



# ION AND WATER CHANNEL PROTEINS IN HUMAN INNER EAR-IMPLICATION TO INNER EAR FLUID HOMEOSTASIS AND MECHANISM OF MENIERE'S DISEASE

UPPSALA  
UNIVERSITET

Wei Liu, Fredrik Edin, Hao Li, and Helge Rask-Andersen

Department of Surgical Sciences, section of Otolaryngology, Uppsala University, SE-751 85, Uppsala, Sweden.

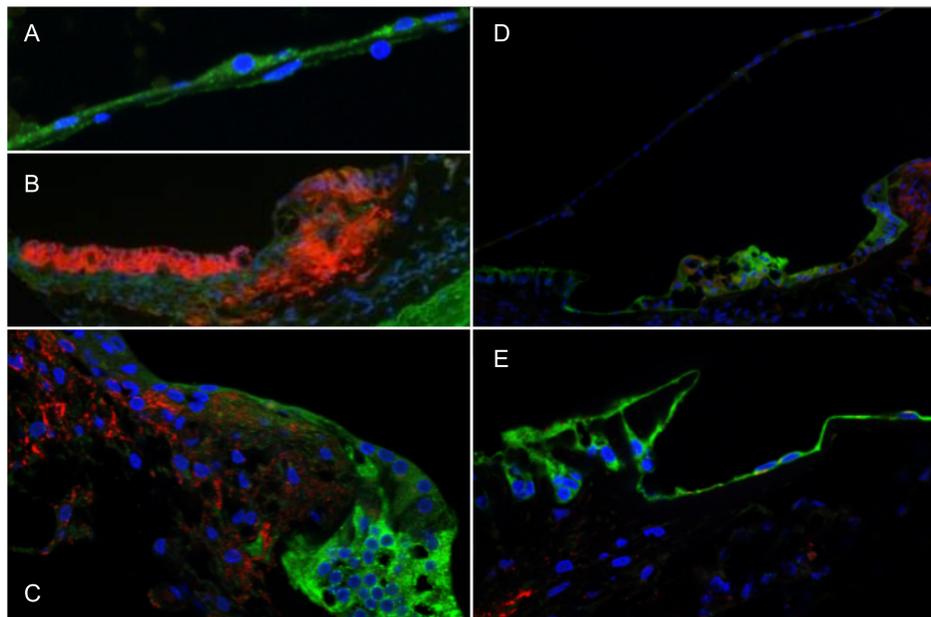
## Abstract

**Introduction** Channel proteins are expressed in the stria vascularis (SV) as well as in other inner ear tissues. They are essential for formation of the endolymph making mechano-transduction possible. Inhibition or mutation of these proteins cause sensorineural hearing loss.

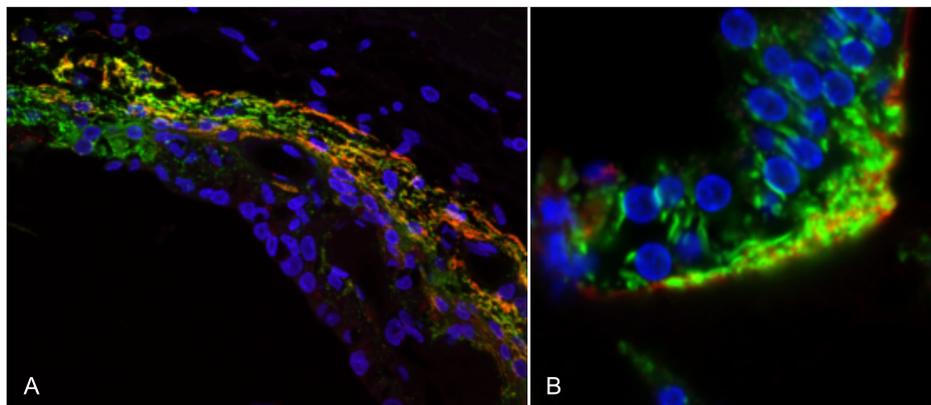
**Material and methods** By using immunohistochemistry combined with confocal and super-resolution microscopy, we searched human cochlea and endolymphatic sac (ES) for proteins related to transportation of ions (ion transporter or ion channel proteins) and water (aquaporins, AQP), the former included Kir4.1, connexin30/26 (Cx30/Cx26), voltage-gated potassium channel proteins, NKCC1, Na<sup>+</sup>-K<sup>+</sup>-ATPase; water channel proteins included aquaporin2/4/5. When cochleae

were harvested from patients undergoing intra-cranial tumor surgery, patients' consent was obtained as well as ethics permission.

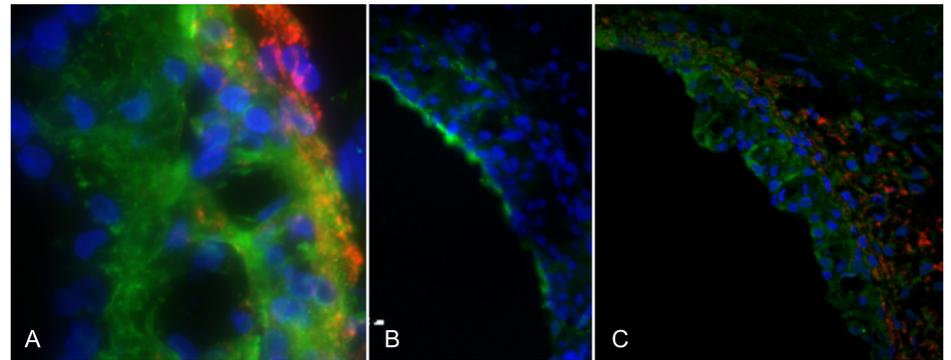
**Results and conclusions** We found that the stria vascularis is equipped with various types of ion channels that are organized elegantly making SV an important structure for endolymph production; spiral ligament and cells lining other part of the scala media may also participate in ion and water circulation (figure 1-3). Human endolymphatic sac epithelial cells express aquaporin 2/4/5 (figure 4). Mapping ion and water channels in human inner ear helps understand the production and circulation of the endolymph in the inner ear and the mechanisms underlying endolymph circulation anomalies.



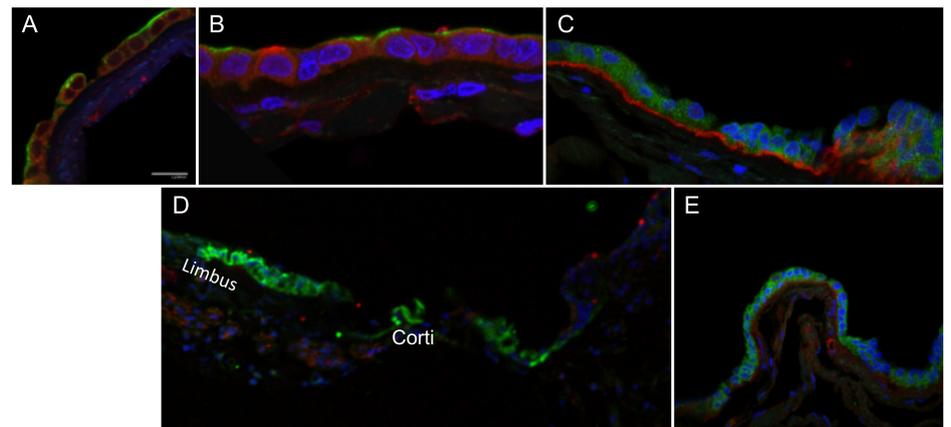
**Figure 1.** The Na<sup>+</sup>/K<sup>+</sup>-ATPase helps maintain resting potential, effect transport, and regulate cellular volume. Its alpha subunit is found in Reissner's membrane (A-green), SV (B-red), root cells as well as type II fibrocytes (B-red, C-green), outer and inner sulcus (D-green), interdental cells (E-green)



**Figure 2.** Cx30 and Cx26 are gap junction proteins expressed in stria vascularis/spiral ligament (A-green and red), organ of Corti and spiral limbus (not shown here). They are encoded by the GJB6 and GJB2 gene respectively. Their mutations have been found to lead to both syndromic and nonsyndromic deafness. The gap junction channels mediate direct diffusion of ions and metabolites between the cytoplasm of adjacent cells. Gap junctions serve the important purpose of recycling potassium ions that pass through hair cells during mechanotransduction back to the endolymph. B. Cx30 immunoreactivity between root cells (green; red fluorescence indicates laminin immunostaining) close to outer sulcus.



**Figure 3.** Kir4.1 (A-green), an inward rectifier potassium channel protein encoded by the KCNJ10 gene in humans, is expressed in the intermediate cells of human SV. Kv7.1 (KvLQT1, B-green) is a voltage-gated potassium channel protein encoded by the KCNQ1 gene. Kv7.1 is present in the apical cell membrane of marginal cells that transport potassium into endolymph. Na-K-Cl cotransporter (NKCC1) (C-green) is a protein, found in the stria vascularis, that aids in the active transport of sodium, potassium, and chloride. Encoded by gene SLC12A2, NKCC1 is inhibited by furosemide or other loop diuretics, resulting in deafness. The red fluorescence indicates Cx26.



**Figure 4.** AQP2 (A-red) is the aquaporin regulated by vasopressin (B-red). They are found in epithelial cells of the endolymphatic sac. The green fluorescence indicates cytokeratin. AQP4 is expressed in the epithelial cells in human ES (C-green, red fluorescence represents laminin); such cells also line the outer/inner sulcus, spiral limbus (interdental cells) and in the organ of Corti (supporting cells) (D-green). Aquaporin-5 is expressed in epithelial cells of the ES (E-green).

**Reference:** 1. Florian Lang et al. American Journal of Physiology – Cell Physiology 2007 Oct. 293 (4):1187-1208.  
2. Wei Liu et al. Hear Res. 2009 Apr. 250(1-2):55-62.

**Acknowledgements:** This study was supported by grants from the Foundation Tysta Skolan and Sellanders Foundation.