Blocking Notch pathway leads to new route to hair cell regeneration to restore hearing

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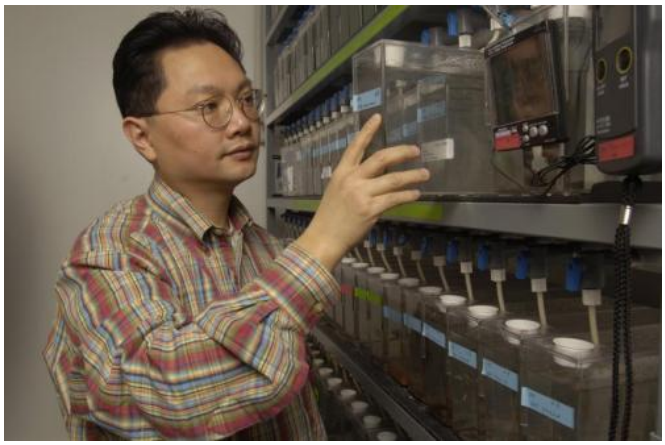

Zhen-Yi Chen, Ph.D., of the Eaton-Peabody Laboratories at Mass. Eye and Ear and an Associate Professor of Otology and Laryngology at Harvard Medical School. Credit: Eric Antoniou

Sensory hair cell loss is the major cause of hearing loss and balance disorders. The postnatal mammalian inner ear harbors progenitor cells which have the potential for hair cell regeneration and hearing recovery, but the mechanisms that control their proliferation and hair cell regeneration are yet to be determined. Now scientists from the Eaton-Peabody Laboratories at Massachusetts Eye and Ear/Harvard Medical School and Fudan University, Shanghai, China, have shown that blocking the Notch pathway, known to control the elaborate hair cell distribution in the inner ear, plays an essential role that determines cochlear progenitor cell proliferation capacity. Their research was published today in *PNAS* Early Edition.

"A high level of Notch activity prevents progenitor cell division and hair cell regeneration in the postnatal inner ear," said Zheng-Yi Chen, Ph.D., of the Eaton-Peabody Laboratories at Mass. Eye and Ear and an Associate Professor of Otology and Laryngology at Harvard Medical School. "We learned something new about this mechanism. It is known that inhibition of Notch activity can convert inner ear supporting cells to hair cells. In this paper, we have shown that Notch inhibition also promotes cell division. Under the condition, the inner ear progenitor cells re-enter cell division to regenerate hair cells in postnatal cochlea. This study thus provides a new route to block Notch activity to increase progenitor cell population by cell division, and to regenerate new hair cells. Our work could have potential in leading to developing new strategies to achieve hair cell regeneration for hearing restoration."

The researchers show that Notch inhibition initiates proliferation of supporting cells that give rise to new hair cells in postnatal mouse cochlea in vivo and in vitro. Through lineage tracing, they identified that a majority of the proliferating supporting cells and cell division-generated hair cells induced by Notch inhibition are originated from the Wnt-responsive leucine-rich repeat-containing G protein coupled receptor 5 (Lgr5+) progenitor cells. They demonstrated that Notch inhibition removes the brakes on the canonical Wnt signaling and promotes Lgr5+ progenitor cells to mitotically generate new hair cells.

"Our study reveals a new function of Notch signaling in limiting proliferation and regeneration potential of postnatal cochlear progenitor cells, and provides a new route to regenerate HCs from progenitor cells by interrupting the interaction between the Notch and Wnt pathways," Dr. Chen said.

More information: Notch inhibition induces mitotically generated hair cells in mammalian cochleae via activating the Wnt pathway, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1415901112

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