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EDITORIAL

STEM CELLS

Special Series: Stem Cells and Hearing Loss

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Traditionally, *STEM CELLS* hosts exciting series of articles on important issues related to stem cell biology, early development, differentiation, and regenerative medicine. All parts build the complex mosaic, which should help fight debilitating human diseases, including hearing loss (HL). According to the World Health Organization, HL is a major global health problem of pandemic proportions. Four hundred sixty-six million people worldwide have disabling HL, and this number is expected to increase to 900 million people by 2050 (https://www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss). Unfortunately, current treatments for HL are primarily limited to different devices that amplify sounds or directly electrically stimulate the auditory nerve. However, these approaches fail to correct the underlying cause and have substantial performance restrictions. To capture the most recent research, we proudly introduce this new series, which summarizes the stem cell field's progress focusing on HL.[1-5]

In the past 10 years, stem cell technologies have enabled differentiation of human sensory cell types in vitro, providing novel tools to study inner ear development, model disease, and validate various therapeutic approaches.[5] Ethically regulated access to human embryonic and fetal material and human induced pluripotent stem cells (hiPSCs) has allowed the scientific and clinical community to better understand the mechanisms orchestrating normal and abnormal early inner ear development and create conditions for targeted differentiation and genetic editing/manipulation. Animal models and personalized hiPSC lines enable studies of the molecular pathogenesis of inherited HL and HL of unknown etiology. Kempfle et al[1] used a transgenic mouse model to transiently overexpress *Lin28*, a neural stem cell regulator that promotes in vitro proliferation and conversion of auditory glial cells into neurons.[6,7] To study the effects of *Lin28* on endogenous glial cells after the loss of auditory neurons in vivo, the authors produced an auditory neuropathy model. After selective damage of auditory neurons, the upregulation of the *Lin28* in inner ear glial cells induced expression of neural stem cell/precursor cell markers (*Hmga2*, *NeuroD*, *NeuroG*, and *AScl1*) and subsequent conversion into neurons. However, transient postnatal upregulation of *Lin28* after neural damage induced proneural gene expression and reprogramming into cells that expressed neuron-specific marker class III ß tubulin. This work elegantly demonstrates the potential of direct reprogramming of inner ear cells and their conversion into desirable sensory neurons as a regeneration therapy for neural replacement in auditory neuropathy. Marta Roccio[2] summarizes the generation of sensory cells through the directed differentiation of pluripotent stem cells, as well as the latest "cell conversion approaches."[2] Undoubtedly, the improvement of both strategies necessitates the improvement of suboptimal in vitro growth conditions. For instance, to trigger successful differentiation and ectoderm induction toward inner ear cells, the mesendoderm fate needs to be blocked with inhibitors of TGFβ and Wnt signaling.[8,9] Applying directed differentiation protocols in 3D culture, or organoids, has been recently successfully translated to human pluripotent stem cells.[10,11] These protocols work by generating 3D aggregates of pluripotent stem cells, promoting the differentiation by providing exogenous BMP ligands.

In contrast, the otic fate is promoted using bFGF first, subsequently a Wnt signaling agonist, and the niche-specific extracellular

matrix (ECM). The pivotal role of ECM in the fate determination of inner ear progenitor cells was highlighted by Xia et al.[4] The authors concluded that the biological behavior of inner ear progenitor cells in an encapsulated culture system is critically dependent on the mechanical cues from the ECM.[4] The authors nicely show that ECM promoted the survival and expansion of progenitor cells inducing the accumulation of Ras homolog family member A (RhoA), an essential factor in the maintenance of stem cells and their differentiation,[12,13] which causes the polymerization of actin cytoskeletons. These changes, in turn, resulted in increased Yes associated protein (YAP) nuclear localization and enhanced expansion of inner ear progenitor cells, partially through upregulating the canonical Wnt signaling pathway. Herewith, the authors provided the first characterization of the action of YAP as mediators of mechanotransduction signaling to promote the proliferation of inner ear progenitor cells.

Considering age-related, acoustic, ototoxic, and genetic insults, which are the most frequent causes of irreversible damage of inner ear hair cells and spiral ganglion neurons,[14,15] new methods of genome editing could bring additional opportunities to understand the pathogenesis of HL and identify novel therapies.[3] In this review, Stojkovic et al[3] summarized the CRISPR/Cas9 platform and its potential to accelerate basic and translational research in HL. One of the work's conclusions is that stem cells' usage for therapeutic purposes still faces several significant obstacles, particularly concerning efficiency, efficacy, and safety.[3] Finally, for therapeutic purposes, cultured stem cells must be precisely integrated within their microanatomical niche after being introduced into the inner ear.[5] Whether this will be done via intraperilymphatic or intraendolymphatic injection approach, technical challenges remain,[16-20] concerning the following: (a) how to reach the ultimate destination, the Rosenthal canal, (b) how to cross the tightly sealed cochlear scala media or break the tight junction complex between hair cells and supporting cells, (c) how to surpass the endolymph, which contains a high level of potassium, and (d) how to define the balance between the intrinsic factors (stage of differentiation of grafted cells) with the extrinsic factors (host background and means of delivery). These questions are justifiably raised by Zine et al[5] and request intensive research and technical improvements to tackle HL successfully.

Nevertheless, we are confident that the progress achieved in the past decade will unceasingly continue to flourish. Meanwhile, we are witnessing the multistep strategies, including large-scale postmortem studies with a comprehensive meta-analysis of genome, epigenome, and transcriptome of patients with specific types of HL. Banks of undifferentiated and differentiated patient-specific hiPSCs, enhanced organoid models by additional bodily systems under dynamic microfluid chips, and many other emerging approaches will provide powerful tools for accelerating drug and/or cell therapies. As the *STEM CELLS* journal remains curious and determined to push these research frontiers, we will be thrilled to recurrently share and celebrate with you the ground-breaking work in the field of HL. We hope that you enjoy reading this exciting series and continue to contribute to the joint mission of improving life quality for millions of people with HL worldwide.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

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