Unravelling the roles of lysine acetylation by Elp3 during inner ear development

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The inner ear is composed of the vestibular system that controls balance, and the cochlea, which is dedicated to hearing. In both parts of the inner ear, sensory epithelia comprise supporting cells surrounding the sensory hair cells. These cells bear at their apical surface a staircase-structured bundle, consisting of multiple rows of actin-based stereocilia and a single tubulin-based kinocilium. This hair bundle allows the transduction from mechanical stimuli, initiated by sound or gravitational changes, to electrical signals that will then be transmitted by neurons from the spiral ganglion (innervating hair cells of the cochlea) or the vestibular ganglion. The inner ear organogenesis requires a tightly regulated transcriptional program that can be affected by post-transcriptional and post-translational modifications among which lysine acetylation. Given the importance of acetylation homeostasis in controlling developmental processes, we planned to investigate its role in inner ear formation and focused our attention on Elp3 acetyl-transferase, a member of the Elongator complex recently implicated in neurogenesis.

To determine the role of Elp3 in the inner ear, we first analysed the spatio-temporal pattern of ELp3 mRNA expression and showed that it was expressed in the entire early otocyst at E11.5 and persisted later in the sensory epithelium of the cochlea (the organ of Corti), in the spiral ganglion, in the stria vascularis and in the vestibule.

To unravel *in vivo* functions of Elp3 in the inner ear, we used conditional knock-out mice in which Elp3 gene is deleted from early otocyst (Elp3 cKO). We submitted these mice to a battery of vestibular testing (i.e. stereotyped circling ambulation, head bobbing, retropulsion, and absence of reaching response in the tail-hanging test) and found significant abnormalities. Besides, compared to wild-type mice, the auditory brain stem response of Elp3 cKO indicated that these mice are severely deaf.

At the cellular level, we did not find any structural abnormalities nor cell patterning defects that could explain deafness or balance dysfunction in Elp3 cKO mice. However, we detected some defaults in the planar orientation of their auditory hair cell bundle. In addition, the length of the kinocilium was significantly reduced both in vestibular and cochlear hair cells from Elp3 cKO mice compared with wild type littermates. We were also able to demonstrate an increased level of apoptosis in the Elp3 cKO spiral ganglion at E14.5 leading to a reduced number of fibers innervating the cochlear hair cells as well as a reduced number of their synaptic ribbons at P0 and P15.

In conclusion, our results clearly show a role for Elp3 both in hearing and balance. We plan to go deeper in the mechanisms involved through the identification of the proteins that are targeted for acetylation by Elp3.