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Review Article

Role of microRNA in inner ear stem cells and related research progress

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Abstract: Deafness is one of the major global health problems that seriously affects the quality of human life. At present, there are no successful treatments for deafness caused by cochlear hair cell (HC) damage. The irreversibility of mammalian hearing impairment is that the inner ear's sensory epithelium cannot repair lost hair cells and neurons through spontaneous regeneration. The goal of stem cell therapy for sensorineural hearing loss is to reconstruct the damaged inner ear structure and achieve functional repair. microRNA (miRNA), as a class of highly conserved endogenous non-coding small RNAs, plays an important role in the development of cochlea and HCs. miRNA also participates in the regulation of stem cell proliferation and differentiation, and plays an important role in the process of regeneration of inner ear HCs, miRNA has a broad application prospect of clinical treatment of hearing loss, which is conducive to solving the medical problem of inner ear HC regeneration.

Keywords: Hair cell, stem cell, miRNA, inner ear, hearing loss

Introduction

According to WHO analysis data in 2018, 5% of the world's population suffers from hearing loss, of which 432 million are adults and 34 million are children. In addition, it is estimated that more than 900 million people will experience disabling hearing loss in 2050 (www.who.int). Therefore, how to intervene or treat hearing loss has become a global issue. The mammalian inner ear is a highly differentiated and complex structured organ. The mature inner ear hair cells (HCs) lack the ability to regenerate. Therefore, with the accumulation of hair cell damage, hearing loss will occur [1]. With the advancement of diagnosis and treatment technology, there have been many new developments in the treatment and intervention methods for deafness. Including cochlear implant therapy, gene therapy, drug-induced stem cell differentiation, molecular therapy, etc [2, 3]. In addition, with the deepening of research on inner ear stem cells in recent years, it has been discovered that by regulating signaling pathways such as Wnt, Notch, Atoh1, and β-catenin, the potential of supporter cells to differentiate into HCs can be activated in the inner ear of newborn mice [4-7]. Therefore, finding the most effective way to induce inner ear stem cells to differentiate into HCs will provide a very valuable reference for the intervention of hearing loss due to hair cell damage.

microRNAs (miRNAs) are a class of evolutionarily conserved single-stranded small molecule RNA sequences that contain approximately 19-23 nucleotide sequences [8]. miRNA is a non-protein-encoding RNA and usually plays a role in post-transcriptional regulation of gene expression in the body [9]. With the increase of research on miRNA, it has been found that it has a wide range of biological functions, such as regulating cell differentiation, proliferation, development, apoptosis and immune response [10-12]. Previous studies have reported that miRNAs are involved in the regulation of neural stem cell differentiation. In addition, miRNAs also play an important role in the regulation of bone marrow mesenchymal stem cell differentiation [13]. With the increase of research on

the regulation mechanism of miRNA and its relationship with stem cells, it becomes possible to use miRNA to regulate the proliferation and differentiation of inner ear stem cells to protect or restore hearing.

miRNA formation and regulation

miRNA is a type of non-coding small RNA that is endogenously expressed in cells consisting of 19 to 25 nucleotides. miRNA is widely found in vertebrates, drosophila, nematodes, plants, and even viruses. miRNA can form an RNA-induced silencing complex (RISC) by binding with Argonaute (AGO) protein, completely or incompletely complementary pairing with the target mRNA, leading to mRNA degradation (complete pairing) or inhibiting its translation (incomplete pairing) to achieve post-transcriptional levels regulation of gene expression [8]. In the nucleus, miRNAs are encoded by nucleotides located in the intergenic region and transcribed by RNA polymerase II to form a longer primitive miRNA (Pri-miRNA) with a stem-loop structure. Then the pri-miRNA is processed into a precursor miRNA (pre-miRNA) with a hairpin structure with a length of 70~100 nt in the nucleus under the action of a complex composed of the RNase III family Drosha enzyme and the double-stranded RNA-specific binding protein DGCR8. Pre-miRNA is then transported to the cytoplasm by a nuclear transporter (Exportin-5), and is cleaved into shorter double-stranded strands miRNA by the RNase III-Dicer and transactivating response RNA-binding protein (TRBP) complex. After the double-stranded miRNA is melted, one of the strands will be degraded, and the other strand forms a single-stranded miRNA, which is the mature miRNA (mature miRNA) [14, 15]. In animals, mature miRNAs can be combined with specific ribonucleoprotein AGO protein to form a silencing complex (RNA-induced silencing complex, RISC). RISC can recognize target genes and mediate mRNA degradation or inhibit translation through complementary binding with mRNA 3'UTR or Open Reading Frame (ORF) regions, thereby achieving the goal of regulating target gene expression [16, 17]. The way in which the target mRNA is treated by the RSC depends on the characteristics of the mRNA. If mRNA and miRNA are highly complementary, miRNA will guide the target mRNA to break at specific sites and activate endonucleases to degrade mRNA. If they are partially complementary, miRNA will specifically bind to the target mRNA through 3'UTR, which will inhibit translation after transcription of mRNA, but will not affect the stability of mRNA. Therefore, the correct recognition of the binding region between miRNA and target mRNA will directly affect the regulatory function of miRNA. In addition, some studies have found that some miRNAs can accelerate mRNA deadenylation, reduce the effective abundance of mRNA in the cell, and thus down-regulate gene expression [18, 19]. In some plants, miRNAs can mediate methylation of their loci or target genes, thereby regulating gene expression at the epigenetic level [20]. One miRNA can regulate multiple target genes, and multiple miRNAs can also regulate one gene expression at the same time, so the miRNA regulatory network is both complex and sophisticated.

The role of miRNA in other organs and tissues

It has been found that miRNA expression in animals, plants, and fungi is significantly tissue-specific and plays a variety of regulatory roles in cell growth and development. At present, there are more than 2,000 miRNAs found in the human body and regulating 30% of gene expression [21], not only participating in the regulation of normal physiological processes in the body, such as cell proliferation, differentiation, development, apoptosis, etc. It is also closely related to the occurrence and development of tumors [22], heart disease [23], and neurological diseases [24]. miRNAs play an important role in tumorigenesis and development, and abnormalities in the mutual regulation between miRNAs and genes can lead to tumorigenesis. The biological function of miRNAs in tumors mainly depends on the diversity of their regulation of target genes. Tumors related miRNAs can be generally divided into onco miRNA and suppressor miRNA. Suppressive miRNA negatively regulates tumorigenesis, and its down-regulation or inactivation will directly lead to the occurrence and development of tumors, such as Let-7, miR-9, miR-34, and miR-145, miR-451, etc [25-29]. Onco-miRNAs are positively correlated with tumorigenesis and can form a complex regulatory network with target genes and upstream transcription factors to regulate tumorigenesis, such as miR-130b, miR-182, miR-222, miR-137, miR-708, miR-96, miRNA-21, etc [30-33]. In addition, miRNAs also play important roles in cognition and me-

mory. Alzheimer's disease-related research found that miR-188-5p expression dysregulation may be the pathophysiological cause of synaptic dysfunction and cognitive-related diseases [34]. miR-148a has been shown to play an important regulatory role in T cell and B cell mediated chronic inflammatory diseases and autoimmune diseases, and its abnormal expression may be one of the pathogenesis of autoimmune diseases [35-37]. miR-155 can regulate the recruitment and retention of inflammatory cells in the synovium of rheumatoid arthritis patients by affecting the production of chemokines and the expression of pro-inflammatory chemokine receptors [38, 39]. miR-23b can inhibit the activation of NF-κB induced by pro-inflammatory cytokines and the expression of inflammatory cytokines by targeting TAB2, TAB3 and IKK-α, thereby inhibiting autoimmune inflammation [40]. Cardiovascular related research has found that miR-1 is directly involved in the regulation of the pathological process of myocardial infarction, including myocardial cell apoptosis, inflammation, angiogenesis, fibrosis, and affecting the survival and proliferation activity of myocardial cells [41, 42]. In aging-related research, it was found that miRNA-335 and miRNA-34a can inhibit the production of two antioxidant enzymes, such as Superoxide Dismutase 2 (SOD2) and Thioredoxin 2 (TRX2), in the mitochondria, thereby increasing the production of intracellular ROS and promoting cell aging [43]. Therefore, micRNA plays a very important role in the pathological process of many diseases. However, due to the diversity and complexity of miRNA regulation, it is difficult to locate a specific disease in a particular miRNA. Future research on miRNA should not only be limited to miRNA itself, but also focus on the identification and functional analysis of miRNA target genes in order to explore the related molecular mechanisms more thoroughly.

The role of miRNA in auditory system related diseases

Auditory system consists of peripheral auditory system and central auditory system. The peripheral auditory system includes the outer ear, the middle ear, and the inner ear. The inner ear has mechanosensory HCs that convert acoustic energy into neural signalling [44]. Mammal inner ear HCs cannot be regenerated, so once damaged, they can cause permanent hearing loss. The loss of cochlear HCs will also cause the spiral ganglion degeneration, which will affect the effect of cochlear implantation. Hearing loss can usually be divided into two types: conductive hearing loss and sensorineural hearing loss [45]. Conductive hearing loss is caused by structural abnormalities in the outer and middle ears. Sensorineural hearing loss is caused by damage or dysfunction of inner ear HCs, auditory neurons synapses, or stria vascularis. Currently known causes of these tissue or cell damage include aging, genetic mutations, noise trauma, ototoxic drugs and other metabolic diseases [2, 44].

miRNA plays an important role in the formation of the inner ear during embryonic development and the maintenance of inner ear function after birth. Over 100 miRNAs have been detected in various types of cochlear cells, such as miR-183, miR-96, miR-182, miR-124, miR-34a, miR-376, and miR-135b [46, 47]. miR-183, miR-96, and miR-182 in the cochlea affect the maturation of cochlear function through the temporal and spatial specificity of their expression [48]. Researchers have reported that abnormal expression of miRNAs can directly lead to loss of inner ear structure and hearing dysfunction. miRNA-124 regulates inner ear structure development and cell type differentiation [49]. miR-96 is closely related to the maturation of the ciliated bundles of inner ear hair cells and the development of cochlear nerves, and its mutation will cause non-syndromic progressive hearing loss [50, 51]. miRNA-34a can affect hair cell apoptosis through SIRT1/p53 signaling pathway [52]. miR-183 is not only important for the development and function of animal sensory organs, but also plays an important role in the occurrence and development of noise-induced hearing loss [53, 54]. With the development of experimental technology and the deepening of scientific understanding, the important role of miRNAs in hearing development and deafness is being continuously discovered.

The role of stem cells in the inner ear

In many mammalian organs, stem cells can sustain continued tissue formation by generating tissue progeny while renewing themselves through division. Renewal and replenishment of cells in blood, bones, epithelium and many other tissues. In the past few decades, stem

cell treatment has made great progress in clinical application [55]. For example, bone marrow transplantation is used to treat lymphoma, leukemia and various autoimmune diseases [56]. Pluripotent stem cells derived from retinal pigment epithelium is used to treat blindness (US National Library of Medicine. ClinicalTrials.gov). Gene-edited stem cells are used to treat bullous epidermolysis due to genetic defects [57].

In many non-mammalian animals, researchers have observed HC regeneration, such as fish and birds [58, 59]. In addition, some studies have reported that after induction of inner ear HCs death in newborn mice (P3-P4), some support cells in the cochlea can be observed to differentiate into hair cells. These indicate that the cochlea support cells of newborn mice have the potential to differentiate into HCs [60]. We believe that these supporter cells that differentiate into HCs are due to their stem cell properties during this period. There are also reports that the capacity to generate HCs was limited to a subset of supporting cells: inner pillar cells and third-row Deiters cells [61]. Notch and Wnt signaling pathways have important regulatory effects on stem cell self-renewal and differentiation in various tissues [62-64]. Therefore, some researchers have used specific inhibitor to inhibit the Notch pathway in the *in-vitro* cultured neonatal mouse basilar membrane. After 72 hours, it was observed that new HCs appeared in abnormal areas, and the new cells could express myosin VIIa and phalloidin which are HC specific marker. Notch inhibitor treatment not only causes an increase in the number of HCs but also reduces hearing loss caused by noise [65, 66]. In addition, studies have reported that activation of the Wnt/β-catenin pathway in the cochlea of newborn mice can also induce supporter cells to differentiate into HCs [4, 6]. For example, Atoh1, a downstream factor of Wnt/β-catenin pathway overexpresses in the cochlea of embryos and newborn mice, can promote the transformation of support cells into HCs [67]. Recent studies have found that in adult mouse cochlea, there are two main stages in inducing support cells to differentiate into HCs. The activation of Myc/NICD induces support cells into reprogramming and proliferation stage, and then inactivates Myc/NICD and overexpresses Atoh1, thereby inducing reprogrammed support cells to differentiate into HC-like cells. These newly generated HC-like cells can form connections with neurons [68]. With the deepening of research on inner ear stem cells, new discoveries provide more ideas and methods for the treatment of hearing loss due to HC loss.

The role of miRNAs in inner ear stem cells

In recent years, many researchers have found that miRNAs can affect the differentiation and proliferation of stem cells by participating in the post-transcriptional regulation of stem cells, and the regulation of specific miRNA expression levels can induce stem cells to differentiate into specific tissue cells [69, 70]. Therefore, miRNA is closely related to the fate decision of stem cells, which provides new ideas with important value for the treatment of diseases. In the embryonic stem cell related research, it was found that miRNA-1 and miRNA-133 can promote the mesoderm formation of embryonic stem cells. Among them, miRNA-1 can promote the differentiation of mouse and human embryonic stem cells into heart cells, while miRNA-133 can prevents differentiation of sarcoplasmic progenitor cells [71]. In mesenchymal stem cells (MSCs) related researches, it was found that miR-145, miR-495, miR-29a directly regulate the differentiation of MSCs into chondrocytes [72-74]. miR128 negatively regulates the expression of Wnt3a, and inhibition of miR128 can induce the differentiation of MSCs into neuron-like cells [75]. miR-124 can regulates MSCs differentiation into cardiomyocytes by inhibiting STAT3 gene expression [76, 77]. miR-9 promotes stem cell differentiation into neural cells by regulating Notch pathway and zinc finger protein 521 expression [78, 79]. Therefore, miRNAs play an important role in the differentiation of pancreas, heart muscle, nerves, osteoblasts, and chondroblasts. In addition, miRNAs also have the ability to regulate cell reprogramming, such as the mir-200c, mir-302 family and mir-369 family can directly induce somatic cell reprogramming [80, 81], and the miR-34 family has an inhibitory effect on somatic cell reprogramming [82].

In inner ear HC regeneration related research, overexpression of miR-96 and miR-182 leads to abnormal inner ear HC generation [83]. Due to vestibular HCs have a certain degree of regenerative ability, researchers have compared the expression differences of miRNA between cochlea and vestibule of newborn mice, and found that let-7a, let-7b, miR-24, miR-

220, miR-423, miR-190, miR-204, miR-195 and miR-125b have significant differences [84]. Previous research reported that miR-182 can affect the differentiation of cochlear stem cells to HCs by regulating Sox2 and Tbx1 expression [85]. The low expression of miR-182 in cochlear support cells can inhibit trans-differentiation of the support cells into HCs, and its overexpression promotes the differentiation of cochlear stem cells into hair cells, resulting in an increase in the number of cochlear hair cells [85]. The miR-183 family can regulate the Wnt/β-catenin signaling pathway by inhibiting the expression of LRP6 [86], and Wnt signaling can promote cochlear sensory precursors proliferation [4], so we believe that miR-183 is closely related to the proliferation and differentiation of inner ear stem cells. In addition, miR-183 can also inhibits the Notch signaling pathway by inhibiting the expression of NICD3 and NICD4, thereby affecting HC differentiation and regeneration [87]. These findings corresponds to previous research that inhibiting the Notch signaling pathway and activating the Wnt signaling pathway can effectively promote the proliferation and differentiation of $Lgr5^+$ cochlear precursor cells into hair cells [88]. In addition, previous research have reported that miR-384-5p can negatively regulate *Notch1* expression [89]. These findings indicate that miRNAs can affect the development of the inner ear through its epigenetic function, especially the regulation of inner ear stem cell proliferation and differentiation. Therefore, miRNA provides a potential tool for gene editing to achieve the regulation of the cell fate and differentiation of inner ear stem cells.

Conclusions

It is known that the loss of HCs in mammals is non-renewable, and stem cells play an important role in the development and regeneration of many other tissues due to their stem maintenance and differentiation capabilities. Therefore, the use of stem cell-related technologies to make auditory system damage repair, especially the regeneration and repair of damaged HCs, has become a hot spot in deafness research. Researches have shown that inner ear stem cells can self-renew and have multiple differentiation potential that can differentiate into HCs under appropriate induction conditions. However, there are still many problems in the application of inner ear stem cells. For example, the distribution and duration of inner ear stem cells in the inner ear are still limited and the molecular mechanism of in vitro differentiation of inner ear stem cells into hair cells is not clear. Although newborn HCs can express HC-related marker proteins, they still do not meet the standard of typical HC mature structure and functions. Therefore, new methods and technologies are needed to intervene in the process of HC regeneration. Since hundreds of transcripts are simultaneously regulated by miRNAs, miRNAs can be considered potential therapeutic tools for the manipulation of the processes of cell differentiation and the fate of hearing cells and the repair or the regeneration of HCs.

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Disclosure of conflict of interest

None.

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