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Mini Review

Stem Cell Transplantation for Cochlear Hair Cell Regeneration in Sensorineural Hearing Loss

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INTRODUCTION

Cochlea forms a very important part of the hearing mechanism. Most of the inner ear disorders which include the loss due to hair cells of cochlea or spiral ganglion neurons are among the difficult to treat and such cells die soon.[1] In mammals, cochlea is a complex structure. The very complex structure of cochlea is attributed due to its location deep within the skull which is difficult to be properly assessed.[2,3] Cochlea comprises different types of cell. Among such cell types are auditory hair cells. They are unique cells which might have lost regenerative power after development. Noise exposure or ototoxicity may affect these auditory hair cells very easily. Any damage to these auditory hair cells may even cause permanent hearing loss.[2]

Several technologies such as hearing aids and cochlear implants[2] has been a great source of help which can benefit people with hearing loss but they are not efficient to permanently cure hearing loss.[2] These options of treatment may be cumbersome for many patients as they may not be ready to accept them easily and may not even wear them.[2] Stem cells(SCs)transplantation as proven to be an effective tool for the treatment of sensorineural hearing loss. It helps in regeneration of various tissues and organ systems.[2] At present many diseases such as cancers, diabetes, human immunodeficiency virus(HIV), hearing loss and many other infectious diseases can be treated well with the use of stem cell therapy.[2-5] Stem cell transplantation has been reported to cure many such diseases now which were earlier thought to be incurable there by this technique is helping to improve quality of life of people suffering from these diseases.

Stem cell transplantation for hearing loss aims at cochlear hair cell regeneration and thus aids in achieving restoration of hearing loss.These self-renewing cells can differentiate into any type of cells if the required conditions for its differentiation is provided thus can help to repair damaged tissues. Though stem cell therapy has proven to be very efficient for treatment of many diseases it has many limitations as well. Clinical trials have been carried on rats and mice which might help to produce hair cell regeneration in mammalian cochlea. Though many adult stem cells has been used for the process of hair cell regeneration in cochlea. But there are no sufficient evidences through stem therapies due to inadequacy of stem cells.[3] There are also the literature findings which reports that the stem cell transplantation may be often associated with immune rejection, tumor formation or transplantation failure.[3]

Stem cell therapy

Stem cells are self-renewing cells which has the property of undifferentiated potency.[2] If there are no cells in cochlea which has tendency to differentiate then SCs are the most suitable option of treatment for sensorineural hearing loss.[3]They can replicate into any type of cells of body if provided appropriate intercellular communication,environment and intracellular gene regulation.[2]Cochlear repair becomes easier with the use of cells derived from such somatic stem cells. Such cell-based therapeutic approaches are gaining more scope for treating hearing loss and many other diseases which could not be helped through drug therapy.[2] It has been postulated that in mammalian ear, the supporting

layer cells contain major progenitor cells which can be used for hair cell regeneration. [2], [6-13]. It has been reported that adult stem cells were found in mouse utricle, a part in inner ear which is responsible for motion and balance. [2]Severaldifferentsourcesof stem cells have been discovered now in inner ear which can help replacement of auditory neurons such as neural stem cells [14, 15]bone marrow stem cells[16], Wharton jelly,[2] amniotic fluid,[2] dental pulp stem cell[2] etc.

Types of Stem Cells

Embryonic stem cells: They are considered as the most appropriate source of stem cells for the development of sensory hair cells.[2,17,18] They are pluripotent cells derived from the inner cell mass of blastocysts and are capable to differentiate into almost all cell types of the adult body.[2] Embryonic cells have the potential of self-renewal that can be accredited to the expression of specific genes such as *NANOG, SOX2* and *OCT4*.[2,19] Embryonic stem cells can differentiate into hair-like cells when transplanted into embryonic ears. The major limitation of using embryonic SCs is that they are more prone to immune rejection by the host, deregulation of genes can hamper pluripotent nature of these SCs. These limitations may cause decreased potential of embryonic SCs to fight against major effects such as diabetes, kidney failure.[20] Present literature highlight in order to avoid immune rejection, therapeutic cloning has been found to be one of the most efficient method to produce identical embryonic cells.[2] The major apprehension of using such embryonic cells therapy is that they have major tendency to form teratoma.[2] Though the literature supports that such embryonic cells can help in treating hearing loss but simultaneously have major limitations as well.[2] Firstly the site of location of cochlea is not easily accessible, secondly it is difficult to ensure that whether these derived stem cells will survive, integrate and mature in correct location. [2] Also its difficult to ensure that these stem cells derived grafts may not develop into tumours.[2]

Adult stem cells: Adult stem cells are undifferentiated cells that have the power to become different cells in the body such as neural matter, skin cells, heart tissue etc.[2] These somatic cells can be derived through many sources such as bone marrow, umbilical cord blood, neuronal sources, olfactory tissue which resides in the upper nasal cavity.[21-23] Different sources such as olfactory mucosa[24] and epithelium of tongue represents most accessible source of adult cells and progenitor cells.[25] Transplantation of epithelium cells of the tongue may help to lessen permanent threshold shifts resulting from noise induced hearing trauma.[2, 26] Adult stem cells has an advantages role over embryonic cells is that they are less prone to host rejection and less tumorigenic[27]and useful for cochlear transplantation. Previous studies have also reported that these adult stem cells could be tested in animal models of cochlear ischaemia for functional rescue of hearing loss.[2,28,29] Overall they have been found to be advantageous over embryonic cells in that they can be easily transplanted into cochlea.[2] The major limitations of using adult stem cells may be in the process of their implantation and their source of supply.[2]

Mesenchymal stem cells: These cells possess immunomodulatory property.[2] MSCs can be derived from umbilical cord matrix, human placenta, bone marrow, human amnion or human breast milk.[30] There are two types of MSCs i.e. wharton jelly and Human Umbilical cord perivascular cells. At present main focus is on Wharton Jelly type which can be used for central nervous system regenerative medicines.[2] MSCs are characterized by their ability of differentiation under adequate conditions along chondrogenic, adipogenic and osteogenic lineages and best ability to adhere to plastic culture flasks. They find a major role for aiding in central nervous system regenerative medicines. Present literature emphasize on the positive results of the transplantation of MSC derived from bone marrow on active regeneration of cochlear fibrocytes after severe focal apoptosis, without any changes in the organ of Corti thereby significantly improving hearing ratio.[2] It has also been found that the immunomodulatory function of the human MSCs is enhanced when the cells are exposed to an inflammatory environment characterized by elevated local levels of interferon-gamma composition.[31] But several studies have highlighted that MSCs interfere with dendritic cell and T cell function. They may generate local immunosuppressive microenvironment by secreting cytokinesis.[32]

Mechanism of stem cell therapy: The major concern in the transplantation of these stem cells demands the location of their injection into the cochlea. As mentioned before the cochlea is a complex structure situated deep inside the skull hence its easy accessibility is difficult. The different cell types inside the cochlea can be targeted for SCs application. Mostly hair cells are the common targets for SC therapy.[2] The different targets of SCs therapy can be auditory hair cells, spiral ganglion neurons and lateral wall of the cochlea depending on which part is affected. Though such parts can be transplanted by stem cells but they cannot function in isolation. To determine the precise cochlear pathology biopsy or autopsy has to be supplemented.[3] Many techniques suchascochleostomy or round window approaches has used for cochlear implantation surgery but such surgical procedures can disturb the cochlear homeostasis and may result in vertigo and loss of residual hearing.[3] Also once the transplantation of SCs has happened in the cochlea it's a tough challenge for the survival of transplanted SCs owing to varied composition of potassium.[3] In cochlea often auditory epithelium area is chosen for transplantation

With the transplantation process has been successfully completed it does not implies that hearing has also been effectively restored as it requires the generated electric signals to reach the auditory nerve and central nervous system. This conjunction or coupling of transplanted SCs with higher auditory structures is a must for hearing to be restored which is a big challenge and still remains a debatable concern.

Though the advantages of using stem cell transplantation are many but there are many limitations for the use of SCs such as tumor formation, immune rejections, transplantation failure and limitations due to cochlea structure situated deep in the skull pathologies in cochlea are difficult to be tapped. Though severity and hearing level can be determined through audiometric tests but histopathologic findings of the ears cannot be determined without autopsy.[3]

CONCLUSION

Stem cell transplantation is a boon for cochlea cell regeneration and their transplantation may help to control many diseases especially for the management of hearing loss provided there is ample source of SCs availability. There is a high need to identify the different sources of SCs to cater such innovative therapy protocol. Much more clinical trials are needed in mammals to prove the efficacy of SCs therapy. If combined with gene therapy or transdifferentiation stem cell transplantation can provide us more confirmatory results. Many more literature is needed to confirm the coupling mechanism of transplanted SCs in cochlea with higher auditory structures such as auditory nerve and central nervous system for the mechanism of hearing in mammals to be understood clearly.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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