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Author(s)	Liu, Y; Hui, CC; Sham, MH
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The roles of Irx3 and Irx5 genes in inner ear sensorineural patterning

YC LIU, CC Hui and MH Sham
Department of Biochemistry, The University of Hong Kong

Irx3 and Irx5 are members of the Iroquois family TALE homeodomain transcription factors, which function as patterning genes in multiple developmental processes. In the developing limb bud, Irx3 and Irx5 are critical for establishing early AP polarity and digit specification. In the developing inner ear, we have found that Irx3/5 compound mutant displayed enlarged cochlear lumen, abnormal spiral ganglion, and fusion of inner ear sensory regions. These abnormal phenotypes suggest that Irx3 and Irx5 may have essential role in early inner ear patterning.

The mouse mutant Irx3tauLacZ with β-gal reporter was used to examine the expression of Irx3 in otic vesicle and cochlear epithelium. At E10.5, Irx3-LacZ signal was restricted to medial half of anterior otocyst, which is the neural-sensory region, and extended to posterior-lateral region. At E16.5, Irx3 was expressed in the entire otic epithelium, and became very strong in the lateral wall. At both stages, there were no Irx3-LacZ positive cells in the CVG or spiral ganglion. Irx5 gene showed very similar expression patterns as Irx3. Considering the phenotypes in Irx3/5-/- mutant, and the expression pattern of these two genes, we hypothesize that Irx3 and Irx5 control inner ear patterning from early otocyst stage by regulating neuro-sensory cell competence.

To understand how Irx3 and Irx5 genes affect sensory domain specification and neuroblast delamination, mutant otocyst were analyzed with markers for neuro-sensory fate. Expansion of Sox2-positive domain and loss of posterior Pax2 expression region revealed that the neuro-sensory competent domain was shifted and changed its shape in Irx3/5-/-. Moreover, Irx3/5-/- otocyst showed increased NeuroD positive cell with ectopic stream of delaminating neuroblast. In consequence, Tbx1, which could suppress neurogenesis, became more restricted to the posterior otocyst. These results indicate that Irx3 and Irx5 are required for proper sensory specification and neurogenesis at otic vesicle stage.

Our further study will focus on how Irx3 and Irx5 affect the patterning of the cochlear epithelium and what causes the fusion of saccule and organ of Corti. BMP signaling is a potential regulatory pathway that could maintain proper sensory/non-sensory boundary, and lost of Bmp4 expression domain has been observed in Irx3/5-/- cochlea. Whether BMP signaling is affected in Irx3/5-/- cochlea or other factors will contribute to the abnormal cochlea development in Irx3/5-/- will be further investigated.