suppressor genes, which stops the mole from growing further," says Eberhart.

In the current study, Eberhart and his colleagues found evidence that this same process, which is called oncogene-induced senescence, also occurs in pilocytic astrocytoma and minimizes its spread. As their tumor-model cells became senescent, the activity of p16, a well-known tumor-suppressor gene, increased and acted as a brake to stop further tumor growth.

Next, the researchers checked pilocytic astrocytoma samples from 66 patients, using a tissue registry at the Johns Hopkins Department of Pathology. Most (57 of 66) showed signs of p16 tumor-suppressor activity, and the remaining nine samples had no signs of p16 activity. Of the p16-active tumors, only two samples (3.6 percent) were from patients who had died of their cancer; however, three of the nine samples with inactive p16 (33 percent) were from patients who had died.

"Our hypothesis now is that these tumors become fast-growing and aggressive again when they can somehow find a way to shut off p16 and escape senescence," says Eric Raabe, M.D., Ph.D., fellow in pediatric oncology at Johns Hopkins. "In many cases, a single tumor may contain

some cells that are senescent plus others that have escaped senescence and started proliferating again," he added.

In future work, Eberhart says, he and his colleagues will examine whether a new class of BRAF-inhibiting cancer drugs has the unintended side effect of shutting down p16. "Clinical trials of these BRAF inhibitors are now just starting in the U.S. and Europe," he says. "We think it's important to determine whether these drugs end up affecting the process of oncogene-induced senescence."

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