Inner Ear Research

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Unravelling molecular mechanisms of auditory hair cell loss to find new therapeutic possibilities to treat hearing loss

Hearing impairment has a significant impact on people's live affecting their social life, access to education and career opportunities. According to WHO estimation, 466 million people worldwide are currently affected by hearing loss, including 34 million children. Approximately one third of the people over 65 live with disabling hearing loss and more than 1 billion young people are at risk of developing gradual hearing loss due to regularly and prolonged exposure to loud sound. As reported by the non-profit organization Hear-it, disabling hearing loss costs 260 billion per year in Europe.

Hearing loss may result from a variety of factors such as genetic factors, infectious diseases, noise overexposure, ototoxic drugs and natural aging process. The main functions of the outer and the middle ear are transducing and amplification of sound, while the cochlea in the inner ear is the auditory sensory organ. The outer hair cells of the organ of Corti are mechanically active, while the inner hair cells of the same organ convert the stimulus into neuronal impulses via afferent synapses to the dendrites of primary auditory neurons. Loss of sensorineural elements of the inner ear, hair cells and auditory nerve, lead to sensorineural hearing loss. Since sensory cells of mammals do not regenerate, hearing loss is often progressive and irreversible. Although the causes of hearing loss are known, the molecular mechanisms underlying cochlear degeneration and auditory function remain incompletely understood. Understanding the molecular mechanisms of the sensory cell damage will provide the basis to develop new prophylactic and therapeutic approaches.

Our research group has conducted investigations on mechanisms that maintain the hearing function and survival of sensory cells. We have tested several candidates as otoprotective agents that could attenuate inner ear damage and hearing disabilities. We observed that the use of simvastatin, a statin commonly used for the treatment of hyperlipidemia, resulted in a dose dependent risk of neurotoxicity suggesting cautions about using it as otoprotective drug. Further drugs used for the treatment of diabetes and dyslipidemia were tested. Pioglitazone, tesaglitazar and fenofibric acid, that are peroxisome proliferator-activated receptor (PPAR) agonists, have shown protection against the ototoxic drug gentamicin via regulation of production of reactive oxygen species. Similarly, telmisartan, a partial agonist of PPAR , protected hair cells from gentamicin-induced damage. Furthermore, protection of hair cell against gentamicin has been successfully achieved by using brimonidine, an alpha-2 adrenergic receptor agonist. In addition, we examined the effect of pasierotide, an analog of the neuropeptide somatostatin. In-vitro, pasierotide antagonized gentamicin-induced hair cell death via nuclear factor of activated T cells. In-vivo, pretreatment with pasierotide decreased hearing thresholds in gentamicin-exposed mice.

In response to noise, ototoxic drugs and aging process; sensory cells activate various anti- stress signaling pathways. A number of those signaling pathways of cochlear degeneration are known, however other pathways still need to discover. We were the first research group reporting the involvement of Sestrin-2, stress-responsive protein, in the protection of hair cell against gentamicin exposure. We have found that Sestrin-2 exerted its protective effect via AMPK/mTOR pathway. Recently, we have reported that sodium-hydrogen exchange 6 (NHE6) was important for hearing function, as NHE6 knockout mice showed significant hearing impairment compared to wild type. Further studies to unravel the ototoxicity mechanism included the examination of mitophagy. We found that gentamicin had no

impact in the activation of mitophagy in auditory hair cells. Our investigations on insulin receptors in the mammalian cochlea suggested that insulin increased glucose uptake into hair cells via glucose transporter 3.
The findings obtained from our research studies will contribute to attenuate inner ear damage and to understand restoration of hearing that will provide valuable information for translational medicine.

Connection to Clinical Practice

Daniel Bodmer and Alexander Bausch
USB and Strekin AG

Clinical trial of STR001 in Sudden Sensorineural Hearing loss

STR001 contains the antidiabetic drug pioglitazone as active substance. Our investigations have shown that pioglitazone protected hair cells against the ototoxic drug gentamicin. In addition, the research group of Dr. Anna Fetoni reported that pioglitazone promoted hearing restoration in noise-exposed mice. These findings suggested that STR001 could be a potential therapeutic candidate for sensorineural hearing loss and should be examined for further clinical development. Our clinic are participating in the international placebo-controlled phase 3 clinical trial of STR001 on patients suffering from a sudden sensorineural hearing loss.

Selected Publications

Kucharava K, Brand Y, Albano G, Sekulic-Jablanovic M, Glutz A, Xian X, Herz J, Bodmer D, Fuster DG and Petkovic V (2020). Sodium-hydrogen exchanger 6 (NHE6) deficiency leads to hearing loss, via reduced endosomal signalling through the BDNF/Trk pathway. Sci Rep 10, 3609.

Kucharava K, Sekulic-Jablanovic M, Horvath L, Bodmer D and Petkovic V (2019). Pasireotide protects mammalian cochlear hair cells from gentamicin ototoxicity by activating the PI3K-Akt pathway. Cell death & disease 10, 110.

Setz C, Benischke AS, Pinho Ferreira Bento AC, Brand Y, Levano S, Paech F, Leitmeyer K and Bodmer D (2018). Induction of mitophagy in the HEI-OC1 auditory cell line and activation of the Atg12/LC3 pathway in the organ of Corti. Hearing research 361, 52–65.

Ebnoether E, Ramseier A, Cortada M, Bodmer D and Levano-Huaman S (2017). Sesn2 gene ablation enhances susceptibility to gentamicin-induced hair cell death via modulation of AMPK/mTOR signaling. Cell Death Discov 3, 17024.

Sekulic-Jablanovic M, Petkovic V, Wright MB, Kucharava K, Huerzeler N, Levano S, Brand Y, Leitmeyer K, Glutz A, Bausch A *et al.* (2017). Effects of peroxisome proliferator activated receptors (PPAR)-gamma and -alpha agonists on cochlear protection from oxidative stress. PloS one 12, e0188596.