Some brain tumors may be mediated by tiny filament on cells

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UCSF scientists have discovered that a tiny filament extending from cells, until recently regarded as a remnant of evolution, may play a role in the most common malignant brain tumor in children.

The study, conducted in mice and in human brain tissue of medulloblastomas, coincides with a study by another team of UCSF scientists showing that the structure, known as primary cilium, also may play a role in basal cell carcinoma, the most common form of skin cancer. (See related article.)

The findings, both reported online on August 23, 2009 in "Nature Medicine," are the first direct evidence of a role of primary cilia in cancer, which the researchers say could lead to a new strategy for diagnosing subtypes of cancers and to potential targets for therapy.

"These findings are very exciting," says the senior of the medulloblastoma study, Arturo Alvarez-Buylla, PhD, UCSF Heather and Melanie Muss Professor of Neurological Surgery and a member of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF.

"In the last few years, primary cilia have been shown to be essential for the cell-signaling that drives both human development, including the differentiation of stem cells into neurons, and some diseases, including polycystic kidney disease. The fact that the two UCSF studies implicate primary cilia in two totally different tissues suggests the finding is likely

to be very general."

Significantly, in both UCSF studies, the findings in mice revealed that primary cilia had opposing roles in cancers depending on which mutated genes initiated the aberrant cell-signaling events to begin with. When one particular mutated protein was activated, removal of the cilium prevented the onset of disease; when another particular gene was activated, absence of the cilium allowed cancers to develop.

Remarkably, an analysis of human tissue in the medulloblastoma study revealed that primary cilia were present in a subset of human tumors, but absent in others. The presence and absence correlated with the cell-signaling pathways that were activated in the tumors. This suggests, the researchers say, that, as in mice, some tumors in humans need to remove the primary cilia to grow, while other require its presence to grow.

The explanation, says the lead investigator of the medulloblastoma study, Young-Goo Han, PhD, a postdoctoral fellow in the Alvarez-Buylla lab, has to do, in part, with the way in which the primary cilium is structured and functions.

Unlike their beating cousins, known as motile cilia, or flagella -- which swish protozoa through pond water and undulate in the airways -- primary cilia are generally immobile, and function as cellular antennae. They receive signals from other cells, allowing for their transmission, in a process known as signal transduction, down a pathway of signaling proteins -- some of which are located precisely in the cilia -- into the cytoplasm, ending at the cell's nucleus, where the signals' commands are issued.

One of the key signaling molecules in development is a secreted lipoprotein known as Hedgehog, which regulates tissue patterning, cell proliferation, and many other biological processes. Recently, scientists

have discovered that Hedgehog signaling functions through the primary cilium. As Hedgehog approaches a target cell, it binds to its receptor, Patched1 (Ptch1), on the cilia, opening the gate for another protein, known as Smoothened (Smo) to enter into the cilium. There, Smo, an essential activator of the Hedgehog pathway, initiates the biochemical cascade that leads to the activation of a "downstream" protein known as Gli2, which in part communicates the Hedgehog signal to the cell's nucleus.

Aberrant Hedgehog signaling is well known to lead to human cancers, including basal cell carcinoma and medulloblastoma. However, it was not known if the cilium, itself, played a role in the development of cancers.

Han engineered mice to continuously express a mutant form of Smo, known to cause cancers in humans. In these mice, the mutant form of Smo moved to the cilium, independent of Ptch1, driving the development of medulloblastoma. When Han genetically removed the cilium, no tumors developed.

Predicting that continuously activating a protein in the signaling pathway downstream of Smo and primary cilia would induce tumors whether or not the cilium were present, Han activated Gli2 - and removed the cilium. To the team's astonishment, all of the mice developed medulloblastoma only when primary cilia were removed.

The explanation may be, the researchers say, that removing the primary cilium prevented it from carrying out one of its other jobs - activating proteins in its pathway whose jobs are to suppress Hedgehog signals.

Next, the team examined 38 samples of autopsied brain tissue donated to the UCSF Medical Center Neurological Surgery Tissue Bank and to the Neuropathology Laboratory at St. Jude Children's Research Hospital.

Primary cilia were present in most cases of one form of the disease, known as desmoplastic medulloblastoma, and mostly absent in another, known as anaplastic medulloblastoma. Of 24 tissue samples analyzed for their gene-expression profiles, primary cilia were identified almost exclusively in tumors driven by Hedgehog or Wnt signaling.

The findings have prompted the team to begin investigating primary cilia's role not only in other subsets of medulloblastomas but also in glioblastomas, the most common brain tumor in adults, with an eye toward identifying a diagnostic strategy and therapeutic targets.

More broadly, they are considering other questions. Most cells have a primary cilium, notes Alvarez-Buylla. "I think people have paid little attention to this thin, cellular extension or have thought of it just as a remnant of a ciliated organism. It's become clear that it's much more fascinating than that: It may play critical binary roles in many decisions cells make, and may be particularly important in cancer. In some cancers, the activating role of primary cilia is hijacked in order to keep the growth signal on; in other cancers, it is removed to eliminate the off switch."

Source: University of California - San Francisco