

DECEMBER 04, 2009

Researchers Identify Gene that Spurs Deadly Brain Cancer

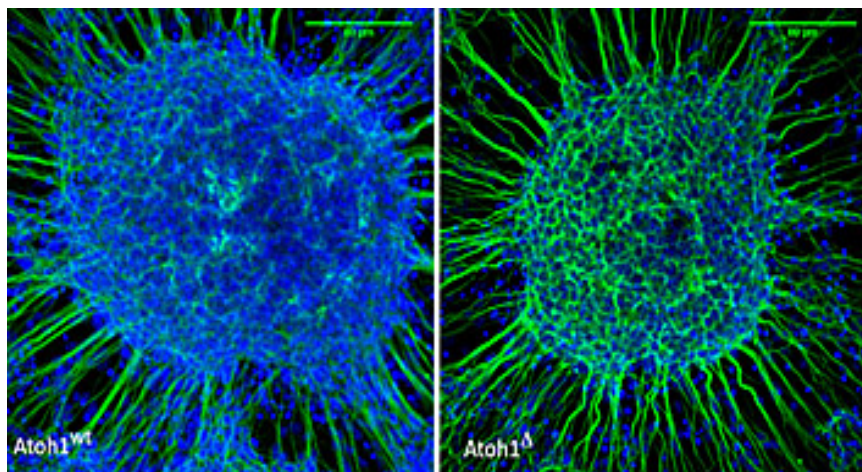


Image Title: The image shows cerebellar granule precursors grown in presence of sonic hedgehog. Deletion of Atoh1 blocks proliferation and induces differentiation as shown by the green staining for neuronal beta-tubulin (right panel). Nuclei are visualized by the blue staining. - Courtesy of Huda Y. Zoghbi/HHMI at Baylor College of Medicine

Howard Hughes Medical Institute (HHMI) researchers have identified a new factor that is necessary for the development of many forms of medulloblastoma, the most common type of malignant childhood brain cancer.

HHMI investigator Huda Y. Zoghbi and colleagues at Baylor College of Medicine prevented medulloblastoma from developing in mice by shutting down production of the protein Atoh1 in susceptible brain cells. The team's findings, reported in the December 4, 2009, issue of *Science*, suggest Atoh1 may be a new target for medulloblastoma treatment.

“When we cloned the gene for Atoh1 in 1996, we had no clue that it had any medical relevance,” said Zoghbi, a neuroscientist and neurologist. “Now we know that it’s critical for many medical issues, the most recent one being this common childhood cancer.”

"If we allow these tumors to develop, and then we take away *Atoh1*, would that make a difference?"

- Huda Y. Zoghbi

Atoh1 (also known as *Math1*) is a transcription factor that works in the nuclei of cells to keep certain genes switched on. It is evolutionarily ancient, appearing in slightly varying forms in various species, from fruit flies to humans. In cells where *Atoh1* is active, it seems to be switched on only during fetal development, when cells proliferate rapidly to fill out the various parts of the nervous system.

However, in the region of the brain known as the cerebellum, *Atoh1* is active after birth in the fast-dividing granule neuron precursor (GNPs) cells that eventually stop dividing and become mature granule neurons. "The cerebellar granule neurons are unique in that most of their development happens after birth, both in mice and humans," Zoghbi said.

A few years ago, experiments done in several laboratories hinted that *Atoh1* might be required to keep GNPs in their fast-dividing state and make them more susceptible to developing into medulloblastoma tumors.

"The question for us was whether we could really prove, not just in the cell culture dish or in microarrays but in animals, that *Atoh1* plays this role in medulloblastoma," Zoghbi said.

Ordinarily, to begin to discern the function of a gene such as *Atoh1*, researchers would engineer a strain of mice that lack the gene. But that had been tried in the 1990s, and the results were less than satisfying. Researchers found that *Atoh1*-knockout mice failed to develop properly in the womb, and died at birth. To study *Atoh1*'s function after birth, Zoghbi's team, led by postdoctoral researcher Adriano Flora, devised a more advanced technique. First they bred a strain of mice with a genetic off-switch connected to their *Atoh1* gene; then they injected a chemical into the brains of healthy newborn mice, to trigger this off-switch and eliminate the production of *Atoh1* in GNPs. As a result, the GNPs immediately stopped proliferating and started maturing into granule neurons.

That result showed that *Atoh1* helped keep GNPs in their ever-dividing state. Further experiments revealed that *Atoh1* revs up GNPs by switching on a gene called *Gli2*, a well-known member of the Sonic Hedgehog signaling pathway that helps cells divide. The Sonic Hedgehog pathway is also inappropriately switched on in many cancers, including medulloblastoma.

“At this point we asked whether we could affect the development of medulloblastoma in mice by shutting down *Atoh1*,” Zoghbi said.

To find out, the team applied their local *Atoh1*-shutdown technique to a special strain of mice with a specific genetic mutation that makes them develop medulloblastoma. In these mice, a mutant gene is switched on after birth, sending the Sonic Hedgehog signaling pathway into overdrive, causing precancerous lesions and tumors in the cerebellum. But when Zoghbi’s team switched off *Atoh1*, these cancerous changes never occurred.

Establishing *Atoh1* as a key player in the origin of medulloblastoma makes it a potential target for new drug treatments, Zoghbi said. But to Zoghbi, an important next step is to determine whether the protein is still needed to keep tumors growing after they’ve become established: “If we allow these tumors to develop, and then we take away *Atoh1*, would that make a difference?” Her lab and others are also now racing to determine what keeps *Atoh1* inappropriately switched on in medulloblastoma cells, and what normally switches it off.

Zoghbi emphasized that she originally took up the study of *Atoh1* as an exercise in pure biology, with no idea that it would have relevance to disease. “That just underscores the tremendous importance of doing science for science’s sake,” she said.