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Review Article

Approaches of auditory hair cells induction from stem cells

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Abstract

Hair cells are the sensory epithelial cells of both the auditory and the vestibular systems in the inner ear of all vertebrates. Auditory hair cells are located in the organ of corti on a thin layer of basement membrane in the cochlea of the inner ear. Damage to hair cells decreases hearing sensitivity. When these delicate hair cells in the cochlea are damaged, sound signals cannot be sent to the brain. In general, damage to the mammalian inner ear, is not returnable. In fact, a key goal in the treatment of sensorineural hearing loss is to find appropriate procedures to replace the missing hair cells. Cell therapy is one of the treatment options for hearing loss. In this regard, studies focus on ways which hair cells can be provided from exogenous and endogenous stem cells. This review identified ways to induce auditory hair cells regeneration from stem cells as the potential therapeutic approaches for the hearing loss.

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Introduction

The inner ear is comprised of two main components including cochlear and vestibular systems. Cochlea is a bony, snail like and fluid-filled structure. Auditory and vestibular systems have hair-like cells that are the sensory receptors. The sensory organs of the inner ear serve to detect sound and balance. Auditory hair cells are located in the organ of corti within the cochlea of the inner ear (1, 2). Since the mechanical energy of sounds is very weak, cochlea amplifies received vibrations. Hair cells in the cochlea are responsible for converting mechanical vibrations of sound into the electrical currents which activate the bipolar spiral ganglion neurons (SGNs). Nerve impulses are transmitted to the brain through the auditory nerves (3). Dysfunction of the sensory cells and auditory nerves in the inner ear is known as sensorineural or nerve-related hearing loss. Cochlear implants use as an option for treatment of hearing impairment. This devise acts by direct electrical stimulation of SGNs (4). In addition, use of biological approaches for regeneration of mammalian cochlear hair cells provides a more comprehensive treatment for the hearing loss. For example, therapies via genetic engineering of viral vectors or stem cells transplantation have been proposed for regeneration of the damaged cochlea (5, 6). For cell therapy, several sources of adult and embryonic stem cells have been used for the replacement or restoration of injured hair cells [7]. Here, effective approaches, which can induce stem cells differentiation into cochlear hair cells or SGNs, are highlighted.

Possible biological approaches for hair cell induction

Damage to hair cells and SGNs in the inner ear can lead to hearing impairment or deafness in human. Mammalian cochlear hair cells cannot be spontaneously replaced or regenerated which led to permanent hearing loss. Most of the researches try to find the therapeutic strategies to cure deafness (8). Today, biotechnological methods are developing into the treatment for auditory sensory loss in the inner ear (9). Cochlear hair cells formation regulated by differentiation and trans-differentiation mechanisms, which are influenced by combining extrinsic and intrinsic factors (10). Between the contributing factors, formation of SGNs and sensory hair cells is mainly dependent on expression of basic helix-loop-helix (bHLH) transcription factor, Atoh1 (Atonal homolog) or Math1 during development. Knockout of Atoh1 gene in mice leads to absence of both cochlear and vestibular differentiated hair cells (11), while the gene therapy through viral mediated delivery of Atoh1 in mice results in ectopic hair cells formation (12,13). In addition, neurotropic factors play an important role in inner ear development. Studies have been demonstrated importance of neurotrophic factors such as brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and their receptors during inner ear formation and innervation development (14-17). BDNF and NT-3 are expressed by hair cells and supporting cells that are necessary for the inner ear innervation during normal development (18, 19). Studies have been shown that neurotrophins enhance survival and function of SGNs in the deafened cochlea in animal model (20).

As well as, recent research supports that cell therapy can be considered as a promising alternative for treating variety of degenerative diseases (21, 22). Possibilities of cells therapies for hair cells regeneration are under investigation. Since sensory hair cells have been a key issue for studies of the inner ear regeneration, we focus on main strategies for auditory hair cells induction from the exogenous and endogenous stem/ progenitor cells.

Strategies to induce hair cell differentiation in stem cells

Researchers develop several strategies for inducing exogenous and progenitor cells into the mechanosensitive hair cells and auditory neurons regeneration in the inner ear (23, 24).

Growth Factors

Growth factors can stimulate cellular survival, proliferation and differentiation, and were studied in many sensory hair cell induction conditions (25, 26). Previous works provide evidence for the existence of resident stem cells in the cochlea. Researchers isolated stem cells from the human fetal cochlea and cultured them in the conditioned medium includes some growth factors like basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), insulin-like growth factor 1 (IGF-1), and retinoic acid. They have been reported that these cells differentiate into cells, which have morphological characteristics of hair and nerve cells. As well, they express hair cells specific genes and proteins such as NESTIN, GATA3, SOX2, and PAX2. However, these hair cells were not completely functional and did not send appropriate projections to the target tissues (27, 28).

In addition, Shinohara et al. have been demonstrated that BDNF and ciliary neurotrophic factor (CNTF) intervention increase SGNs survival and function in a deaf guinea pig model (29). It has been reported that glia cells derived neurotrophic factor (GDNF) administration to the inner ears of deafened animal has a protective effect on SGNs survival and electrical responsiveness (30, 31).

Co-culture techniques

Stem cells co-culture techniques have provided efficient strategy to facilitate neural differentiation. The differentiation of stem cells into the auditory neuron lineage was promoted by co-culture with auditory neurons or hair cell explants isolated from rat pups on the fifth postnatal day (32). Co-transplantation of mouse embryonic stem cells and a neuronal co-graft consisting of dorsal root ganglion impact on stem cells differentiation in guinea pig cochlea (33), as well, Taura et al. have revealed induction of hair cells from pluripotent stem cells when were stimulated by co-culture with the mouse utricle stromal tissue (34). It has been shown that co-culture of cochlear explants associated with neural progenitors derived from human embryonic stem cells can lead to direction of neural process toward the sensory hair cells in cochlear explants in an in vitro condition (35). Several neural stem cell derived neurons expressed synapsin1 at the nerve ending close to hair cells in co-culture models (36-38). Gunewardene et al. have also found that co-culture of human induced pluripotent stem cells (hiPSC) with hair cells in the earliest stages of hair cells development show an increase in number of synaptic formation in comparison with co-culture of hiPSC-derived neurons at the late stage of hair cells differentiation (39).

Gene Therapy

Atoh1, the bHLH transcription factor homolog of the drosophila atonal gene, is necessary for hair cells differentiation during inner ear development. Math1 overexpression in the cochlea can lead to new hair cells production in both in vitro and in vivo assay (40, 41). Liu et al. have been reported that Math1 overexpression can induce mechanosensitive sensory hair cells differentiation from VOT-E36 cells, which were dissected from mouse ventral otic epithelial cells around the embryonic day 10.5 (42). Han et al. have been shown that survival and differentiation of embryonic neural stem cells into hair cells following transplantation into guinea pigs cochlea potentiates by Atoh1 gene transfer [43]. Moreover, Yang et al. have revealed that induction of inner ear hair cell-like cells from Math1-transfected cells of the lateral epithelial ridge of cochlea occurs through the process of trans differentiation without cell division (44). Another research has shown that majority of neural stem cells were placed into the modiolus of the deafened mouse cochleae differentiate into a glial cell and only a small percentage produce neurons. Treatment of these cells with neurogenin (a family of bHLH transcription factors) prior to transplantation can induce neural differentiation (45).

Conclusion:

Although use of biotechnological approaches for the inner ear hair cells induction from stem cells are developing into the regeneration of the missing hair cells, but future studies are needed to identify critical strategies to stimulate key mechanisms involved in functional hair cell production from the exogenous and endogenous stem cells.

Conflict of Interest:

The authors report no conflict of interests.

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