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Aims:-Hearing loss affects about half a billion people worldwide, with at least 50% of cases having a genetic cause. Over 700 syndromes include hearing loss as a feature. One of these is Norrie disease, a rare, X-linked recessive deaf-blindness condition. Boys with Norrie disease are born severely visually impaired with disrupted retinal vasculature. The majority then develop progressive hearing loss, severely reducing their quality of life. However, the later onset of hearing loss provides a window of opportunity for treatment.

Norrie disease is caused by mutations in NDP, encoding a secreted signaling molecule norrin, which binds to co-receptors FZD4, LRP5 and TSPAN12 on the surface of target cells. This activates canonical WNT intra-cellular signaling, stabilizing β-catenin, which modulates downstream gene expression. Mice with a loss-of-function mutation in Ndp (Ndp-KO) show early abnormalities in the microvasculature of the cochlea, followed by the death of sensory hair cells and progressive hearing loss. In a recent study in Ndp-KO mice we showed that the Norrie phenotype can respond to systemic AAV-mediated NDP gene replacement therapy, preventing the progression of hearing loss. To develop NDP gene therapy for Norrie patients we aimed to improve understanding of the requirement for norrin signaling in cochlea cells.

Methods:- In this study we hypothesized that vascular endothelial cells are the primary target of Norrin signaling in the cochlea. We simulated the effect of Norrin signaling to endothelial cells only, using a tamoxifen-inducible Cdh5CreERT2 driver transgene and the Ctnnb1 flex3 allele to activate β-catenin constitutively in Ndp-KO mice. We evaluated the effect of this intervention cochlear pathology and hearing function.

Results:- β-catenin stabilization in vascular endothelial cells at postnatal day 10 prevented stria vascularis abnormalities and rescued vascular barrier function and gene expression. Importantly, it prevented the sensory hair cell death and hearing loss. scRNA seq analysis of cochlea cells showed that Norrin co-receptor expression coincides only in vascular endothelial cells, while NDP is expressed by basal cells, fibrocytes and glia. These results show that maintaining vasculature integrity and a suitable cochlear micro-environment is an important function of norrin signaling.

Conclusions:- Our findings support a disease mechanism where hair cells die due to the defective cochlear microvasculature and neither hair cells or other cochlea cells require direct norrin signaling for survival. The results from the current study are being used to inform the further development, targeting and timing of NDP gene therapy for clinical translation.

Keywords:- NDP, deafness, gene therapy, cochlea, retina