Am J Stem Cells 2024;13(4):212-221
www.AJSC.us /ISSN:2160-4150/AJSC0155783

Review Article

Exploring the application of stem cell technology in treating sensorineural hearing loss

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Received February 4, 2024, Accepted July 8, 2024; Epub August 25, 2024; Published August 30, 2024

Abstract: Sensorineural deafness mainly occurs due to damage to hair cells, and advances in stem cell technology, especially the application of induced pluripotent stem cells (iPSCs) and adult stem cells, provides new possibilities for hair cell regeneration. This review describes the basic knowledge of stem cells and their important applications in regenerative medicine, as well as recent progress in stem cell research in the field of hair cell regeneration, especially the induced differentiation of hair-like cells. At the same time, we also point out the challenges facing current research, including differentiation efficiency, cell stability issues, and treatment safety and long-term efficacy considerations. Finally, we look forward to the direction of future research, and emphasize the importance of the cell differentiation mechanism, simulation of the inner ear microenvironment, safety assessment, and personalized treatment strategies. In conclusion, despite many challenges, stem cell technology has shown great potential in the field of hearing research and is expected to bring revolutionary treatment options for patients with sensorineural hearing loss in the future.

Keywords: Sensorineural hearing loss, stem cell technology, hair cell regeneration, regenerative medicine, inner ear microenvironment

Introduction

Sensorineural hearing loss (SNHL) is a common hearing disorder that results primarily from dysfunction of the inner ear or auditory nerve. According to epidemiological studies, SNHL, as one of the most common hearing disorders worldwide, affects 1.59 billion people, accounting for 20.3% of the total population, with the lives of about a quarter of those being seriously affected [1]. The impact of SNHL on patients is profound. In addition to the impact on communication and quality of life, SNHL can lead to social isolation, emotional problems, and decreased cognitive function, effects which are especially significant in the older population. Therefore, finding more effective treatments to restore or improve the function of damaged hearing has become an urgent problem to be solved.

SNHL has a variety of causes, including genetic factors, age-related degeneration, noise exposure, side effects of certain medications, and various diseases [2, 3]. Its pathogenesis mainly involves damage to or death of inner ear hair cells. The inner ear hair cells are responsible for converting sound waves into electrical signals that are subsequently transmitted to the brain via the auditory nerve. Unlike in birds, the inner ear hair cells of mammals cannot naturally regenerate once they are damaged or die. For this reason, the current primary treatments for SNHL include medication, hearing aids, and cochlear implants. Drug therapy focuses on specific causes of deafness, such as inflammation or viral infections, but there are limited effective drug treatment options for most people with SNHL [4, 5]. Hearing aids enhance sound signals and help patients improve their hearing, but they do not cure deafness or restore normal hearing. Cochlear implants, for people with moderate to severe SNHL, use electronic devices to directly stimulate the auditory nerve, bypassing damaged hair cells, to provide auditory perception.

https://doi.org/10.62347/AEIV5813

While hearing aids and cochlear implants have had some success in improving hearing, their therapeutic effectiveness is not without limits. Hearing aids help users hear better by amplifying sound and are intended for people with mild to moderate sensorineural deafness. However, for people with moderate to severe deafness, amplifying sound alone does not fundamentally solve the problem of hearing loss. Cochlear implants can provide auditory perception for patients with severe to extreme deafness, but not all deaf patients are suitable or willing to undergo such surgery, and the hearing experience provided by cochlear implants is different from normal hearing, especially in complex hearing environments.

Therefore, although these devices offer help in alleviating hearing impairment in some patients, their limitations are obvious and new treatments are urgently needed. In this regard, stem cell therapy technology, as an emerging research hotspot and development direction with great potential, opens up new possibilities for the treatment of SNHL. Using the regenerative capacity of stem cells, stem cell therapy has the potential to repair or regenerate damaged hearing cells at the molecular level, which is expected to address the root cause of hearing loss rather than just relieve symptoms. This approach not only offers new hope for deafness treatment, but also represents an important direction for future medical research.

Overview of stem cell technology

Definition and classification of stem cells

Stem cells, with their unique capacity for self-renewal and multidirectional differentiation, are key elements in biological development and tissue repair. They can be divided into several categories: (1) Embryonic stem cells (ESCs) are derived from early embryos and have unlimited self-renewal capacity and totipotent differentiation potential, capable of differentiating into all types of cells in the body. (2) Adult stem cells are found in a variety of tissues in the adult body, such as bone marrow, fat, and brain tissue, and have relatively narrow differentiation potential, usually limited to differentiation into specific types of cells for the maintenance and repair of the tissues in which they are located. Induced pluripotent stem cells (iPSCs), obtained by reprogramming adult cells (such as skin cells), have totipotent differentiation potential and self-renewal capacity similar to ESCs, but do not cause ethical controversy. (3) Mesenchymal stem cells (MSCs) are mainly derived from bone marrow, fat and other tissues, and chiefly differentiate into bone, cartilage and fat cells; they are widely used in a variety of tissue engineering and regenerative medicine fields. Because of their diverse sources and differentiation potential, these stem cells provide new therapeutic possibilities for disease treatment, especially for diseases that are difficult to cure, and show broad research and clinical application prospects. With the deepening of research, stem cell technology is expected to play a more important role in medicine in the future, especially in repairing damaged tissues, treating genetic diseases and treating organ failure.

The application of stem cells in regenerative medicine

The expanding application of stem cell technology in the field of regenerative medicine shows great potential for the treatment of a variety of diseases. Tissue engineering is one of the key application areas for this technology, in which stem cells are used to produce biomaterials that replace damaged or diseased tissue, such as skin, bone, heart tissue, etc. Combined with scaffold materials, these cells can be grown into tissue with a specific shape and function outside the body and then implanted into the patient to repair or replace the damaged tissue. Stem cells, especially iPSCs, also play a role in disease modelling and drug screening, providing unique disease models for specific genetic diseases, and facilitating the understanding of disease mechanisms and the development and safety testing of new drugs. In cell replacement therapy, stem cells can be used to generate healthy cells to replace those that are damaged or lose function in diseases such as Parkinson's disease, diabetes, sensorineural deafness, and others.

Autologous cell therapy is another key application. By taking, expanding and activating a patient's own stem cells and then injecting them back into the body, immune rejection can be avoided. This approach is used to treat autoimmune diseases, tissue damage and certain types of cancer. The combination of stem cell technology with gene therapy, particularly through the use of gene-editing technologies such as CRISPR/Cas9, offers the possibility of correcting genetic defects in stem cells to provide potential treatments for inherited diseases.

As an innovative therapeutic approach, stem cell technology has shown great potential in treating SNHL. Stem cells, especially pluripotent and adult stem cells, offer new avenues for repairing damaged inner ear hair cells and auditory nerves due to their ability to self-renew and differentiate into multiple cell types [6]. In recent years, potent stem cells have been developed from a variety of cell populations, including MSCs, iPSCs, and specific inner ear stem cells, which have shown the ability to restore hearing in animal models.

In addition, 3D bioprinting technology related to stem cell therapy, gene editing technology and advanced drug delivery systems all offer more precise and personalized strategies for treating SNHL. These technologies can not only promote the targeted differentiation and tissue regeneration of stem cells, but also enhance the efficacy and safety of stem cell therapy by precisely regulating specific genes or signalling pathways. Despite the promising applications of stem cell technology, which may provide innovative solutions to many medical dilemmas that cannot be solved by traditional treatments, the field still faces many challenges. These challenges include precise control of cell differentiation, long-term stability, and potential tumour risk, which need to be addressed through continuous research and development. With advances in technology and a deeper understanding of stem cell behaviour, the application of stem cell technology in regenerative medicine will continue to expand, opening up new paths for future medical research and clinical practice.

Application of stem cell technology in deafness treatment

Challenges of hair cell regeneration

Hair cell regeneration is an important area of research in the treatment of SNHL. In recent years, many studies have focused on revealing the mechanism of cochlear hair cell regeneration and its application prospects. Revuelta [7] and his team focused on novel strategies for hair cell regeneration in age-related hearing loss. Their research shows that the damage and loss of hair cells in the cochlea is irreversible with age, which leads directly to sensorineural deafness. By utilizing stem cells and gene therapy strategies, the regeneration of hair cells can be promoted to a certain extent, providing new treatments for hearing loss in the elderly. They demonstrated that regeneration of hair cells can be promoted in a geriatric model through stem cell and gene therapy strategies, demonstrating the potential of these treatments to restore the function of hair cells damaged by aging. The scientific basis for this finding lies in the plasticity of stem cells and the target-specific nature of gene therapy, which enables interventions to target specific mechanisms of hair cell damage.

A study by Jang et al. [8] on the application of nerve-induced human MSCs (NI-hMSCs) demonstrated significant potential for cochlear cell regeneration by reprogramming MSCs through specific neural induction processes to confer nerve cell-like properties. The achievement of this result fundamentally depends on a deep understanding and precise manipulation of cell destiny. During neural induction, specific signalling pathways are activated and specific transcription factors are regulated, causing the original MSCs to acquire new functional properties, such as the ability to respond to specific extracellular matrix components, and the ability to promote cell proliferation and differentiation in the unique microenvironment of the cochlea.

In addition, the key to the successful application of NI-hMSCs in cochlear cell regeneration also lies in their adaptive response to the special microenvironment of the cochlea. The cochlear microenvironment provides cells with a series of biochemical and physiological signals that are necessary to maintain cell characteristics and promote the proliferation and differentiation of specific cell types. NI-hMSCs play a key role in cochlear cell regeneration precisely because they are able to accurately recognize and respond to these complex microenvironmental signals, prompting their transformation to the desired cell type.

Therefore, this study not only provides a new direction for cochlear cell regeneration, but also provides an important scientific foundation for in-depth understanding of the mechanism of action of stem cells in specific tissue repair. Research by Jang et al. not only advances our understanding of the potential of stem cells in regenerative medicine, but also provides important experimental data and theoretical basis for future clinical applications.

Although remarkable progress has been made in the field of hair cell regeneration, Parker [9] and Groves [10] point out that many challenges remain, such as how to precisely control stem cell differentiation and improve regeneration efficiency. They highlight key scientific and technical questions that need to be addressed in future studies, as well as the need to translate the results of laboratory research into clinical applications. Waqas et al. [11] explore the use of stem cell-based therapies to restore SNHL in mammals. Their research highlights the great potential of stem cell technology to promote hair cell regeneration and repair damaged hearing, while also pointing out technical and ethical hurdles to overcome, such as problems with the collection, differentiation, and precise implantation of stem cells into damaged areas, illustrating the technical and ethical issues that need to be addressed in moving this technology from the laboratory to clinical applications. Future research needs to ensure the efficiency and precision of stem cell differentiation while also taking into account the ethical acceptability of therapeutic approaches.

In addition, further research should explore how to improve the survival rate and functional integration of stem cells after implantation, as well as how to evaluate and optimize long-term therapeutic effects. The work of Takeda et al. [12] shows how implantation of human ESC-derived precursor cells in the mouse cochlea can be facilitated by selective elimination of cochlear hair cells. This study not only demonstrates the potential of using stem cell technology to restore hearing, but also reveals a possible pathway to achieve hair cell regeneration by removing damaged hair cells to create space for the implantation of new cells. The success of this method reveals that the application of stem cells in the treatment of deafness depends not only on the differentiation potential of the stem cells themselves, but also lies in the precise manipulation and optimization of the internal microenvironment of the cochlea. By eliminating the hair cells that do not work properly, the dysfunctional cells are not only removed, but also the necessary physiological space and microenvironmental conditions are created for the colonization and differentiation of stem cells. This approach embodies a new way of thinking, which is to achieve more successful therapeutic effects through comprehensive intervention in the internal environment of the cochlea.

Wu et al. [13] discussed the role of microRNA in inner ear stem cell research and related advances. MicroRNAs regulate the expression of specific genes by binding to the 3' untranslated region (3'UTR) of the target mRNA, inhibiting its translation or promoting its degradation. Research into inner ear stem cells has shown that microRNA plays a key role in regulating stem cell differentiation and hair cell regeneration, with the expression patterns of specific microRNAs directly influencing the fate decisions of the stem cell, including whether it differentiates into hair cells or other cell types. This mechanism provides the molecular basis for the key role of microRNAs in cell differentiation. These data provide a new perspective for understanding the molecular mechanisms of hair cell regeneration and highlight possible molecular targets for the development of new therapies. Waqas and Chai [14] reviewed different approaches to regenerating hair cells and spiral neurons in the inner ear. Their review covered not only stem cell therapy, but also strategies as diverse as gene therapy and drug therapy. This shows that the study of hair cell regeneration is a multidisciplinary, multi-strategy field that requires the integration of different techniques and approaches to achieve the ultimate therapeutic goal. Therefore, combining the regenerative potential of stem cell therapy, the molecular precision of gene therapy, and the manoeuvrability of drug therapy has become an effective way to achieve hair cell regeneration.

Taken together, these studies not only advance our understanding of stem cells in regenerative medicine, but also provide important experimental data and theoretical basis for future clinical applications. However, translating these laboratory findings into effective clinical treatments still requires numerous challenges to be addressed, including controlling cell differentiation, improving regenerative efficiency, and overcoming ethical and technical issues. Future research will need to integrate different techniques and approaches to achieve the ultimate therapeutic goal of offering new hope to patients with SNHL.

Molecular mechanisms and the role of signal regulation in hair cell regeneration

In recent years, remarkable progress has been made in the study of the molecular mechanisms and signal regulation of hair cell regeneration. From the molecular level to the cellular level to the whole tissue system level, hair cell regeneration involves multiple steps and factors that are complex and finely regulated.

Zhong et al. [15] conducted an in-depth study on the central role of ATOH1, a key transcription factor, in the development of mammalian inner ear sensory epithelium and the differentiation and regeneration of hair cells, providing important insights into the mechanism of hair cell regeneration. During inner ear development, ATOH1 expression is an early marker of hair cell differentiation, driving undifferentiated precursor cells to differentiate into hair cells by activating the expression of downstream genes. Thus ATOH1 not only plays a vital role in the normal developmental process of hair cells, but also shows great potential in promoting the regeneration of damaged hair cells. Based on ATOH1 research, new gene therapies or drug therapies could be developed to promote regeneration of hair cells by directly activating ATOH1 or its downstream signalling pathways. This strategy may provide new treatment options for patients with hearing loss due to hair cell damage. The review article by Shibata et al. [16] delved into the potential of gene therapy in hair cell regeneration, specifically the strategy of efficiently delivering key regenerative factors, such as ATOH1, to the damaged inner ear via methods such as viral vectors. Not only does this approach demonstrate great potential to activate or increase hair cell regeneration through precise genetic manipulation, but it also marks the beginning of a new era of promoting hair cell regeneration through gene editing.

In combination with stem cell therapy, gene therapy offers a dual strategy for hair cell regeneration. On the one hand, the differentiation of stem cells into hair cells is promoted through gene editing; on the other hand, it can also repair damaged hair cells or improve their ability to regenerate. The study by Maharajan, Cho, and Jang [17] is an important milestone in the field of deafness treatment, which delves into the potential of MSCs for use in cochlear regeneration. Their work not only highlights the remarkable effectiveness of MSCs in promoting the regeneration of damaged hair cells, but also highlights the great potential of this therapeutic strategy in restoring hearing loss. Through detailed experimental studies, the team revealed how MSCs support the repair and regeneration of damaged cochlea by secreting growth factors and promoting improvements in the local cellular environment. As a class of stem cells with high plasticity, MSCs are able to secrete a variety of growth factors and cytokines, which play important roles in cell proliferation, differentiation and tissue repair. In the context of cochlear regeneration, MSCs directly promote the regeneration and repair of damaged hair cells by secreting specific growth factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). Waqas et al. [11] explored the role of other stem cell sources in the regeneration of the inner ear, which further confirmed the versatility and plasticity of stem cells, providing a unique and effective strategy for replacing damaged hair cells. When these stem cells are used in combination with other regenerative factors, their therapeutic potential is even more significant.

The development of single-cell RNA sequencing (scRNA-Seq) technology has provided a completely new perspective for research into hair cell regeneration. Regenerative factors, such as growth factors and specific signalling proteins, promote the directed differentiation of stem cells and enhance their regenerative capacity. When used in combination with stem cells, these factors can more effectively promote the replacement of damaged hair cells and the overall repair of the cochlea. Lush et al. [18] used this technique to reveal which specific stem cell populations contribute to the regeneration of hair cells after FGF and Notch signalling is blocked. This high-throughput sequencing technique allows researchers to gain insight into the molecular and cellular heterogeneity involved in hair cell regeneration, providing valuable information for the development of targeted therapies. The FGF and Notch signalling pathways play a central role in many types of tissue development and cell differentiation, including the development of inner ear hair cells. The blocking of these two signalling pathways is thought to be a key step in activating the differentiation of inner ear stem cells into hair cells, thereby promoting hair cell regeneration.

Combining different research methods and treatment strategies, the field of hair cell regeneration is moving towards a more diverse and integrated approach. For example, research by Waqas and Chai [14] and Chen et al. [19] has not only included gene editing and stem cell therapy, but also explored other possible regeneration strategies such as drug intervention. The development of gene-editing techniques, particularly the CRISPR-Cas9 system, has opened up the possibility of precisely modifying genes involved in influencing hair cell regeneration, allowing researchers to solve the puzzle of hair cell regeneration at the molecular level. Stem cell therapy, which relies on the pluripotency and plasticity of stem cells, provides a new cell resource for inner ear regeneration by inducing stem cells to differentiate into hair cells or to repair damaged hair cells. Drug intervention strategies are a relatively direct and practical treatment strategy to reduce damage to hair cells by activating the intrinsic regenerative pathway or providing protection. The diversity of these studies not only demonstrates the broad potential of the field of hair cell regeneration, but also provides insights into understanding the natural regeneration process of inner ear hair cells after damage and how to enhance this process through various strategies.

Research in the field of hair cell regeneration has revealed the important role of multiple molecular mechanisms and signalling regulation. From the key role of ATOH1 to the application of gene therapy, stem cell therapy, and the contribution of single-cell RNA sequencing technology, each advance has provided us with a deeper understanding of how to promote hair cell regeneration and possibly restore hearing. With a deeper understanding of the mechanisms of hair cell regeneration, combined with advanced gene-editing techniques, stem cell therapy strategies, and single-cell analysis tools, scientists are gradually unlocking the secrets of hair cell regeneration. The cumulative results of these studies offer new therapeutic hope for patients with sensorineural hearing loss, indicating that in the near future, we may be able to effectively ameliorate or even completely restore hearing loss caused by hair cell damage.

Stem cell technology and its application in the treatment of hearing loss

Sensorineural deafness is a common hearing disorder for which one of the treatment strategies is regeneration of hair cells. Research by Lopez-Juarez et al. [20] has provided breakthrough insights into stem cell technology in the treatment of SNHL. They successfully implanted human stem cell-derived auditory progenitor cells into the damaged cochlea, demonstrating the great potential of these stem cells in restoring hearing function. Through experimental validation in animal models, this work not only reveals the ability of human stem cells to promote cochlear repair in practical applications, but also lays a solid foundation for further development of stem cell-based therapeutic strategies. The results of the study show that by precisely controlling the differentiation and implantation of stem cells, it is possible to restore hearing loss caused by damage or loss of hair cells, thus opening a new chapter in the treatment of sensorineural deafness using regenerative medicine approaches.

The work of Dufner-Almeida et al. [21] provides a comprehensive look at the current status and challenges of harnessing stem cell technology for the treatment of hearing loss. In their review, current scientific progress in the field of hair cell regeneration is discussed in detail, while pointing out the wide gap between laboratory and clinical application. In particular, they highlight the technical obstacles to the realization of stem cell therapy for hearing loss, including the targeted differentiation of stem cells, effective implantation into damaged cochlea, and how to ensure the functional integration and persistence of new hair cells.

In their study, Denans, Baek and Piotrowski [22] took an innovative approach to explore a generic pathway for hair cell regeneration by comparing different sensory organs. Their analysis not only revealed the common mechanisms of hair cell regeneration across species, but also highlighted the key roles of specific molecular and cellular actions in this complex process. Their work provides an important scientific foundation for understanding how hair cells regenerate in humans and other animals, laying a cornerstone for the development of potential therapeutic strategies. The sensory organs of different species, although they may differ in function and structure, may have retained some common regeneration mechanisms throughout evolution. By comparing hair cell regeneration mechanisms in different species, such as fish, amphibians and mammals, the study reveals possible common molecular and cellular pathways in these processes.

Work by Zhang et al. [23], which represents a significant advance in the field of deafness treatment, successfully promoted the regeneration of hair cells in the human inner ear by activating the ATOH1 gene using small activating RNA (saRNA) technology. This study not only reveals the central role of ATOH1 in hair cell development and regeneration, but also demonstrates the potential to restore hearing by precisely regulating gene expression. The work by Zhang and his team opens new avenues for gene therapy for deafness, providing an innovative way to promote the repair and regeneration of damaged hair cells by activating key regenerative genes. The strategy of restoring hearing by activating the ATOH1 gene breaks through the limitations of traditional treatment methods, provides a brand new gene therapy pathway for deafness treatment, and shows the broad application prospects of gene therapy in the treatment of complex diseases.

Deng and Hu [24] demonstrated a novel mechanism of hair cell regeneration, and successfully induced hearing restoration by applying DNA demethylation technology in an adult mouse model of chemical deafness. The breakthrough of this study lies in its revelation that by altering the epigenetic level of gene expression, regeneration and repair of damaged hair cells can be promoted, thereby restoring hearing. DNA demethylation is an epigenetic regulatory mechanism that activates the expression of genes by removing methyl groups on DNA. In the context of hair cell regeneration, this means that genes associated with hair cell regeneration that are normally suppressed in adult mice can be reactivated by demethylation, thus promoting the repair of damaged hair cells and the generation of new hair cells. Through DNA demethylation, Deng and Hu not only provided a new molecular mechanism for hair cell regeneration, but also opened up a new research and therapeutic path for using stem cell technology to treat sensorineural deafness.

Research by Maharajan, Cho and Jang [17] provides important insights into the potential of MSCs to promote cochlear regeneration. Their work focused on the unique properties of MSCs, such as their pluripotency and immunomodulatory ability, that make MSCs ideal for restoring damaged hearing and promoting hair cell regeneration. MSCs have the ability to regulate the immune response, reduce inflammation and promote the stability of the internal environment of the cochlea. This property is extremely important for reducing the inflammatory response after cochlear injury and creating a more favourable environment for hair cell regeneration. The research team demonstrated the efficacy of the application of MSCs in a cochlear injury model, underscoring their therapeutic potential in alleviating sensorineural deafness.

A review article by Qiu [25], which delves into the potential of stem cell technology in the treatment of hearing loss, marks an important advance in this field. They meticulously analysed different types of stem cells, including ESCs, iPSCs, as well as adult stem cells, and the ability and potential mechanisms of these stem cells to promote hair cell regeneration in the ear. The paper emphasizes that despite numerous technical and ethical challenges, stem cell technology offers an unprecedented opportunity to restore hearing by replacing damaged hair cells or stimulating self-repair mechanisms in the inner ear.

Boddy et al. [26] successfully generated auditory line cells from unintegrated human iPSCs by using mRNA reprogramming technology, marking an important breakthrough in the field of deafness treatment. This work not only demonstrates that auditory cells with therapeutic potential can be effectively generated through advanced cell reprogramming techniques, but also demonstrates the safety and effectiveness of this approach, providing an important scientific basis for the future application of stem cell technology in the treatment of deafness. The successful application of the latest mRNA reprogramming technology in this study shows the broad application prospect of this technology in the field of cell therapy, especially the potential to precisely control the direction of cell differentiation.

In the field of stem cell therapy for hearing loss, a deeper understanding of the molecular mechanisms and signalling pathways of stem cell differentiation into hair cells is key to developing more effective differentiation induction strategies. This involves a deep insight into the fate decisions of stem cells and how to facilitate their transformation into the desired cell type by precisely regulating cell behaviour. At the same time, the development of new cell delivery systems and implantation techniques will be equally critical to improving the precision of cell localization and survival in the cochlea. This will require not only innovative engineering solutions to ensure that stem cells can efficiently reach their target locations, but also that these cells, once they reach the cochlea, can survive and function there. In addition, assessing the functional integration of new hair cells is also a complex but necessary process that requires the use of model systems and advanced biotechnology to explore in depth the interactions between new hair cells and the natural cells of the inner ear. This is not only about whether the new hair cells are able to properly integrate with other cell types within the cochlea, but also whether they are able to maintain their function and contribute to hearing restoration in the long term. Therefore, this series of research efforts all points to a common goal: to promote the transformation of stem cell therapy for hearing loss from theory to practice through in-depth research and technological innovation from multiple angles.

To sum up, stem cell technology shows great potential for the treatment of hearing loss, especially in promoting the regeneration of hair cells. Although many challenges remain, including optimization of the technology, safety evaluation, and translation to clinical applications, recent research results offer hope for overcoming these challenges. Future research is needed to further explore the potential of stem cell technology to develop more effective and safer deafness treatment strategies.

Discussion and summary

Stem cell technology shows significant potential in hearing research, particularly in the treatment of sensorineural deafness and hair cell regeneration. Hair cells, an important component of the inner ear that convert sound waves into nerve signals, fail to regenerate naturally in most mammals when damaged, leading to permanent hearing loss. Stem cell technology, in particular research using iPSCs, offers the possibility of regenerating damaged hair cells. iPSCs can be reprogrammed from a patient's own cells, reducing the risk of immune rejection, and have thus become a research focus.

However, despite the huge application promise of stem cell technology, there are several challenges in hair cell regeneration. For example, improving the efficiency and stability of stem cells in differentiating into hair cells, ensuring that the resulting hair cells are functionally identical to natural hair cells, and understanding the influence of the inner ear microenvironment on stem cell differentiation are all important research directions. In addition, the long-term effects and safety of stem cell therapy have not been fully validated.

Future research will focus on several key areas, including delving into the molecular mechanism by which stem cells differentiate into hair cells, studying the interaction of stem cells with the inner ear microenvironment, evaluating the safety and long-term effects of the treatment, and developing personalized stem cell treatment strategies. These studies are expected to break through current technical limitations and provide more effective and safe treatment options for patients with SNHL. All in all, stem cell technology shows great potential for hair cell regeneration and treatment of SNHL, and future research will be key to the development of effective treatment strategies that offer hope to those affected by this type of deafness.

Conclusion

Stem cell technology has shown unprecedented potential in the treatment of sensorineural hearing loss, offering new hope for overcoming the problem of hair cell damage that has long plagued the medical community. By delving deeper into the applications of iPSCs and adult stem cells, scientists have begun to uncover the secrets of hair cell regeneration and bring new hope to deaf patients. Although researchers have made remarkable progress in inducing differentiation of stem cells into hair-cell-like cells, they still face multiple challenges in practical application, such as differentiation efficiency, cell stability, and the safety and long-term effect of treatment. Future research needs to focus on understanding the mechanisms of cell differentiation in detail, simulating the inner ear microenvironment to facilitate proper stem cell localization and functionalization, and conducting comprehensive safety evaluations to ensure the efficacy and safety of therapeutic strategies.

At present, stem cell treatment of deafness is still in the preliminary research and preclinical trials stages, but some positive results have been achieved. For example, some studies have shown that specific types of stem cells are able to differentiate into hair cell-like cells in the damaged cochlea, promising to restore or improve hearing function [26, 27]. These studies not only provide new insights into the pathology and regeneration mechanisms of the inner ear, but also lay the foundation for the development of novel treatments for deafness.

In the future, with the further development of stem cell technology and related biomedical engineering, stem cell therapy is expected to become one of the effective ways to treat SNHL. This requires not only a comprehensive consideration of the type, source, safety and effectiveness of stem cells, but also a solution to technical challenges, such as how to improve the efficiency of targeted differentiation of stem cells in the cochlea, and how to ensure long-term functional maintenance and stability. With continued research and innovation, stem cell technology has great application potential and social significance in the future treatment of SNHL. By synthesizing current research and innovation, this review aims to achieve a comprehensive understanding of progress in treating deafness based on stem cell-based regenerative hair blast cells, the challenges faced, and potential future directions in this field.

Acknowledgements

This work was supported by the 535 Talent Project of First Affiliated Hospital of Kunming Medical University (2022535D08), the Yunnan Provincial Science and Technology Department Basic Research Project (202201AY070001-078), and the Yunnan Province Innovative Talent Training Object 2023.

Disclosure of conflict of interest

None.

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References

[1] Tordrup D, Smith R, Kamenov K, Bertram MY, Green N and Chadha S; WHO HEAR group. Global return on investment and cost-effectiveness of WHO's HEAR interventions for hearing loss: a modelling study. Lancet Glob Health 2022; 10: e52-e62.

[2] Gregory GE, Munro KJ, Couper KN, Pathmanaban ON and Brough D. The NLRP3 inflammasome as a target for sensorineural hearing loss. Clin Immunol 2023; 249: 109287.

[3] Young YH. Contemporary review of the causes and differential diagnosis of sudden sensorineural hearing loss. Int J Audiol 2020; 59: 243-253.

[4] Kempfle JS and Jung DH. Experimental drugs for the prevention or treatment of sensorineural hearing loss. Expert Opin Investig Drugs 2023; 32: 643-654.

[5] Kil J, Harruff EE and Longenecker RJ. Development of ebselen for the treatment of sensorineural hearing loss and tinnitus. Hear Res 2022; 413: 108209.

[6] Bergman JE, Davies C, Denton AJ, Ashman PE, Mittal R and Eshraghi AA. Advancements in stem cell technology and organoids for the restoration of sensorineural hearing loss. J Am Acad Audiol 2021; 32: 636-645.

[7] Revuelta M, Santaolalla F, Arteaga O, Alvarez A, Sánchez-del-Rey A and Hilario E. Recent advances in cochlear hair cell regeneration-A promising opportunity for the treatment of age-related hearing loss. Ageing Res Rev 2017; 36: 149-155.

[8] Jang S, Cho HH, Kim SH, Lee KH, Jun JY, Park JS, Jeong HS and Cho YB. Neural-induced human mesenchymal stem cells promote cochlear cell regeneration in deaf Guinea pigs. Clin Exp Otorhinolaryngol 2015; 8: 83-91.

[9] Parker MA. Biotechnology in the treatment of sensorineural hearing loss: foundations and

future of hair cell regeneration. J Speech Lang Hear Res 2011; 54: 1709-31.
[10] Groves AK. The challenge of hair cell regeneration. Exp Biol Med (Maywood) 2010; 235: 434-46.
[11] Waqas M, Us-Salam I, Bibi Z, Wang Y, Li H, Zhu Z and He S. Stem cell-based therapeutic approaches to restore sensorineural hearing loss in mammals. Neural Plast 2020; 2020: 8829660.
[12] Takeda H, Dondzillo A, Randall JA and Gubbels SP. Selective ablation of cochlear hair cells promotes engraftment of human embryonic stem cell-derived progenitors in the mouse organ of Corti. Stem Cell Res Ther 2021; 12: 352.
[13] Wu X, Zou S, Wu F, He Z and Kong W. Role of microRNA in inner ear stem cells and related research progress. Am J Stem Cells 2020; 9: 16-24.
[14] Waqas M and Chai R. Approaches to regenerate hair cell and spiral ganglion neuron in the inner ear. 2020.
[15] Zhong C, Fu Y, Pan W, Yu J and Wang J. Atoh1 and other related key regulators in the development of auditory sensory epithelium in the mammalian inner ear: function and interplay. Dev Biol 2019; 446: 133-141.
[16] Shibata SB, West MB, Du X, Iwasa Y, Raphael Y and Kopke RD. Gene therapy for hair cell regeneration: review and new data. Hear Res 2020; 394: 107981.
[17] Maharajan N, Cho GW and Jang CH. Therapeutic application of mesenchymal stem cells for cochlear regeneration. In Vivo 2021; 35: 13-22.
[18] Lush ME, Diaz DC, Koenecke N, Baek S, Boldt H, St Peter MK, Gaitan-Escudero T, Romero-Carvajal A, Busch-Nentwich EM, Perera AG, Hall KE, Peak A, Haug JS and Piotrowski T. scRNA-Seq reveals distinct stem cell populations that drive hair cell regeneration after loss of Fgf and Notch signaling. Elife 2019; 8: e44431.
[19] Chen Y, Zhang S, Chai R and Li H. Hair cell regeneration. Adv Exp Med Biol 2019; 1130: 1-16.
[20] Lopez-Juarez A, Lahlou H, Ripoll C, Cazals Y, Brezun JM, Wang Q, Edge A and Zine A. Engraftment of human stem cell-derived otic progenitors in the damaged cochlea. Mol Ther 2019; 27: 1101-1113.
[21] Dufner-Almeida LG, Cruz DBD, Mingroni Netto RC, Batissoco AC, Oiticica J and Salazar-Silva R. Stem-cell therapy for hearing loss: are we there yet? Braz J Otorhinolaryngol 2019; 85: 520-529.
[22] Denans N, Baek S and Piotrowski T. Comparing sensory organs to define the path for hair cell regeneration. Annu Rev Cell Dev Biol 2019; 35: 567-589.
[23] Zhang YL, Kang M, Wu JC, Xie MY, Xue RY, Tang Q, Yang H and Li LC. Small activating RNA activation of ATOH1 promotes regeneration of human inner ear hair cells. Bioengineered 2022; 13: 6729-6739.
[24] Deng X and Hu Z. Hearing recovery induced by DNA demethylation in a chemically deafened adult mouse model. Front Cell Neurosci 2022; 16: 792089.
[25] Qiu Y and Qiu J. Stem cells: a new hope for hearing loss therapy. Adv Exp Med Biol 2019; 1130: 165-180.
[26] Boddy SL, Romero-Guevara R, Ji AR, Unger C, Corns L, Marcotti W and Rivolta MN. Generation of otic lineages from integration-free human-induced pluripotent stem cells reprogrammed by mRNAs. Stem Cells Int 2020; 2020: 3692937.
[27] Zine A, Messat Y and Fritzsch B. A human induced pluripotent stem cell-based modular platform to challenge sensorineural hearing loss. Stem Cells 2021; 39: 697-706.