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

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The inner ear is composed of a vestibular part 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 hair 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.

First, we have analysed Elp3 expression by in situ hybridization on wild type mice at different developmental stages (from E11.5 until P6) 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 stria vascularis and in the vestibule.

To study the functional consequences of protein acetylation by the Elongator complex in the inner ear, we studied conditional knock-out mice (Elp3 cKO) in which Elp3 is depleted from the otic vesicle at E8.5. These mice, at stage P15, showed obvious balance dysfunction that was confirmed by a complete battery of behavioural tests: stereotyped circling ambulation, head bobbing, retropulsion, and absence of reaching response in the tail-hanging test. Unfortunately, the Elp3 cKO mice die before the onset of hearing, thus precluding any evaluation of hearing disorders.

Balance defects in mice depleted for Elp3 is not due to vestibular structural abnormalities, since paint-filling experiments showed a normal inner ear anatomy compared to wild type mice. Moreover, immunostainings in the vestibule and in the organ of Corti indicated that cell patterning was not impaired in the absence of Elp3 since specialised cells are present and correctly organised at embryonic day E18.5 and later on. However, we were able to detect some defaults in hair cell bundle integrity and orientation in the auditory portion of inner ear from Elp3 cKO mice. 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 at P0 and P15.

In conclusion, we have confirmed the expression of Elp3 in the inner ear and pointed out a role for this acetyl-transferase in balance function. Our results clearly show the implication of Elp3 in ciliogenesis, hair cell innervation and neuronal survival and we plan to go deeper in the mechanisms involved through the identification of the proteins acetylated by Elp3.