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Jagged1-Notch3 interaction and the cell fate in the prosensory patch

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In the inner ear development of mammals, Notch signaling pathway is considered to play two contrasting roles, initially lateral induction to induce the formation of prosensory patch and subsequently lateral inhibition to decide cell fate into hair cell (HC) or supporting cell (SC). However, the active components and associated regulation are poorly known. In order to investigate the Notch pathway mechanism in the ear morphogenesis, we established a conditional knockout model to inactivate Jagged1, a Notch ligand, early in mouse embryo in the ear area. $Pax8^{Cre/+}$ allele was employed to delete exon4 of *Jag1* flunked by flox sequences. This Jagged1 conditional knockout, $Pax8^{Cre/+};Jag1^{flox/flox}$ allele, is firstly reported to be able to be normally born and survive as wild type, whereas manifesting hearing impairment and balance disturbance. The previous Jag1 conditional knockouts from other labs died before delivery probably because of using another Cre-carrier $Foxg1^{Cre/+}$ allele. In our study, the helical cochlea was found with normal amounts of turns and all the vestibular organs, including saccule, utricle and ampullae, were seen without remarkable malformation. Only patches of outer hair cells (OHCs) were missing, especially in the middle and basal turns. Ectopic HC-like cell was found on the strial side of normal OHCs. The stereociliary bundles

on the crista were misorientated. The mild malformation suggested that Jagged1-mediated Notch signaling may be compensated at the early formation of prosensory patch, or Jag1 may regulate the prosensory patch formation coordinately with other pathways, but at least, it is not determinative. More likely, it plays an important role in the fine tuning of inner ear maturation at a later stage within the prosensory patch.

From previous studies the mechanisms of Jag1 in the inner ear development are controversial and elusive, designating as lateral induction and lateral inhibition, it is presumed that other Notch receptor besides Notch1, which is always and only investigated, would interplay with Jag1 and modulate the cell fate determination during the inner ear development. Previously another Notch protein, Notch3, was proved in RNA level in the developing inner ear. In our study Notch3 immunostaining was found positive in controls. Whereas it was not expressed at E13.5 in the developing ear area of the Jagged1 conditional knockout, which indicates a positive feedback between Jagged1 and Notch3 probably exists. Jagged1-Notch3-mediated mechanism was devoid in the differentiation soon afterwards in Jag1-cko. Taken together with the mild malformation of the inner ear, instead of obvious defect, Jagged1-Notch3 interaction probably regulates the cell fate decision within the prosensory patch through fine tuning.