Extensive supporting cell proliferation and mitotic hair cell generation by *in vivo* genetic reprogramming in the neonatal mouse cochlea

Subject Code: H13

With the support by the National Natural Science Foundation of China, the research team led by Prof. Li Huawei (**李华伟**) at the Otorhinolaryngology Department, Affiliated Eye and ENT hospital, State Key Laboratory of Medical Neurobiology of Fudan University, achieved the mitotic hair cell generation through a genetic reprogramming procedure, which was published in the *Journal of Neuroscience* (2016, 36(33): 8734—8745).

Permanent hair cell loss is the main cause of the hearing loss and balance disorders in mammals. Since the supporting cell shares a common progenitor with the hair cell during the development of the inner ear, which is regarded as a promising resource for the regeneration of hair cells. Recently, it has been identified that a subpopulation of supporting cells—$Lgr5^+$ cells could re-enter the cell cycle and differentiate into hair cells under certain conditions, and consequently serve as the progenitors of the inner ear. Thus, the activation of the progenitors after hair cell loss is a promising approach for the recovery of hearing, as well as the dysfunction of balance. Our previous study has shown that the inhibition of Notch signaling in $Sox2^+$ cells could activate the proliferation of $Lgr5^+$ progenitors in the neonatal cochlea, and the Notch signaling serves as a negative regulator for the proliferation of supporting cells induced by the activation of Wnt signaling.

In the present study, they observed a more extensive proliferation of supporting cells, as well as a higher ratio of transdifferentiation from proliferated supporting cells into hair cells, by up-regulating Wnt signaling and down-regulating Notch signaling simultaneously in the $Sox2^+$ supporting cells in the mouse cochlea. Moreover, the proliferated hair cells were further increased by up-regulating Atoh1 combined with Notch inhibition and Wnt activation in the $Sox2^+$ supporting cells.

In order to further investigate the mechanism underneath the interaction between Wnt and Notch signaling during the activation of progenitor cells in the neonatal mouse cochlea, Li's group generated another mouse model, in which β-catenin and Notch1 were double knockout in $Sox2^+$ SCs. The results provided direct evidence that Notch1 acted as a negative regulator of the proliferation of progenitor cells in the neonatal mouse cochlea through β-catenin activation and Notch signaling served as an upstream regulator of Wnt signaling for maintaining the quiescence of progenitor cells in the neonatal mouse cochlea during HC generation.

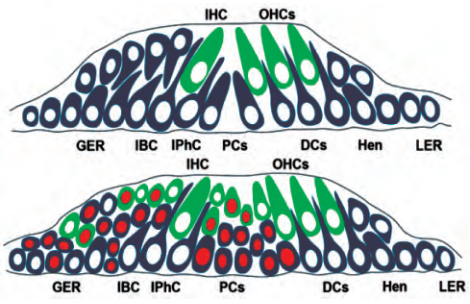

Figure The model of the mitotic hair cell generation.

Furthermore, Li's group compared the gene transcripts in the sensory epithelium of the cochleae among different groups to investigate the molecular mechanism underneath the extensive proliferation and differentiation. The assessment of genome-wide gene expression profiles might provide more hints for understanding the mechanisms behind mitotic HC generation and suggest new approaches to stimulate mitotic HC regeneration after HC loss.