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Gene Triggers Formation of Sensory Cells in the Ear

A team of scientists from the Howard Hughes Medical Institute (HHMI) at Baylor College of Medicine has discovered the gene responsible for triggering embryonic cells in the inner ear to develop into sound- and motion-sensing hair cells.

[Huda Zoghbi](#), HHMI investigator at Baylor, said that this finding raises the possibility of introducing the gene into the inner ear to replenish hair cells lost to age and environmental trauma, two prevalent causes of deafness and balance problems.

The Zoghbi lab found that a mouse gene called *Math1* signals precursor cells in the inner ear to become hair cells. This decision occurs during embryonic development at a time when other precursor cells are developing into support cells that surround the hair cells and anchor them in place within the inner ear.

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at the proper time and at the right
concentration."

- **Hugo J. Bellen**

The microscopic hairs that sprout from such cells cover inner ear surfaces like wheat in a Kansas field. When sound or head motion creates ripples across the array of hairs, that motion is translated into nerve impulses that the brain interprets as sound or movement.

Zoghbi, whose main research explores disorders of balance, began this collaboration with [Hugo Bellen](#), also an HHMI investigator at Baylor, in 1996 when he brought to her attention a line of uncoordinated fruit flies that lacked a gene called *atonal*. The scientists knew that genes for such crucial functions are usually "conserved" throughout the animal kingdom when one species has such genes, other animals species usually do, too. So they embarked on a search for genes similar to *atonal* in the mouse, in the hopes

of gaining insight into peripheral nervous system development in vertebrates.

Zoghbi's group soon isolated a mouse gene, which they named "Mouse atonal homolog1," or *Math1*, that was similar to the fly gene. The genes are nearly identical in structure, yet the researchers found that the fly and mouse genes operate in different parts of the nervous system. In the fly, the *atonal* gene is active in peripheral nerves those found outside of the brain and spinal cord. By contrast, the mouse version functions in many areas of the spinal cord and in the cerebellum, a region of the brain important in controlling motion. Surprisingly, mice with a non-working *Math1* gene died immediately after birth, implying a more critical role for the gene in the mouse than in the fruit fly.

To determine why mice with the *Math1* mutation died, and to reveal sites of *Math1* activity that may have been missed before, the scientists developed other mutant strains of mice in which *Math1* was replaced with an indicator gene that would stain blue any cells where the gene was normally active.

"These new mice showed for the first time that this gene was normally expressed in inner ear cells," said Zoghbi. "And once we examined these structures closely, we discovered that the hair cells are lacking in the mutant mice."

But, said Zoghbi, we couldn't rule out that *Math1* was merely important for hair cells to continue to grow, and not for their formation.

"So, we went back to the earliest point in embryonic development, when the first hair cells begin to differentiate, and we found absolutely no hair cells," she said. "Certainly, *Math1* could be important for maintenance of hair cells, but we now know for sure that it is critical for their genesis."

Zoghbi, Bellen and their colleagues theorize that all such inner ear cells begin as "mother" cells, and in the absence of *Math1*, all will become support cells. Once *Math1* triggers a cell to become a hair cell, it also inhibits the cells around it, forcing them to become support cells.

In their next experiments, the scientists plan to explore whether *Math1* can somehow be introduced into mature inner ear cells perhaps using a harmless virus to regrow hair cells lost to disease or aging.

"The art is to deliver the gene to the proper cell at the proper time and at the right concentration," said Bellen. "Obviously, the process is fraught with problems. For instance, we don't know if neurons will reconnect with hair cells once they are restored.

"My gut feeling from published experiments is that you can turn inner ear cells into hair cells," he said. Bellen cited, as an example, studies that reveal that chickens can regrow functioning hair cells once they are removed.

More broadly, the scientists will explore how *Math1* controls development throughout the nervous system, attempting to understand why mice lacking the gene die immediately after birth.