REVIEW PAPER

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Comparison of Three Types of Mesenchymal Stem Cells (Bone Marrow, Adipose Tissue, and Umbilical Cord-Derived) as Potential Sources for Inner Ear Regeneration

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Abstract

In this review, we compared the potential of mesenchymal stem cells derived from bone marrow, adipose tissue and umbilical cord as suitable sources for regeneration of inner ear hair cells and auditory neurons. Our intensive literature search indicates that stem cells in some of adult mammalian tissues, such as bone marrow, can generate new cells under physiological and pathological conditions. Among various types of stem cells, bone marrow-derived mesenchymal stem cells are one of the most promising candidates for cell replacement therapy. Mesenchymal stem cells have been reported to invade the damaged area, contribute to the structural reorganization of the damaged cochlea and improve incomplete hearing recovery. We suggest that bone marrow-derived mesenchymal stem cells would be more beneficial than other mesenchymal stem cells.

Keywords: mesenchymal stem cells, hearing loss, regenerating inner ear, hair cell.

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INTRODUCTION

Hearing loss is one of the most prevalent disabilities. Approximately over 5% of the world's population-360 million people-suffer from disabling hearing loss (328 million adults and 32 million children). Hair cells and spiral ganglion neurons are usually damaged in most people with hearing loss. Hearing loss is also the most common sensory disorder in humans. Recent developments in stem cell technology have offered new opportunities to treat deafness. The present review seeks to investigate different types of mesenchymal stem cells (MSCs) (derived from bone marrow, adipose tissue, and umbilical cord) as potential sources for regeneration of inner ear cells. Since cells with stem/progenitor properties appear to be no longer present in the mammalian cochlea three weeks after birth[1,2], this work mainly focuses on the utilization of exogenous cells and their differentiation into the missing auditory cells. A wide range of stem/multipotent progenitor cells have been tested for their capability to differentiate toward inner ear sensory cells *in vitro* and *in vivo*[3-5]. Several groups have shown the possibility of mouse embryonic stem cells (mESCs) to differentiate into hair cells[6,7] and auditory neuron-like cells[8-11]. Differentiation methods to induce hair cell-like cells from ESCs or induced pluripotent stem cells (iPSCs) seem to be effective but require great proficiency[6,7]. The beneficial phenotypic plasticity of ESCs is always challenged by ethical questions on derivation and use of these human cells and other concerns such as the likelihood of immune reactions and tumor formation[12-14].

Alternative sources are mesenchymal tissues. Indeed, inner ear hair cells have been successfully generated *in vitro* by a mesenchymal-to-epithelial transition[15]. Considering the potential of MSCs to differentiate into neural type cells, these cells would be good candidates for regenerative cell-based therapies[16-20]. Multipotent MSCs are capable to restore damaged mesenchyme via differentiation into mature cells of bone, cartilage, muscle, fat or fibrous tissues. MSCs exhibit remarkable self-renewal capacity and the ability to differentiate not only into osteoblasts, chondrocytes, adipocytes, myocytes, but even also into neurons *in vitro* and *in vivo*[21] and therefore, MSCs have been successfully used in otorhinolaryngology. MSCs produce bioactive anti-inflammatory agents and support regeneration of injured tissues[22-25]. Among the various types of stem cells, bone marrow-derived MSCs (BMSCs) are one of the most promising candidates for cell replacement therapy.

Biological characteristics of MSCs

MSCs are characterized with self-healing, self-renewing, highly proliferative, differentiation potential, and adherent growing features. Despite expression of CD105, CD73 and CD90, these cells do not express CD45, CD34, CD14, CD19 and HLA-DR surface molecules. MSCs can be induced to differentiate toward bone cells, fat cells, cardiac muscle cells, nerve cells and epithelial cells transformation[26,27]. And the resulting cells must be characterized via evaluation of above mentioned markers.

Growth factors to induce BMSCs differentiation for regeneration of inner ear cells

In the presence of specific growth factors such as Sonic hedgehog and retinoic acid, BMSCs have the capacity to differentiate into sensory neurons[27-29]. In a recent study on BMSCs, the inner ear specific genes such as *NF-M, neurog1, gluR4, neuroD, calretinin, neuN, tau*, and *GATA3* were up-regulated in the presence of bone morphogenetic protein 4 (BMP4), demonstrating their capacity to differentiate into auditory neuron-like cells *in vitro*[30]. Rat BMSCs cultured in a medium containing glial cell-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) for 14 days were differentiated into neuronal progenitor cells which in turn can differentiate into neuronal cells, and therefore might be useful for the treatment of sensorineural hearing loss (SNHL)[31]. It has also been reported that hMSCs differentiation into an intermediate neural progenitor stage is essential to obtain inner ear sensory lineages. In a study conducted by Alonso et al., neuron-like cells were obtained from neural progenitors grown in serum-free medium containing EGF and retinoic acid and then hair cell-like cells and auditory cells were generated from neuron-like cells[32].

Hearing recovery after transplantation of MSCs

Deafness animal models have been used to transplant MSCs differentiated into sensory neuron-like cells[27,33]. Indeed a useful approach for inner ear supplementation with stem cells can be hMSCs systemic application[34]. For instance, the number of spiral ganglion neurons (SGNs) in guinea pig model is increased after transplantation of neural differentiated hMSCs resulting in mild hearing recovery after transplantation[33].

The BMSCs have been fruitfully transplanted into young mice cochlea via the perilymphatic perfusion technique and further differentiated into fibrocyte-like (SLF-like) cells[35]. The hearing recovery after transplantation of MSCs into the inner ear cells may be occurred through two mechanisms. First, MSCs transdifferentiation into SLF-like cells may lead to compensate for lost SLFs, and second, transplanted MSCs may stimulate the host SLFs regeneration. Both mechanisms contribute to functional recovery of damaged SLF network and thus, transplantation of MSCs into the inner ear of rats with damaged SLFs significantly accelerates hearing recovery[36]. The potential of neural-induced human MSCs (NI-hMSCs) to help replace the lost cochlear cells in hearing loss mammals has been investigated. Indeed, grafted NI-hMSCs migrate into the spiral ganglion where they expressed the neuron-specific marker, NeuN[37]. A study on transplantation of undifferentiated mouse BMSCs into normal and ouabain-treated gerbil cochleae and determination of their migratory patterns has demonstrated that survival of transplanted MSCs into the modiolus of the cochlea may result in regeneration of damaged SGNs[38]. In a similar study, rats

with transplanted MSCs in the lateral wall demonstrated a significantly higher hearing recovery comparing to negative controls suggesting that MSCs transplantation results in hearing recovery through the repair of injured cochlear fibrocytes[39]. Furthermore, bone marrow-derived cells may have the ability to attenuate cochlear injury by replacing or regenerating mesenchymal cells and fibrocytes in the inner ear[40]. These findings suggest that BMSCs can differentiate into neuronal progenitor cells and therefore may represent a promising biological element for treatment of inner ear disease, such as SNHL[31]. Furthermore, cells originating from bone marrow particularly those derived from hematopoietic stem cells (HSCs), seem to have the capibility to engraft into the inner ear[41].

Recombinant BMSCs

Upon transplantation, BMSCs expressing recombinant IL-4 have the ability to remediate the inflammatory injury in autoimmune inner ear diseases[42]. In an attempt to provide a regenerative therapy for deafness in 2014, Buddy and co-workers successfully forced hBMSCs to express essential genes in the otic lineages[43]. Additionally, *BDNF* gene-modified MSCs are known to have a protective effect on the spiral ganglion cells[44]. Another example is genetic manipulation for Atoh1 which is a master gene for the differentiation of the hair cells. Indeed administration of Atoh1 expression can be highly beneficial for hair cell development and regeneration[45]. The neurosensory progenitors from bone marrow can also be converted to sensory hair cells through overexpression of Atoh-1[46]. Moreover it is known that BMSCs can be induced to differentiate into hair cells through a combination of growth factor stimulation and expression of the transcription factor Atoh-1[46].

Activation of BMSCs homing for hearing recovery

In an attempt to determine the homing capacity of BMSCs, Tan and co-workers transplanted BMCs from green fluorescent protein (GFP) transgenic mice into the irradiated mice and then induced hearing injury by acoustic deafening. They observed GFP+ cell migration to the deafened cochlea particularly at the perilymphatic compartment walls, spiral ligament and limbus regions[47]. A new promising strategy for the activation of stem cell homing factors is induction of stem cell homing factors (SDF-1 and MCP-1) in the host cochlear tissue, and their receptors (CCR2 and CXCR4) in transplanted MSCs[48]. This knowledge suggests that activation of stem cell homing can be an effective strategy for hearing recovery.

Adipose tissue derived MSCs

Adipose-derived stem cells (ASCs) can be isolated easily from blood vessels of adipose tissue[49]. These multipotent cells reside in the stromal vascular fraction and exhibit great plasticity and multilineage differentiation potential[50]. ASCs are capable to differentiate into all mesodermal lineages such as adipose tissue and other connective tissues (bone, cartilage, and muscles)[51]. However there are evidences that ASCs can be helpful in hearing repair. An original proof for developments of ASC-based treatments for deafness is that ASCs can migrate to the tissue damage location and express trophic factors[52]. Systemic infusion of ASC has been reported to significantly protect hair cells and improve hearing function in guinea pig with autoimmune hearing loss[52].

Additionally, the paracrine activity of hASC is known to help hearing restoration. The hASCs cause decrease in proliferation of antigen-specific Th1/Th17 cells by inducing the production of anti-inflammatory cytokine interleukin-10 in splenocytes. They also induce the generation of antigen-specific CD4+ CD25+ Foxp3+ Treg cells with the capacity to suppress autoantigen-specific T-cell responses[53]. In a study on guinea pig, the capability of ASCs to differentiate into neuron-like cells was investigated representing ASCs obtained from the neck as a good cell source for autologous cell-based regenerative methods[54]. ASCs are able to migrate to the location of tissue damage and express trophic factors throughout intracochlear implantation in guinea pig model of acoustic trauma[52].

A strategy based on combination of total protein extract transfer from VOT-E36 otic epithelial cells and Atoh1 overexpression represents a novel method to convert ASCs into hair cell-like cells. Atoh1 overexpression successfully transforms VOT-E36 cells into hair cell-like cells which further can attract contacts from spiral ganglion neurons in a co-culture medum[55]. The above mentioned evidences suggest that ASCs may be suitable tools to be used in regenerative medicine, because of their high plasticity and trophic features. Combined with conventional therapies, such as cochlear implantation, the feasibility of local ASCs delivery can contribute to future innovative biological strategies to enhance the endogenous reparative processes in the early stage of injury.

Umbilical Cord MSCs (UCMSCs)

Abundance of umbilical cords, low immune rejection and nontumorigenic properties, have made UCMSCs to be considered an excellent source for cell transplantation therapies and regenerative medicine[56]. It is known that the expression of Atoh1 leads to induce the differentiation of hUCMSCs into cells that are morphologically and immunocytochemical similar to inner ear hair cells[57].

Interestingly, there are evidences that UCMSCs are beneficial even without genetic manipulation. For instance, intravenous transplantation of intact UCMSCs can itself improve hearing thresholds via relocation and increasing in the number of spiral ganglion neurons (SGNs)[58]. Furthermore, other findings indicate that the migration of transplanted human cord blood CD133+ hematopoietic stem cells (HSC) to the inner ear leads to the resumption of deafened cochlea of oto-injured mice[59]. The implanted cells are further integrated into the cochlea of the inner ear suggesting a possible strategy for rehabilitation of inner ear. In addition, the number of spiral ganglion cells and outer hair cells are increased and

according to auditory brainstem response (ABR) tests, the hearing level improved[60].

Olfactory stem cells (mesenchymal-like stem cells)

The nasal olfactory stem cells from the human olfactory mucosa can be efficiently used for autologous stem cell-based therapies mainly due to their high abundance and easy accessibility [61]. Olfactory stem cells have been successfully injected into the cochlea of mice with excellent outcomes. The transplantation of adult human olfactory mucosa-derived stem cells has been also found to help preserve auditory function during early-onset progressive sensorineural hearing loss[62]. There are also evidences that the human mesenchymal-like stem cells derived from nasal tissue can repair spiral ganglion loss in experimentally injured cochlear of neonatal rats[63].

DISCUSSION

Due to highly promising nature of stem cells for regenerative medicine, intensive researches are being conducted to treat various diseases using embryonic, adult or induced pluripotent stem cells[64]. Cell based researches include a wide range of attempts such as treatments to aid nerve protection[65,66] and regeneration or recovering cardiac tissue[67]. In this regard, various aspects of developmental biology and molecular signaling networks must be considered[68,69]. Multi differentiation potential of MSCs and their capability to migrate into acute injury location make these cells suitable candidate for gene and cell therapy[70-74]. MSCs have been demonstrated to be helpful in treating inner ear inflammatory damage because they exhibit multidirectional differentiation potential, immunosuppressive function and low immunogenicity[75]. Among MSCs, BMSCs have been widely studied and are comparably more practical[58]. Various studies indicate potential of BMSC to deliver therapeutic molecules and restore cochlear cells. BMSC transplantation could be utilized through three different strategies for inner ear treatment; restoration of missing cells, providing growth factors and delivering genes. Current findings on MSCs treatment efficacy in otorhinolaryngology are based on animal models. The true impact on clinical treatment will not be revealed until clinical trials confirm functional outcomes in human medicine. Two limitations of MSCs replacement is the process of MSCs relocation into the inner ear and the fact that stem cells do not spontaneously divide to replace damaged sensory cells. In spite of high plasticity, the capability of trans-differentiation along non-mesodermal lineages is highly questionable. Particularly, possible neural trans-differentiation of MSCs, such as ASCs, is still being challenged[76-78]. Studies have confirmed the ability of the easily obtained and autologously available adult human stem cell to repair auditory neuron loss. However research should progress toward the establishment of cell-based therapies for certain forms of deafness[63]. *In vitro* studies have shown the differentiation of mouse MSCs into glutamatergic sensory neurons[28] and HC-like cells[46,79]. Since bone marrow transplants have been used by clinicians for decades, it would be more likely to move from animal trials using hMSCs, and hematopoietic stem cells toward clinical trials[67].

CONCLUSION

Stem cell therapy for sensorineural hearing aims to repair the hair cells and spiral ganglion cells to improve the auditory function. MSC transplantation for the treatment of hearing loss has opened up a new way of thinking. This review suggests that BMSCs are more capable to migrate and survive into the cochlear tissues which them suitable to be used in transplantation as a strategy for regenerating inner ear and treatment of SNHL.

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