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## New Clues to Origin of Childhood Brain Tumors

Using cells obtained from cancer-stricken mice, scientists from the Howard Hughes Medical Institute (HHMI) at Stanford University have showed that reducing production of sterols — chemicals, such as cholesterol, that are a vital part of cell membranes — can prevent the rapid growth of medulloblastoma cells in culture. Medulloblastoma is the most common form of malignant childhood brain cancer. The cancer is due to a breakdown in normal communication between cells.

The findings of the new study, which was published in the May 15, 2006, issue of the *Proceedings of the National Academy of Sciences (PNAS)*, are important because they trace molecules connected to sterol metabolism that have powerful effects on medulloblastoma cells. The new work potentially paves the way for novel treatments, said senior researcher Matthew P. Scott, a Howard Hughes Medical Institute (HHMI) investigator at Stanford University.

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Medulloblastoma is a brain cancer that occurs most commonly in the first decade of life with half of cases arising in children under six years of age. It has a mortality rate of 20-40 percent and accounts for 20 percent of the incidence of all childhood central nervous system tumors.

The need for new treatments is acute since even those who recover from the tumors can be functionally impaired due to damage caused by the tumor and treatments. The tumors form in the cerebellum, the part of the brain that plays an important role in sensory perception and motor control, and can spread to other parts of the brain and spinal cord.

The cancer can also occur in adults, but much less frequently. It is apparently sparked when undifferentiated cells are redirected from the course of normal

development to form cancer cells. The exact cause is unknown, although scientists have established an association with genetic damage to the Hedgehog signaling pathway, damage which can also increase the frequency of skin cancers.

Previous studies by Scott's laboratory showed that a flaw in Sonic hedgehog signaling, a critical cell-signaling pathway essential for development, can cause the growth of medulloblastomas in humans and mice.

The Sonic hedgehog signaling pathway, which was first discovered in fruit flies and so named because of the bristly fruit-fly mutants that result when the pathway is disrupted, is a critical cellular communication conduit that governs much of early development in animals, including humans. It is used to control the embryonic sculpting of numerous tissues, including the brain, spinal cord, limbs, skeleton and skin.

The Hedgehog signaling system has numerous molecular components that govern how signals are transmitted between cells and helps guide them down various developmental pathways. A flaw can derail normal development, causing birth defects and some forms of cancer.

The Hedgehog signals instruct the cells to become one type of cell or another type of cell, Scott explained, and only some types are supposed to grow.

Work in many laboratories has identified a series of steps in Hedgehog signaling. Multiple molecules along that chain can affect the activities of genes whose activity is regulated by Hedgehog, and some of these genes control cell division. Normally cell division is tightly restrained, but damage to one of the components of Hedgehog signaling can lead to loss of control and the growth of a tumor, said Scott.

In the case of medulloblastoma tumors, a series of experiments carried out by Scott and Stanford colleague Ryan B. Corcoran showed that cholesterol or chemicals derived from cholesterol, known as oxysterols, spark transduction of the Hedgehog signal and enable medulloblastoma cells to proliferate.

These medulloblastoma cells only grow well if they are getting something from the sterol synthesis pathway, which produces sterols, steroids, and other chemicals, Scott said. What we found is that cholesterol will do it, and molecules derived from cholesterol, called oxysterols, work even better.

Knowing this, he said, it may be possible to devise novel strategies to inhibit sterol synthesis to block the proliferation of medulloblastoma cells. Inhibition of Hedgehog signaling by sterol synthesis inhibitors may offer a novel approach to the treatment of medulloblastoma and other Sonic hedgehog pathway-dependent human tumors, wrote Corcoran and Scott in their *PNAS* article.

In their studies, Scott and Corcoran explored the use of statins, a family of cholesterol lowering drugs, as potential agents for slowing or stopping the proliferation of medulloblastoma cells. The growth of the cancer cells was

inhibited by blocking the sterol synthesis pathway, he said. At present, therapies used to treat medulloblastoma include surgery, radiation and chemotherapy, or a combination of those interventions.

Scott said that while the results of the new study are promising, he cautioned that the work is still in its early stages. He noted that his group's work was conducted in cells grown in well known and controlled culture conditions, and that cells in a live animal or a patient may behave differently.

It is hard to say what is going on normally in cells (in an animal) as opposed to cells in culture. The cells we have in culture are just zooming along and the restraints that would normally shut them down are not there, said Scott.

Cells in an animal, he explained, may be influenced by other variables or subtleties of the signaling system that could complicate scientists' understanding of the processes that, in the case of medulloblastoma, make good cells go bad.

However, Scott said results of the new study provide a basic insight that might inspire improved therapies.

Down the line, the hope is that understanding the steps in the signaling process will help us figure out what goes wrong, he said. It may then be possible to help children who are afflicted with this disease.