Notch inhibition induces mitotically generated hair cells in mammalian cochleae via activating the Wnt pathway

With the support of the National Natural Science Foundation of China and the Ministry of Science and Technology of China, Prof. Li Huawei's laboratory at the Eye & Ent Hospital of Fudan University discovered a new function of Notch and a new route to regenerate hair cells from inner ear progenitor cells, which was published in *PNAS* (2015, 112(1): 166—171).

Notch signaling pathway is known as a fundamental pathway that regulates the cell-fate determination in the inner ear. In the present study, they show that Notch signaling also acts as a negative regulator that inhibits the proliferation of $Lgr5^{+}$ progenitors and maintains the homeostasis of cochlear sensory epithelium on cell numbers. More importantly, they provide the first piece of evidence illustrating the interaction between Notch and Wnt signaling in the postal mouse cochlea: Notch inhibition activates the canonical Wnt pathway in the progenitor cells, which leads to the mitotic regeneration of hair cells; but Notch inhibition induces direct supporting cell-to-hair cell transdifferentiation, which is Wnt-independent. Their findings may be useful in dissecting the mechanisms regulating mammalian inner ear proliferation and hair cell regeneration.

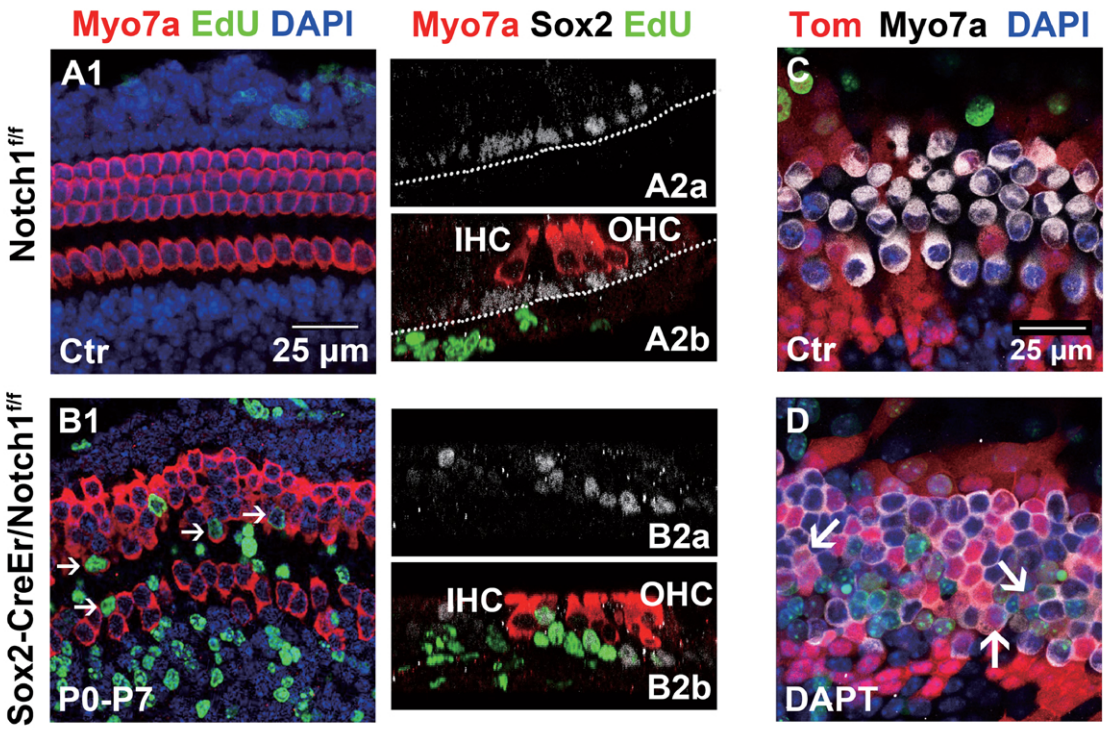

Figure Notch inhibition in Sox2+ SCs initiates the proliferation of SCs and mitotic HC generation. (A) In Notch1f/f control cochlea, no EdU+/Sox2+SC was detected at P3/P7. (B) In contrast, in the Sox2-CreEr/Notch1f/f cochlea, numerous EdU+/Sox2+ SCs and several EdU+/Myo7a+HCs were detected in the Pillar cell region. (C) Using Lgr5-CreER; ROSA26-tdTomato mice, DMSO-treated control cochlea had no EdU+ in tdTomato cells, which included third Deiter's cells, inner pillar cells, inner phalangeal/border cells, and GER cells. (D) DAPT-treated cochlea showed EdU+/td Tomato+/Myo7a+(↑) HCs in the sensory epithelium.