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Research progress of neural stem cells in the treatment of sensorineural hearing loss

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Abstract: *Sensorineural hearing loss (SNHL) is caused by degeneration of hair cells or auditory neurons; adult mammalian cochlear hair cells have no self-repairing ability, and once damage occurs, it will be permanent. Neural stem cells (NSCs) transplantation for treating inner ear diseases has a broad application prospect. Firstly, they can be induced to differentiate into hair cell-like cells to complement or replace damaged hair cells. Second, neural stem cell-derived cells can be integrated into the inner ear microenvironment and interact with host cells to promote inner ear repair. However, the main challenges of neural stem cell transplantation therapy are to improve the survival rate of transplanted cells and to ensure their proper differentiation. Continuous research progress is expected to advance this field and bring new hope for treating inner ear diseases. The aim of this review is to summarise the progress of this field of research, with a view to providing theoretical foundations and research directions for future clinical applications.*

Keywords: *Sensorineural hearing loss, Neural stem cells, Cell transplantation*

1. Introduction

There are many causes of Sensorineural hearing loss (SNHL), the main ones being trauma, exposure to ototoxic drugs, genetic mutations, viral infections, inflammation, or endolymphoedema [1]. SNHL is caused by organic lesions of the spiral apparatus, the auditory nerve, and the auditory center that impede the perception and analysis of sound or affect the transmission of sound information, resulting in various types of hearing loss or hearing loss [2]. Currently, the main clinical and scientific treatments for sensorineural hearing disorders include medication, gene therapy, cochlear implantation (CI), stem cell replacement therapy, and hearing aids[3]. However, cochlear implantation itself is traumatic to the inner ear, the long-term effects of which have yet to be evaluated[4], and the loss of spiral neurons reduces the effectiveness of hearing aids and cochlear implants, which depend heavily on the degree of preservation of the Spiral ganglion neuron (SGN)[5]. Therefore, the current use of cochlear implants and hearing aid wear does not treat the root cause of sensorineural deafness. Stem cells replacement therapy, on the other hand, refers to the in vitro directed induction of stem cell differentiation into specific cell types and transplantation of the directed induced differentiated specific cells into the diseased organs to replace the diseased and dead cells so as to achieve the purpose of treating the disease[6]. Currently, the main types of stem cells used for inner ear cell repair studies are embryonic stem cells, neural stem cells, mesenchymal stem cells, inner ear stem cells, and induced pluripotent stem cells [7]. NSCs are cells with self-renewal ability, continuous division and proliferation, and multidirectional differentiation potential, which have shown remarkable application prospects in several therapeutic fields. NSCs transplantation therapy, as an innovative therapeutic approach, has been widely used in the treatment of a variety of diseases. In this article, we will focus on the research progress of NSCs in the treatment of sensorineural deafness, with a view to providing new ideas and strategies for the treatment of this disease.

2. Biological characterization of NSCs

2.1 Concepts and characteristics of NSCs

NSCs are a type of stem cell that is undifferentiated and present in the brain and spinal cord. Like other stem cells, NSCs has the characteristics of division proliferation and diverse differentiation and has

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the ability of self-renewal, which can be differentiated into neurons, astrocytes, oligodendrocytes, and other types of neural tissue cells, which are specialized stem cells [8].

NSCs have the following characteristics[9]: First, they have the ability to self-renew, which means that they can divide and proliferate continuously under the right conditions. In primary culture, NSCs can form stem cell clones within 24 hours and grow rapidly in the following days. Second, NSCs have multidirectional differentiation potential, which means that they can differentiate into a variety of neural cell types, including neurons, astrocytes, and oligodendrocytes. Third, NSCs are able to secrete a variety of cytokines to stabilize the surrounding microenvironment. Fourth, NSCs are able to migrate directionally in the direction of developmental cords during development, and transplanted NSCs can respond to neurogenic signals from the lesion site, migrate toward the lesion site, and differentiate into specific cells. Fifth, NSCs are responsive to injury and disease, and when the central nervous system is damaged, endogenous NSCs can be activated to participate in the repair process of the organism. Finally, NSCs have low immunogenicity, which means that they are not prone to cause immune rejection, which is conducive to improving the success rate of transplantation and the cure rate of the disease.

2.2 Mechanisms and advantages of NSCs therapy for sensorineural deafness

When exploring stem cell therapies in the field of the inner ear, the focus has been on two main strategies: activation of endogenous stem cells to promote their self-proliferation and directed differentiation and introduction of exogenous stem cells for cell replacement and functional recovery. However, the application of endogenous stem cell therapy also faces a series of challenges, including (1) the precise mechanism to regulate stem cell self-renewal; (2) ensuring the precision and efficiency of stem cell differentiation to the desired cell type; (3) as well as facilitating the effective integration and functional reconstruction of transplanted stem cells in the host. Therefore, the transplantation of exogenous stem cells has become a current research focus[10].

When adult NSCs are implanted into the cochlea partially embedded in the cochlear epithelium, some of the cells can differentiate into neurons, hair cells, or supporting cells. The NSCs have good tissue integration, and under the influence of neurogenic signals from the diseased hair cells, the NSCs migrate to the site of neuropathy and subsequently differentiate into specific cells (e.g., hair cells, neurons, etc.), so that auditory function is restored [11]. The advantages of NSCs are as follows:

(1) The common origin of inner ear cells and NSCs from ectoderm and neural precursor cells, and the fact that auditory follicle cells are subject to meristematic factors during development, which allows the inner ear cells and transplanted NSCs to be receptive to neuronal signaling at later stages of development [7].

(2) Adult NSCs, as an important resource in neuroregenerative medicine, are derived from the patient's own characteristics, which allows them to be safely transplanted back into the patient's brain tissue after in vitro culture and expansion. This characteristic effectively avoids the occurrence of immune rejection and offers the possibility of solving the immune and ethical obstacles that have long restricted the application of NSCs. Through personalized stem cell sources, the application of adult NSCs can not only promote the recovery of a patient's neurological functions but also has the potential to solve the immune rejection and ethical problems that have restricted the application of NSCs, which may be an important way to realize the treatment of SNHL in the future[12].

(3) It is also noteworthy that NSCs in vivo can be regulated by cytokines in the local microenvironment, and differentiate in the direction of the missing cells in the lesion, and participate in the repair of neural tissue structures [13]. This mechanism provides new ideas for the treatment of neurodegenerative diseases and lays the foundation for the development of neuroregenerative medicine.

3. Current analysis of NSCs therapy for sensorineural deafness

Ideally, the stem cells used for transplantation should effectively replace damaged hair cells and neurons in the inner ear. In order to regenerate the inner ear during hearing restoration, the transplanted cells should survive in the inner ear and be accurately localized in anatomically and functionally correct locations. Therefore, ensuring the survival, precise localization, and on-demand differentiation of transplanted stem cells are crucial aspects in the treatment of SNHL with stem cell transplantation.

In the following discussion, we will analyze in depth the injection site which are the effects on stem cell transplantation for SNHL.

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3.1 The choice of stem cell transplantation route after SNHL

Ideal transplantation sites should be characterized by minimal damage to the cochlear structure and implantation as close to the target site as possible, allowing for a wide distribution of donor cells throughout the auditory organ[14]. Current approaches to stem cell transplantation into the inner ear include round window(RW) injections, cochlear wall(CLW) injections, posterior semicircular canal injections, internal auditory canal injections, scala tympani(ST) injections, and modiolus injections [15]. The success of stem cell transplantation depends heavily on the precision of the surgical design, which not only ensures the accuracy of the cell injection but also minimizes surgical trauma and hearing damage [16]. In order to re-establish auditory circuits, functional connections to hair cells and cochlear nuclei are essential, and by optimizing the surgical approach, the likelihood of improved auditory brainstem response (ABR) can be increased. The location of cell transplantation has a significant effect on their projection in the auditory conduction pathway [17]. When performing the procedure of stem cell transplantation, it is critical to ensure that these cells can accurately and efficiently travel to the target area in the cochlea without adversely affecting the function and normal anatomy of the inner ear or other organs, so it is crucial to explore the delivery routes of the stem cells that can fulfill the above conditions.

The ST injection route causes less inflammation, and the opening at the ST causes less nerve damage and has a little postoperative hearing effect, but the ST injected cells are less likely to migrate to the bony spiral canal and are therefore too ineffective for SGN replacement therapy[14]. It has been shown[18] that when NSCs transduced with neurogenin 2 were injected through the drum step, the cells adhered to the outside of the bone spiral canal and did not enter the bone spiral canal. He et al.[19] injected NSCs derived from the olfactory bulb of mice through the drum step, and GFP-positive cells were seen in the vestibular and drum steps, with very few entering the bony spiral canal. Because drum step injection does not allow the transplanted cells to effectively reach the vicinity of the SGN, it is not an effective treatment for patients with SGN injury.

In studies, the CLW injection technique has been shown to be accurate and effective, but this method may also provoke hearing loss [15]. One researcher injected NSCs derived from the mouse olfactory bulb through the lateral wall of the cochlea and detected markers only in the CLW, basilar membrane, and Rosenthal's canal in the vicinity of the injection site, which suggests that the CLW route is quite accurate, but the animals had significantly higher ABR thresholds postoperatively, which suggests that this route may cause some hearing damage in rats [5]. Iguchi et al[20] transplanted cells through the lateral wall of the cochlea in mice, and audiometry at three days postoperatively showed a significant increase in cochlear ABR thresholds with no apparent recovery. Moreover, transplantation to the middle level via the lateral wall approach may damage the vascular pattern and cochlear blood supply. Thus, cochlear lateral wall pathways can disrupt cochlear function by altering the cochlear intra-ionic environment and/or endolymphatic potentials [21].

RW injection has the advantages of short operation time, maintaining the normal anatomy of the cochlea, mild inflammatory damage, and less bleeding, but it is technically difficult, prone to ectolymphatic leakage, and the grafted cells are confined to the base of the cochlea only, rather than spreading into the membrane labyrinth [22,23]. Stover et al. [24] demonstrated that the injection of NSCs through the RW did not cause complications such as middle ear infections and vestibular dysfunction. Fu et al.[25] injected NSCs through a RW and observed a considerable number of transplanted NSCs in the endolymphatic space attached to the peritoneum, but no transplanted cells were seen in the Corti, the spiral ligament, suggesting that the round-window injection method may lead to a limitation of the cell migration site.

The Auditory nerve (AN) Stem Path is primarily designed to replace degenerated spiral neurons and can be combined with cochlear implantation. The introduction of cells into the AN has been shown to be more effective with transplanted cells, which can survive for up to 3 months, migrate a considerable distance from the injection site, and form a process of contact with the hair cells, but the pathway allows for less migration to the bony conduit[26,27]. Direct injection into the cochlea may be more invasive, but there is better integration and less dispersion, which may allow the grafted cells to reach the vicinity of the SGNs more efficiently, and the anatomical barriers of the external lymphatic space and the cochlea may act as a barrier to migration, so cochlea injections may be the preferred approach.

3.2 Studies to promote NSCs differentiation and survival

(1) Combination of related drugs promotes differentiation of NSCs: Wang et al. [28] established a sodium salicylate model of deafness and combined NSCs transplantation with a kidney tonic and blood

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activating formula, and the results showed that the therapeutic improvement effect of the combination of the two was superior to that of the NSCs transplantation group, suggesting that kidney tonic Chinese medicines are conducive to the proliferation and differentiation of NSCs. Edaravone has the effect of attenuating the toxicity of excitatory amino acids and inhibiting cell apoptosis, which can promote the good differentiation of NSCs[29]. Zhou et al[30] demonstrated that a combination of stem cell transplantation and traditional Chinese medicine (TCM) intervention in noise-induced sensorineural deaf guinea pigs was effective in increasing the survival rate of cochlear stem cells as well as the proportion that differentiated into hair cells.

(2) Co-transplantation with other cells: In a study by Zeng et al [31] on the transplantation of NSCs combined with olfactory ensheathing cells (OECs) in the cochlea of SNHL model rats, it was pointed out that the results of inducing the proliferation and differentiation of NSCs from in vitro to sensory neurons were not optimistic enough, and that microenvironmental deficiencies were an important factor in the failure of transplantation. One of the possible reasons for the inappropriate post-transplantation microenvironment, in which most NSCs differentiate into glial cells instead of the desired neurons and are at risk of becoming teratomas, is that NSCs need to be continually induced by brain-derived neurotrophic factors, neurotrophins, and other mediators during their differentiation. On the other hand, OECs can secrete BDNF, NT-3, NT-4, and other trophic factors, which can provide a microenvironment for the remodeling and regeneration of neuronal axons and have a supportive and protective effect on the damaged nerves. Therefore, the combined transplantation of the two can promote the targeted proliferation and differentiation of NSCs to the damaged area on the one hand and provide a suitable microenvironment for cell growth on the other hand.

(3) Other factors: Cytokines (e.g., b FGF, EGF, PDG, BDNF, interleukins, lymphocyte inhibitory factor, insulin-like growth factor), neural cell adhesion molecules (N-CAMs), bone morphogenetic proteins (BMPs), the membrane protein AN2, retinoic acid (RA), thyroxine (T3) play an important role in NSCs-induced differentiation [21]. Supplementation of BDNF and chondroitinase ABC enzyme (ChABC) have shown further progress in improving survival and migration, respectively [32].

4. Summary and outlook

Although the differentiation efficiency of NSCs has been effectively improved in recent years by drug combination and other strategies, there are still many pressing problems in exploring the path of cochlear cell repair and regeneration. For example, the high potassiumion concentration and tight junction barrier inside the cochlea pose a serious challenge to the survival of exogenous stem cells. Therefore, creating a more suitable environment for survival in the cochlea is particularly critical. By using a combination of these strategies, researchers hope to create a more suitable survival environment to support cochlear cell repair and regeneration and ultimately achieve the therapeutic goal of hearing recovery. With the continuous advancement of science and technology, we have reason to believe that these challenges will be gradually overcome in the future, bringing new therapeutic hope to patients with hearing loss. In addition, because the cochlea is located in the deep part of the skull, its structural complexity makes even the cochleostomy or round window approach, which is commonly used in CI surgery, suffer from an imbalance of cochlear homeostasis or structural damage that may result from the surgical procedure, which may lead to complications such as residual hearing loss and vertigo. Therefore, cell transplantation still faces great risks and challenges in clinical applications.

Looking ahead, research on the optimization of the cochlear microenvironment, the timing of NSCs transplantation, and the enhancement of the survival rate and differentiation efficiency of NSCs through gene therapy or drug therapy still need to be carried out in depth. Meanwhile, considering the risk of tumors that may be triggered after stem cell transplantation, exploring appropriate stem cell transplantation sites and methods to control the growth of stem cells in order to improve the safety of NSCs transplantation will also be the focus of future research.

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