



Cell Therapy Development in Hearing Loss

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Abstract

Since the potential of stem cells (SCs) in treating diseases is superb, it is believed that the use of SCs is a promising therapeutic approach in hearing damage. More than 250 million people of worldwide are born deaf. The deaf hearing generally originate from defect on sensory receptors (hair cells) or nerves associated with them (spiral ganglion neurons). Hair cells in some animals such as fish, amphibians and birds can regenerate or replace by new cells, but damage to the hair cells in mammals are not being replaced through cell division or regeneration in the inner ear. Cell therapy for hearing loss is still several years away, but researches opens up possibilities for restoring hearing in the future. Here we review developments in cell therapy approach in treatment of hearing loss.

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INTRODUCTION

Hearing loss is the most prevalent sensory defect. Hearing mainly depends on hair cells and their associated spiral ganglion neurons. Loss of hair cells and spiral ganglion neurons in the inner ear cause hearing loss in humans (1). At present, no effective treatment exists to repair the sensory structures in the inner ear. There is no precise treatment for sensorineural hearing loss. Only rehabilitation instruments such as hearing aids are used for approximate compensation of these disorders. However, in cases where hair cells are completely destroyed, cochlear implants may provide hearing (2). The main task of hair cells within the cochlea of the inner ear is conversion of mechanical vibrations of sound into electrical impulses that reach the brain through the auditory nerve (3). When mechanosensitive hair cells are damaged, an individual experiences a reduction or loss of hearing. Obviously, sometimes when the cause is eliminated, the cells rebuild and continue their activities, but in most cases there is no such possibility and hearing loss becomes permanent. Unlike hair cells in lower vertebrates such as birds and fish, auditory hair

cells of mammalian do not spontaneously regenerate (4).

Using SCs to generate hearing cells is a promising therapeutic strategy in cases with hearing damage. It has been discovered that SCs can differentiate to hair cells. In addition, new evidence in animal models indicates that suitable stimulation of SCs in the inner ear induce self-renewal and differentiation into auditory sensory cell (5). Advances in stem cell therapies may provide effective treatment for irreversible damage to auditory system. Researchers try to develop techniques to generate hair cells in the laboratory and graft them into the ear. In this review, the applications of SCs as treatment for hearing loss are discussed.

STEM CELL APPLICATIONS

In recent years, the potential therapeutic role of SCs has been considered in the treatment of various diseases such as diabetes, parkinson, alzheimer and cardiac diseases (6-9). By definition; SCs have the ability for self-renewal, differentiation and the creation of other cell types addition to themselves (10).

The main differences between several groups of SCs are the source of cells that can be obtained from them. There are two main types of SCs. The embryonic stem cells (ESC) exist in the blastocyst inner cell mass and the adult SCs that found in various types of tissue such as bone marrow and blood (11, 12). Recently, stem cell transplantation has been regarded for their repair activity in hair cells and auditory neurons damage. Transplanted cell, including adult stem cell and ESCs were survived for ten weeks after transplantation. Further research showed that implanted cells have the capability to match with the host auditory system structurally, and can even replace spiral ganglion neurons. As well, neuronal differentiation of implanted stem cell was reported previously (13, 14).

GENERATION of HAIR CELLS FROM EMBRYONIC STEM CELLS

Researchers have been attempting to convert SCs to the inner ear mechanosensitive hair cells and sensory neurons. Studies have been shown stepwise differentiation of sensory epithelia from murine ESCs (15, 16). Li. et al reported that inner-ear progenitors have been produced from mouse ESCs in the culture. These progenitors have marker genes that index them as hair cells (17). These ES-cell-derived progenitors express *Math1* (mouse atonal homolog 1) and *Brn3.1*, which have an important role in the generation and maturation of hair cells (18, 19). Koehler et al. have demonstrated that in vitro differentiation of hair cells from ESC possess stereocilia bundles and a kinocilium. Moreover, these stem-cell-derived hair cells have functional characteristics of natural inner ear hair cells and make synaptic connections with sensory neurons that have also originated from ESCs in vitro (16). Other experiments have revealed human embryonic SCs differentiated to inner ear hair cell-like cells in the optimized condition in culture (20).

GENERATION of HAIR CELLS FROM ADULT STEM CELLS

Today, adult SCs isolated from several tissues can be deployed for treatment approaches in the hearing defects. It is known that fibers regrow in the peripheral nervous system after tissue injury. Regrowth of olfactory neurons has been reported to occur spontaneously. In contrast, replacement of lost neural cells has rarely been demonstrated. Although there is little normal turnover in the central nervous system, cells can be recruited to replace lost neurons (21).

Findings have shown that bone marrow mesenchymal stem cells (BMSCs) can differentiate into hair cells. Differentiated cells express hair cells markers and exhibit morphological properties of hair cells stereociliary bundles. Adult stem cells also have been used to deliver therapeutic molecules and gene to the inner ear (22).

BMSCs also have the potential to produce auditory neurons in vitro and in vivo (23, 24). Adult SCs derived from the olfactory neuroepithelium has a differentiation potential to generate hair cells (25). Neural SCs survive in drug-injured mouse inner ear for several weeks after transplantation and exhibit markers of neuron and hair cell (26, 27).

GENERATION of HAIR CELLS FROM ENDOGENOUS STEM CELLS

One promising approach for the sensorineural hearing loss treatment includes activation of endogenous SCs or genetic targeting of surviving supporting cells (28). While several studies have demonstrated delivery and survival of ES and adult SCs in normal and damaged inner ear in vivo, in some cases, a therapeutic effect has been reported (29, 30). Few studies have revealed differentiation and regeneration of resident SCs. It has been shown resident SCs in the mouse utricle can be isolated and propagated in culture. In addition to the utricle in the vestibular system, cochlea in neonates has endogenous SCs (17, 31).

Previous findings revealed that trans-differentiation of supporting cells to hair cells could play a role in regeneration, but this ability was limited to neonatal mice and occurs on the first postnatal day. Molecular aspects such as Atoh-1 expression and notch pathway inhibition have an important role in the conversion of supporting cell to hair cell (32, 33).

DO STEM CELL DERIVED HAIR CELL ARE FUNCTIONAL?

Stem cell therapy is effective in hearing loss when stem cell-derived progenitors differentiate to hair cells with appropriate morphology, electrical activity and capacity for appropriate innervations with target tissues (34). Indeed, stem cell-derived neurons ideally need to extend peripheral projections directed toward the sensory hair cells in the organ of corti, and toward neurons in the cochlear nucleus (35). Expression of synaptic markers such as synapsin1 and synaptophysin have been observed in the afferent dendrites of early postnatal auditory neurons when they reform their connections with hair cells in vitro (36, 37). Expression of synapsin1 was reported in neural stem cell -derived neurons at the nerve ending near the hair cells in co-culture models (38, 39)

Therefore, the expression of synapsin1 is considered as an indicator of stem cell-derived auditory neurons capacity to regenerate or form potentially functional synapses with hair cells (40). Several previous studies have demonstrated that human ESC has the capacity to make new synapses with hair cells in the auditory system (38, 41). Nayagam et al. have observed presynaptic formation between the peripheral projections of auditory neurons and hair cells in early postnatal cochlear explants cultures and adult cochlea (42). Recent in vivo studies reported that partial hearing function restore can be achieved following the transplantation of early stage human ESC-

derived otic neural progenitors into deafened gerbil cochleae (42, 43).

CONCLUSION

Stem cell based therapy is possible for restoring or replacing of hair cells. Generation of functional auditory hair cells is a main aim of stem cell researchers, but there are obstacles in this way, and it requires further studies on signaling cascades and molecular aspects involved in hair cell regeneration.

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CONFLICT of INTEREST

The authors declare no conflict of interest.

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