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Editorial

Hearing Loss: Reestablish the Neural Plasticity in Regenerated Spiral Ganglion Neurons and Sensory Hair Cells 2020

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Hearing loss in one of the most common sensory disorders among people around the world, and it has often been referred to as an "invisible disability." Globally, over 1.5 billion people are currently experiencing hearing loss to some degree in 2021, accounting for 20% of the world's population, of which, an estimated 430 million have hearing loss of moderate or higher severity in the better hearing ear, and this number could increase to 2.5 billion by 2050 according to WHO report. Multiple risk factors could contribute to one's hearing capacity during his/her lifetime course, including genetic factors, ototoxic chemicals, noise exposure, trauma to the ear or head, and age-related degeneration. Among all cases of hearing disorders, 85% of them are under the category of sensorineural hearing loss (SNHL). Although SNHL is induced by various factors through different approaches and mechanisms, the major cause for SNHL is irreversible loss of either inner ear hair cells (HCs) or degeneration of spiral ganglion neurons (SGNs). At present, there is no effective treatments for SNHL available, thus, it is not curable yet. In recent years, many studies are dedicated to working on the regenerative capacity of developing and functional HCs and SGNs, and promising results on animal models present us with the potential of regenerating HCs and SGNs by gene therapy, stem cell induction, and signaling pathway manipulation. This raises the possibility of curing SNHL in the foreseeable future. In 2017 and 2018, we have publishes two special issues of "Hearing Loss: Reestablish the Neural Plasticity in Regenerated Spiral Ganglion Neurons and Sensory Hair Cells." This year, we are delighted to present a new series of articles and reviews covering the up-to-date progress on HC development, HC damage and protection, HC regeneration, SGN development and protection, and inherited hearing loss.

1. Hair Cell Development

(Z) Wang et al. (An *in vitro* study on prestin analog gene in the bullfrog hearing organs) for the first time identify the prestin analog gene in the bullfrog hearing organ functioning as a motor protein by nonlinear capacitance, and this might lead to reveal of possible roles of prestin in the active hearing processes found in many nonmammalian species. N. Li et al. (Alternative splicing of *Cdh23* exon 68 is regulated by RBM24, RBM38, and PTBP1) explore the mechanism of alternative underlying the production of cadherin 23, a key part in forming tip links in the hair cells and elucidate that RBM24, RBM38, and PTBP1 are involved in splicing of *Cdh23* exon 68.

2. Hair Cell Damage and Protection

(N) Sai et al. (Involvement of cholesterol metabolic pathways in recovery from noise-induced hearing loss) explore the molecular mechanisms of acute noise-induced hearing loss in miniature pigs and identify the possible participation of activation of metabolic, inflammatory, and innate immunity pathways in acute noise-induced hearing loss and also report the importance of cholesterol metabolic pathway in recovery of hearing ability following noise-induced hearing loss. K. Wang et al. (Auditory neural plasticity in tinnitus mechanisms and management) provide a comprehensive review on the epidemiology and classification of tinnitus and discuss the currently available treatments based on valid evidence for their mechanisms and efficacy, which leads to the conclusion of no specific medication for tinnitus treatment at present. J. Cai et al. (A neurophysiological study of musical pitch identification in Mandarin-speaking cochlear implant users) investigate the neurophysiological mechanisms accounting for the musical pitch identification abilities of Mandarin-speaking cochlear implant (CI) users and confirm mismatch negativity is a viable marker of cortical pitch perception in Mandarin-speaking CI users. J. Zhang et al. (Differences in clinical characteristics and brain activity between patients with low- and high-frequency tinnitus) compare the differences in clinical characteristics and brain activity between patients with low- and high-frequency tinnitus (LFT and HFT, respectively) by high-density electroencephalography and report significant changes related to increased gamma in the LFT group and decreased alpha1 in the HFT group. Q. Luo et al. (Effects of soundbite bone conduction hearing aids on speech recognition and quality of life in patients with single-sided deafness) demonstrate the effectiveness of SoundBite bone conduction hearing aids for patients with single-sided deafness by using different measurements both in a quiet and noisy environment. N. Zhang et al. (Cisplatin-induced stria vascularis damage is associated with inflammation and fibrosis) for the first time demonstrate that cisplatin induce fibrosis, inflammation, and the complex expression change of cell junctions in the stria vascularis (SV) and report after cisplatin treatment, tight junction, and gap junction proteins are downregulated. J. Chen et al. (Altered brain activity and functional connectivity in unilateral sudden sensorineural hearing loss) report functional alterations in brain regions in patients with sudden sensorineural hearing loss within the acute period of hearing loss, especially in the striatum, auditory cortex, visual cortex, MTG, AG, precuneus, and limbic lobes. G. Zhu et al. (Hsp70-Bmi1-FoxO1-SOD signaling pathway contributes to the protective effect of sound conditioning against acute acoustic trauma in a rat model) investigate the exact mechanisms involved in the protective effect of sound conditioning (SG) in mammals and report the improvement of SGN survival of SG after noise-induced stress response via controlling mitochondrial function and ROS levels, the involvement of Hsp70/Bmi1-FoxO1-SOD signaling pathway in the protection of SC against acute acoustic trauma (AAT) and the underlying mechanisms of decreased sensitivity to AAT following treatment with SC in rats. Y. Mu et al. (Research progress of hair cell protection mechanism) provide a brief review on the latest research progress about hair cell (HC) protection and regeneration mechanism, including HC development, apoptosis, protection, and regeneration, providing evidence to prevent and treat hearing-related diseases in the future.

3. Hair Cell Regeneration

(S) Zeng et al. (Toxic effects of 3,3'-iminodipropionitrile on vestibular system in adult C57BL-6J mice *in vivo*) report the activation of Notch and Wnt signaling during the limited hair cell self-regeneration ability in the adult mouse utricle after vestibular sensory epithelium damage caused by a single injection of 3,3'-iminodipropionitrile. M. Waqas et al. (Stem cell-based therapeutic approaches to restore sensorineural hearing loss in mammals) provide a brief review to discuss the potential of various stem cells to restore sensorineural hearing loss in mammals and explain the current therapeutic applications of stem cells to regenerate or replace the lost hair cells and spiral ganglion neurons in both human and mouse inner ear. L. Kong et al. (Development and functional hair cell-like cells induced by Atoh1 overexpression in the adult mammalian cochlea in vitro) demonstrate that hair cell-like cell (HCLCs) formation is induced in the adult mouse cochleae by using a three-dimensional cochlear culture system and an adenoviral-mediated delivery vector to overexpress Atoh1 and report these HCLCs share similar functions and developmental process to that of normal hair cells.

4. Spiral Ganglion Neuron Development and Protection

(T) Sun et al. (Atrial natriuretic peptide improves neurite outgrowth from spiral ganglion neurons in vitro through a cGMP-dependent manner) demonstrate that atrial natriuretic peptide (ANP), a cardiac-derived hormone presented in mammalian inner ear, and its receptors are expressed in neurons within the cochlear spiral ganglion of postnatal rat and report the influence of ANP on neurite outgrowth of SGNs via the NPR-A/cGMP/PKG pathway in vitro in a dose-dependent manner. B. Feng et al. (Mitochondrial dysfunction and therapeutic targets in auditory neuropathy) present a brief

review on mitochondrial biological functions associated with spiral ganglion neurons and to discuss the interaction between mitochondrial dysfunction and auditory neuropathies (AN), together with current mitochondrion treatment for sensorineural hearing loss. The authors also suggest to explore pharmaceutical therapeutics to protect mitochondrion dysfunction as a feasible and effective treatments for patients with AN. N. Shen et al. (The influence of cochlear implant-based electric stimulation on the electrophysiological characteristics of cultured spiral ganglion neurons) discover that cochlear implant-based electrical stimulation with 50 μA or 100 μA significantly inhibit the voltage depended calcium current of spiral ganglion neurons in vitro while the firing of action potential remains unchanged. S. Hou et al. (Distinct expression patterns of apoptosis and autophagy-associated proteins and genes during postnatal development of spiral ganglion neurons in rat) for the first time demonstrate the distinct roles of autophagy and apotosis in spiral ganglion cells during specific developmental phases in rats in a time-dependent manner identified with morphological changes, specific marks of autophagy and apotosis, apototic bodies and autophagosomes and autolysosomes, and apoptotic activity. Y. Ni et al. (The regenerative potential of facial nerve motoneurons following chronic axotomy in rats) demonstrate that the greatest regeneration potential of the facial nerve of rats exists within 5 months after chronic axotomy identified by growth-associated protein 43 and Shh signaling pathway may involve in the regeneration.

5. Inherited Hearing Loss

(Y) Qiu et al. (Jervell and Lange-Nielsen Syndrome due to a novel compound heterozygous KCNQ1 mutation in a Chinese family) identify the possible pathogenic cause of Jervell and Lange-Nielsen syndrome by a compound heterozygosity for two mutations c.1741A > T and c.477+5G > A in KCNQ1 gene in a Chinese family using next-generation sequencing. Q. Zheng et al. (An age-related hearing protection locus on chromosome 16 of BXD strain mice) report an age-related hearing protection locus on chromosome 16 at 57~76 Mb with a maximum LOD of 5.7 in BXD strain mice by hearing screening of 54 BXD strains at age between 12 and 32 months. L. Wang et al. (Targeted next-generation sequencing identified compound heterozygous mutations in MYO15A as the probable cause of nonsyndromic deafness in a Chinese Han family) demonstrate compound heterozygous mutations c.3658_3662del (p. E1221Wfs∗23) and c.6177+1G > T are two genetic candidates of congenital hearing loss by targeted next-generation sequencing in a Chinese Han family. T. Cui et al. (Four novel variants in POU4F3 cause autosomal dominant nonsyndromic hearing loss) report four novel variants in POU4F3, i.e., c.696G > T, c.325C > T, c.635 T > C, and c.183delG, as cause of autosomal dominant nonsyndromic hearing loss in four different Chinese families using targeted next-generation sequencing and Sanger sequencing. H. Wang et al. (High frequency of AIFM1 variants and phenotype progression of auditory neuropathy in a Chinese population) investigate 50 patients with auditory neuropathy (AN) by Sanger sequencing or next-generation sequencing and confirm among late-onset AN cases, A1FM1 is the primary related gene, and p.Leu344Phe is the most common recurrent variant. P. Xu et al. (Compound heterozygous mutations in TMC1 and MYO15A are associated with autosomal recessive nonsyndromic hearing loss in two Chinese Han families) report two novel compound heterozygous mutations, i.e., p.R34X/p.M413T in TMC1 and p.S3417del/p.R1407T in MYO15A, in two recessive Chinese Han deaf families by targeted next-generation sequencing and Sanger sequencing confirms the intrafamilial cosegregation of the mutations with hearing phenotype in both families. L. Chen et al. (Transcript profiles of stria vascularis in models of waardenburg syndrome) compare the transcript profiles of stria vascularis of Waardenburg syndrome in Mitf-M mutant pig and mouse models using GO analysis and report significant gene changes in tyrosine metabolism, melanin formation, and ion transportation in both models, as well as a huge difference on the gene expression patterns and function. C. Guo et al. (Hearing phenotypes of patients with hearing loss homozygous for the GJB2 c.235delc mutation) investigate the hearing phenotypes of 244 Chinese patients with hearing loss associated with the homozygous c.235delC mutation of GJB2 and report a significant variation in their binaural hearing loss phenotypes, including severity of hearing loss, and audiogram shapes. S. Chen et al. (A novel spontaneous mutation of the SOX10 gene associated with waardenburg syndrome type II) report a novel heterozygous spontaneous c.246delC mutation in SOX10 in a Chinese family with Waardenburg syndrome (WS) type II, which may produce a truncated protein causing failure activation of MITF gene expression, a key regulator of melanoytic development in WS. X. Yu et al. (Targeted next-generation sequencing identifies separate causes of hearing loss in one deaf family and variable clinical manifestations for the p.R161C mutation in SOX10) demonstrate the heterozygous c.481C > T mutation in SOX10 and the homozygous c.235delC mutation in GJB2 as separate pathogenic mutations in distinct affected family members in a Chinese Han family with hearing loss. X. Chao et al. (Cochlear implantation in a patient with a novel POU3F4 mutation and incomplete partition type-III malformation) report a novel a novel frame shift variant c.400_401insACTC of the POU3F4

gene in a Chinese family with X-linked inheritance hearing loss and the patient carrying this mutation and diagnosed with partition type-III malfunction benefit from cochlear implantation (CI) but the effectiveness of CI declines with the age of patient.

In this special issue of "Hearing Loss: Reestablish the Neural Plasticity in Regenerated Sprial Ganglion Neurons and Sensory Hair Cells," we have articles covering from development, protection, and regeneration of hair cells and spiral ganglion neurons, to genetic information of inherited hearing loss. All studies included present us with not only significant perspectives on the physiology and pathology of cochlea but also the latest advances in revealing the underlying molecular/neural mechanisms of hearing loss and the potential of regeneration of functional HCs and SGNs. We believe this special issue will provide vital innovations for future research in hearing area and contribute to medical interventions and treatments of cochlear damage in SNHL.

Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this special issue.

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