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POTENTIAL OF MIRNA-183, MIRNA-29B, AND MIRNA-34A COMBINATION AS A NOVEL ADVANCED SENSORINEURAL HEARING LOSS DIAGNOSTIC AND THERAPEUTIC (THERAGNOSTIC) AGENT

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ABSTRACT

Background: Sensorineural hearing loss (SNHL) is a hearing disability that makes up 90% of all hearing loss in general. This condition reduces quality of life and causes lifelong disability. Current diagnostic and therapeutic agents are considered less than optimal and need to be developed further. MicroRNAs (miRNAs), such as miRNA-34a, miRNA-29b, and miRNA-183, play a role in the pathogenesis of SNHL and thus have potential as specific biomarkers and therapeutic agents. **Objective:** To open a new perspective regarding the use of diagnostic biomarkers and miRNA therapy as a new step towards the era of personalized medicine in SNHL patients. **Methods:** This literature review used a non-systematic review method using the search engines PubMed, Science Direct, and ProQuest. **Results:** Increased expression of miRNA-34a, miRNA-29b, and miRNA-183 causes a decrease in the number of inner hair cells hence causing hearing loss. This means that these miRNAs can be used as biomarkers in the diagnosis of SNHL. Suppression of these miRNAs to certain levels could potentially be a therapy for SNHL, as it showed reduced oxidative stress and apoptosis. Suppression of miRNA-29b expression causes increased proliferation and reduced oxidative stress. However, knock out of miRNA-183 shows disruption in stereociliary bundle development and hair cell maturation hence when using miRNA inhibitors as therapy it is important to take note of dosage. **Conclusion:** miRNA-34a, miRNA-29b, and miRNA-183 have potential as diagnostic biomarkers and therapeutic agents for SNHL by regulating levels of oxidative stress, apoptosis, and the number of inner hair cells. Utilizing these three miRNAs simultaneously can increase the specificity, sensitivity and effectiveness in the diagnosis and therapy of SNHL.

INTRODUCTION

Hearing loss (HL) is a serious condition that not only reduces the quality of life of patients but also causes lifelong disability. According to data from the World Health Organization (WHO) in 2021, 1 in 5 people or more than 1.5 trillion people who suffer from HL, of which 430 million show significant disability due to this condition.[1] In Indonesia, according to the National Commission on Hearing Loss (Komnas PGPKT) in 2014, the prevalence of HL reached 36 million people or 16.8% of the population. Of all HL cases both in Indonesia and in the world, sensorineural hearing loss (SNHL) is the largest contributor to HL cases with a prevalence of 90%. Cross-sectional and longitudinal research evidence shows that dysfunction of the auditory system, including deafness and auditory trauma, causes cognitive deficits that develop through neuroplasticity. Not only that, the economic burden caused by HL was estimated to reach 980 billion USD per year, used to provide health services, social support, and education for patients.[1] SNHL patients also often experience physical and psychological comorbidities. As a result, patients tend to distance themselves from their families and increasing the risk of depression.[2]

SNHL is a hearing loss caused by damage to hair cells in the inner ear, vestibulocochlear nerve, or brain processing centers. The most common causes of sensorineural hearing loss are congenital (syndromic

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and non-syndromic), presbycusis, noise-induced hearing loss, head injury, Meniere's disease, ototoxicity, systemic conditions (such as meningitis and diabetes), vestibular schwannoma, autoimmune conditions, and barotrauma. There are several pathophysiological mechanisms that cause damage to the inner ear resulting in SNHL, including structural abnormalities of the cochlear components, abnormalities in metabolic activity regarding the abnormal transport of ions, disorders in the vascular supply to the cochlea, density in the basilar membrane that prevents motility of outer hair cells (OHC), immunohistochemistry (IHC) transduction ability, and noise trauma.[2]

The most common intervention used for patients with SNHL are assistive devices, such as hearing aids (AUDs) or cochlear implants. Although these are effective for less severe forms of SNHL, they still require some HC function in order to produce sound transduction.[3] These intervention options cannot mimic natural hearing quality. Treatment of SNHL with corticosteroids is also known to have varying degrees of effectiveness. The corticosteroid dexamethasone, given orally or intra-tympanally, as an anti-inflammatory has poor bioavailability in the cochlea due to limited absorption in the inner ear when given orally and is easily cleared by cochlear fluid when injected intra-tympanally. Overall, current treatment options are not yet able to reverse the damage on inner hair cells, but only maintain the function of the existing structures. With these limitations, the search for new strategies as a more specific, sensitive, and effective treatment for SNHL is needed.

Along with the improvement of science and technology in the field of diagnostics and therapy, various studies have revealed various mechanisms of SNHL related to microRNA (miRNA) expression. Research by Ding & Wang in 2022 showed that miRNA plays a role in the pathogenesis of SNHL.[4] Some of the miRNAs involved are miRNA-34a, miRNA-183, and miRNA-29b.[5] Based on research by Wang, et al. in 2023, miRNA-34a is involved in ototoxicity due to increased oxidative stress and damage to cochlear cells that can cause irreversible SNHL.[6] In a study by Xue, et al. in 2016, increased expression of miRNA-29b increased the incidence of apoptosis and suppression of the House Ear Institute-Organ of Corti 1 (HEI-OC1) hair cells, causing SNHL.[7] Likewise with miRNA-183, increased levels of miRNA-183 in the blood are associated with hair cell destruction that can induce irreparable hearing loss as found in the study by Ha, et al. in 2020.[8,9] These facts show that miRNA-34a, miRNA-29b, and miRNA-183 can be used as biomarkers for SNHL diagnosis. Hence, a strategy is needed to reduce the expression of miRNA-34a, miRNA-29b, and miRNA-183.

Although treatment options for SNHL are still limited, the use of gene therapy appears promising. This technology carries the concept of gene silencing and replacement therapy as potential solutions in managing diseases related to gene expression. This is an adaptation of the natural mechanism of living things in controlling their gene expression using RNAi (interference), such as anti-miRNA and miRNA mimics, which aim to regulate target gene expression. This process has very high specificity in suppressing and replacing specific cellular expression of its genes, and as a result would be able to directly target the pathology that caused said patient's SNHL. Therefore, this literature review explores the effectiveness and possibilities that can be done to maximize the benefits and minimize the obstacles of gene therapy technology, especially miRNA. This study aims to open a new perspective on the use of miRNA as diagnostic biomarkers and therapy as a new step towards the era of personalized medicine in SNHL patients.

METHODS

This non-systematic narrative review was done by doing a literature search using the following search engines: PubMed, Science Direct, dan ProQuest. The following keyword was used: "(microRNA OR miRNA OR miR) AND (SNHL OR hearing loss) AND (diagnosis or therapy OR therapeutic OR biomarker)". The following inclusion and exclusion criteria were applied when selecting the literature to be used.

Inclusion criteria:

- Studies with *in vivo*, *in vitro*, and clinical trial research designs
- Articles published within the last 10 years, that is 2014-2024

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Exclusion criteria:

- Articles that do not have complete data or has not been published
- Articles in which the keywords do not match with the title and abstract
- Articles that cannot be fully accessed

After selecting articles found through the search engine, 12 published articles were chosen to be reviewed in this study.

RESULTS

miRNA-34a

Table 1. miRNA-34a as Diagnostic and Therapeutic Parameter for SNHL

Author	Experiment Model	Diagnostic and Therapeutic Parameter	Diagnostic and Therapeutic Agent
Pang, et al. (2016)[15]	C57BL Mice and Human	Diagnostic: Upregulated	Diagnostic: Circulating miRNA-34a levels
Xiong, et al. (2015)[17]	C57BL Mice	Diagnostic: Upregulated Therapeutic: downregulated	Diagnostic: miRNA-34a /Sirtuin 1 (SIRT1)/p53 signaling Therapeutic: Resveratrol (SIRT1 activator)
Xiong, et al. (2019)[16]	C57BL Mice and HEI-OC1 Cell Culture	Diagnostic: Upregulated mitophagy and downregulated mitochondria biogenesis Therapeutic: Downregulated mitophagy and upregulated mitochondria biogenesis	Diagnostic: miRNA-34a/ SIRT1 Signaling and H_2O_2 induced oxidative stress Therapeutic: miRNA-34a/ SIRT1 Signaling and Resveratrol
Pang, et al. (2017)[18]	HEI-OC1 cell culture and C57BL/6 Mice	Therapeutic: Upregulated (miRNA-34a mimic) and downregulated (miRNA-34a inhibitor and siRNA ATG9A)	UDCA, miRNA-34a mimic Inhibitor, miRNA-34a, and ATG9A siRNA
Lin, et al. (2017)[19]	Cochlea of db/db Mice	Diagnostic: Upregulated Therapeutic: Downregulated	Diagnostic: miRNA-34a Therapeutic: miRNA-34a inhibitor
Lin, et al. (2023)[33]	DPN Mice and RSC96 Cell culture	Therapeutic: downregulated (miRNA-34a, S1PR1) and upregulated (SIRT2)	Therapeutic: Dexmedetomidine (Dex)
Wang, et al. (2023)[6]	C57BL Mice and HEI-OC1 Cell Culture	Diagnostic: Upregulated (miRNA-34a) and downregulated (DRP-1) Therapeutic: Downregulated miRNA-34a	Diagnostic: miRNA-34a, DRP-1 Therapeutic: miRNA-34a inhibitor

Pang, et al. (2016) [15] showed that higher levels of circulating miRNA-34a have an association with auditory brainstem response (ABR) threshold in C47BL mice. Higher plasma levels of miRNA-34a ere also indicated in AHL patients.

Xiong, et al. (2015)[17] showed that miRNA-34a overexpression in HEI-OC1 cells inhibits expression, resulting in increased p53 acetylation and cell apoptosis. Knockdown of miRNA-34a increases SIRT1 expression, and also decreases p53 acetylation and apoptosis. Resveratrol was also shown to have prevented HEI-OC1 cell death induced by increased expression of miRNA-34a, and reduced hearing threshold changes as well hair cell loss in C57BL/6 mice after 2 months of administration.

In research by Xiong, et al. (2019) [16] it was found that oxidative stress increases PINK1 and Parkin protein expression, hence increased mitophagy. Oxidative stress also reduced the decrease in expression of PGC-1α, NRF1, NRF2, and TFAM proteins, which indicated decreased mitochondrial biogenesis. This resulted in a disturbed balance between mitophagy and mitochondrial biogenesis, leading to decreased viability of HEI-OC1 cells. Upregulation of miRNA-34a and downregulation of SIRT1 signaling was found to have regulated the cell response to oxidative stress. Resveratrol was then administered. It resulted in reduced mitophagy activity and increased mitochondrial biogenesis. Hence, resveratrol showed protective effects against oxidative damage caused by H2O2, increasing the viability of HEI-OC1 cells. Resveratrol also significantly reduced age-related cochlear hair cell loss, spiral ganglion neuron loss, stria vascularis atrophy, and hearing threshold changes in C57BL/6 mice.

Pang, et al. (2017)[18] used UDCA to inhibit expression of miRNA-34a. miRNA-34a mimic was also used and showed to be able to block

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autophagosome-lysosome fusion (pro-apoptotic gene). Inhibition of miRNA-34a expression accelerated autophagic flux (anti-apoptotic gene), and ATG9A siRNA inhibits autophagosome–lysosome fusion.

Lin, et al. (2017)[19] found upregulated miRNA-34a expression in the cochlea of db/db mice, hence increasing hearing threshold and hair cell loss. Inhibition of miRNA-34a expression reduced cochlear hair cell apoptosis in db/db mice via the SIRT1/HIF-1α pathway, increasing SIRT1 expression and decreasing HIF-1α.

In research by Lin, et al. in 2023[33], dexmedetomidine was administrated. This resulted in decreased expression of miRNA-34a, increased SIRT2 expression, decreased expression of S1PR1, and reduced oxidative stress and mitochondrial dysfunction, protecting against DPN.

Lastly, Wang, et al. (2023)[6] showed that increased miRNA-34a expression is involved in cisplatin-induced ototoxicity, causing increased oxidative stress and damage to cochlear cells, leading to progressive and irreversible sensorineural hearing loss. Increased expression of miRNA-34a also caused a decrease in DRP-1 expression. Inhibition of miRNA-34a reduced oxidative stress and cell death induced by cisplatin, showing potential as a therapy to prevent or reduce cisplatin-induced ototoxicity. It also caused increased DRP-1 expression.

miRNA-29b

Table 2. miRNA-29b as Diagnostic and Therapeutic Parameter for SNHL

Author	Experiment Model	Diagnostic and Therapeutic Parameter	Diagnostic and Therapeutic Agent
Xue, et al. (2016)[7]	C57BL Mice and HEI-OC1 cell culture	Diagnostic: Upregulated Therapeutic: downregulated/ suppression	Diagnostic: RT-qPCR for MiR-29b expression Therapeutic: miRNA-29b inhibitor
Hao, et al. (2019) [21]	Human serum, C57BL/6 Mice, and SK-N-MC and SH-SY5Y cell culture	Diagnostic: Upregulated	Diagnostic: RT-qPCR for MiR-29b expression Therapeutic: anti-miRNA-29b and MIAT

Xue, et al. (2016)[7] showed expression of miRNA-29b increased in aging C57BL/6 mice compared to young ones. Increased expression of miRNA-29b also increased apoptosis & suppressed proliferation of HEI-OC1 cells (hair cells). Cells administrated miRNA-29b mimic had exacerbated mitochondrial dysfunction, and miR-29b mimic suppressed SIRT1 and PGC-1α expression in HEI-OC1 cells. When transfected with miRNA-29b inhibitor, HEI-OC1 cells had reduced apoptosis and promoted proliferation. Attenuated exacerbation of mitochondrial dysfunction and increased SIRT1 and PGC-1α expression were seen.

Hao, et al. (2019)[21] also showed that there was an increase in miRNA-29b expression in older mice. When given anti-miRNA-29b, there was increased proliferation and decreased cell apoptosis.

miRNA-183

Table 3. miRNA-183 as Diagnostic and Therapeutic Parameter for SNHL

Author	Experiment Model	Diagnostic and Therapeutic Parameter	Diagnostic and Therapeutic Agent
Ha, et al. (2020)[8]	Human blood	Diagnostic: Upregulated	Diagnostic: miRNA easy Mini Kit
Gholamreza, et al. (2020)[25]	Human bone marrow mesenchymal stem cells	Diagnostic: Upregulated	Diagnostic: Real time PCR
Geng, et al. (2018)[27]	Mice	Therapeutic: downregulated	Swimming test, ABR recording, immunofluorescence, electron microscope

In research done by Ha, et al. in 2020, it was found that an increase in blood miRNA-183 levels was indicated in hair cell destruction.[8] Gholamreza, et al. (2020)[25] showed that expression of miRNA-183 influenced the stimulation of the formation of auditory neurons, such as Ngn1, SOX2, peripherin, and nestin. Geng, et al. (2018) did knockout to miRNA-183 gene clusters in mice. This resulted in loss of balance in mice, lack of response to sound stimulation, malformation of abnormal "heart-shaped" hair cells in the hair bundle, and disorganization of the hair cells and supporting cells when viewed with an electron microscope.[27]

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DISCUSSION

Utilization of miRNAs as Diagnostic and Therapeutic Agents

Molecular biology explains that there are three important macromolecules, namely DNA, RNA and protein. For decades, RNA was thought to only have a minor role in gene expression by transferring genetic information from DNA to proteins alone, called coding RNA. However, in the late 1960s, it was discovered that there is a subset of RNAs that are capable of controlling gene expression by determining which genes should be turned on and off (non-coding RNAs). Based on their function, non-coding RNAs can be divided into housekeeping RNAs such as transfer-ribonucleic acid (tRNA), ribosome-ribonucleic acid (rRNA), small nuclear ribonucleic acid (snRNA), and small nucleolar RNAs (snoRNAs), as well as regulatory RNAs. Housekeeping RNAs are usually expressed continuously, while non-coding regulatory RNAs are only produced at certain stages in cellular development and differentiation or in response to external stimuli. Among small regulatory RNAs, miRNAs (19 to 25 nucleotides) are the most conserved molecule and functions to regulate gene expression after transcription by binding to target mRNA to reduce its expression.[10,11]

miRNA biogenesis starts from the RNA polymerase II enzyme which produces molecules called pri-miRNA in the cell nucleus. Pri-miRNA is then cut by the drosha ribonuclease III/DGCR8 protein complex into a shorter form called pre-miRNA. These pre-miRNAs molecules are then exported to the cytoplasm by transporter proteins called exportins. In the cytoplasm, pre-miRNA undergoes further cutting by an enzyme called Dicer, which works in a complex with the transactivation response RNA binding protein (TRBP). This process produces a miRNA duplex, which is a pair of two RNA strands of different lengths. One of these two strands, called the miRNA, then combines with the argonaute protein (AGO) to form a complex called the miRNA-induced silencing complex (miRISC). MiRISC functions in targeting certain mRNA molecules in cells. When mature miRNAs bind to their target mRNAs, this can lead to suppression or reduction in the expression of the associated genes. miRNAs can also play a role in cellular communication processes in reversible ways, such as through extracellular vesicles (exosomes), or through interactions with RNA-binding proteins such as AGO or nucleophosmin 1 (NPM1).[12]

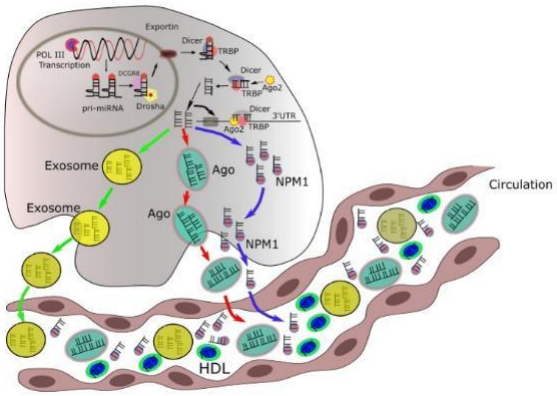

Figure 1. Biogenesis and extracellular export of miRNA

Altered miRNA profiles are found in conditions such as cancer, cardiovascular and neurodegenerative diseases. Hence, miRNAs show great potential as non-invasive biomarkers for early detection and monitoring of disease progression. As therapeutic agents, miRNAs can be used as target therapy to re-regulate pathological biological pathways. This can be done by using synthetic miRNAs and modulation of endogenous miRNA expression as potential strategies to address the underlying biological perturbations in disease.

Utilization of miRNA-34a as a Theragnostic Agent for SNHL

miRNA-34a plays an important role in various physiological processes, including cell cycle regulation, apoptosis, and development. miRNA-34a is known to function as a tumor suppressor by targeting various oncogenes. In addition, miRNA-34a is also important in metabolic regulation, influencing lipid metabolism and insulin secretion.[10,13,14] In pathological conditions, the expression of miRNA-34a can vary depending on the disease. In SNHL, miRNA-34a expression tends to increase, associated with stress responses and cell apoptosis that contribute to damage to hearing cells and loss of hearing function. miRNA-34a is able to induce apoptosis cellular senescence, and mitophagy in the cochleas of mice, resulting in a lowered number of hair cells.[15,16] Hence, increased expression of miRNA-34a can be used as a diagnostic biomarker in

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SNHL cases. Previous research show that increased circulating levels of miRNA-34a are associated with auditory brainstem response (ABR) in C57BL/6 mice and SNHL patients, indicating its use as a biomarker for early detection and monitoring of this condition.[15] Increased miRNA-34a is also associated with the regulation of oxidative stress and cell apoptosis through the miRNA-34a/ sirtuin 1 (SIRT1)/p53 pathway, which affects hair cell viability and worsens SNHL.[16] High expression of miRNA-34a were seen in the cochlea of db/db mice which had increased hearing threshold and hair cell loss, indicating an important role of miRNA-34a in the pathogenesis of SNHL. Thus, miRNA-34a shows great diagnostic value in SNHL, allowing faster and more effective medical intervention.[6]

miRNA-34a has great potential as a therapeutic agent in SNHL. In in vitro and in vivo studies, inhibition of miRNA-34a with an miRNA-34a inhibitor showed a reduction in cisplatin-induced oxidative stress and cell death, indicating therapeutic potential in preventing or reducing cisplatin-induced ototoxicity.[6] Another study showed that resveratrol, an activator of SIRT1, prevented auditory cell death induced by increased expression of miR-34a, and improved hearing thresholds and reduced hair cell loss in C57BL/6 mice.[17] Research using miRNA-34a mimic revealed that miRNA-34a can inhibit autophagosome-lysosome fusion thereby inhibiting autophagic flux, while the use of miRNA-34a inhibitors accelerates autophagic flux and reduces apoptosis in HEI-OC1 cells.[18] In addition, inhibition of miRNA-34a in db/db mice decreased cochlear hair cell apoptosis through the SIRT1/HIF-1α pathway, increased SIRT1 expression and decreased HIF-1α, which exerted a protective effect against hearing loss.[19] Thus, regulation of miRNA-34a expression shows great potential in SNHL therapy through various molecular mechanisms.

miRNA-29b: A New Breakthrough in SNHL Theragnostic

miRNA-29b is a member of the miRNA-29 family which works in the formation and maturation of neuron cells, where miRNA-29b itself has a function in inhibiting BH3-only pro-apoptotic genes thereby increasing neuron growth. When brain ischemia occurs, ischemic areas have increased expression of miRNA-29b, whereas in normal areas exhibit lower levels. In addition, miRNAs have increased expression in Parkinson's Disease patients and low expression in Alzheimer's Disease.[20] Research conducted by Xue, et al in 2016 showed that in aging mice, there was an increase in miRNA-29 expression, a decrease in hearing function, and a decrease in the number of inner hair cells. In old mice there was also a decrease in the expression of SIRT1 due to being targeted by miRNA-29b, which is a sensor that regulates intracellular oxidative stress, and proliferator-activated receptor-gamma coactivator 1α (PGC-1α), which is a transcription co-regulator that can attach to several transcription factors thereby promoting mitochondrial biogenesis and oxidative metabolism. Hence, these two markers indicate mitochondrial function and oxidative stress. In HEI-OC1 cell cultures, when treated with miRNA-29b mimic, there was increased apoptosis, suppression of cell proliferation, and decreased expression of SIRT1 and PGC-1α. From research conducted by Xue, et al in 2016, it can be concluded that miRNA-29b can trigger inner hair cell death in the pathogenesis of hearing loss by suppressing the expression of SIRT1 and hence PGC-1α. This is supported by a decrease in the level of apoptosis in HEI-OC1 cells and an increase in the expression of SIRT1 and PGC-1α when treated with a miRNA-29b inhibitor so that inhibition of miRNA-29b expression has the potential to be a therapeutic agent for hearing loss.[7]

Hao, et al in 2018 also conducted similar research by additionally measuring the expression of MIAT (myocardial infarction associated transcript), a long non-coding RNA (lncRNA) which plays a role in the proliferation and apoptosis of hair cells in various diseases, and has been hypothesized to be a competing molecule with miRNA-29b. In this study, it was seen that there was an increase in the expression of miRNA-29b in aging mice, as well as an increase in proliferation and a decrease in cell apoptosis when given anti-miRNA-29b. This was followed with downregulation of MIAT, SIRT1, and PGC-1α, hence showing that MIAT is also involved in the miRNA-29b signalling pathway in the pathogenesis of hearing loss. This result showed a potential addition to the signalling pathway In conclusion, miRNA-29b can be used as a diagnostic agent for SNHL and the MIAT/miR-29b/SIRT1/PGC-1α signaling pathway can be targeted for therapy .[21]

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Potential of miRNA-183 as a theragnostic tool for SNHL

miRNA-183 is part of the miRNA-183 cluster. miRNA-183 clusters play regulatory roles in cancer, autoimmune diseases, neurological diseases, psychiatric diseases, as well as several others. Transcription of the miRNA-183 clusters is regulated together to form a single polycistronic pri-miRNA.[22]

miRNA-183 is often used as a specific diagnostic biomarker for cancer development. miRNA-183 is associated with tumor size, proliferation capacity, and migration ability.[23] Sequence analysis of the miRNA-183 genomic fragment also shows that the transcription factor binding site is expressed in sensory neural cell genes. One example of the miRNA-183 binding site on CHX10 is a key transcription factor in retinal development. Not only in the retina, miRNA-183 also plays a role in the inner ear.[24]

Expression of miRNA-183 influences the stimulation of the formation of auditory neuron proteins such as Ngn1, SOX2, peripherin, and nestin.[25] miRNA-183 is also related to the development of hair cells and plays a role in the expression of differentiated hair cells. However, in vivo studies show that increased levels of miRNA-183 in cochlear tissue and blood serum in mouse samples are associated with ototoxicity.[26] An increase in miRNA-183 in the blood is indicated in the destruction of hair cells.[8] Hair cell destruction can accumulate due to several factors such as increasing age, level of noise exposure, and genetics.[9] Damage to hair cells located in the inner ear may not be reversible because cells in the inner ear rarely regenerate so that miRNA-183 can be a biomarker for predicting hearing loss by detecting hair cell damage.[8]

Replacement therapy of miRNA-183 appears to have the potential to treat SNHL, as research conducted by Geng, et al. in 2018, shows that mice with knocked out (KO) of miRNA-183 clusters showed disturbances in stereociliary bundle development and hair cell maturation. This was confirmed using an electron microscope which showed disorganization of the hair cells and supporting cells with the apical area being more affected. In addition, these mice showed no response to sound stimuli.[27] However, since previous research also showed that miRNA-183 expression is less in SNHL compared to normal subjects, this means that in order to maintain a normal hearing range the levels of miRNA-183 need to be regulated within a certain threshold.[8] Therefore, SNHL therapy using miRNA-183 inhibitors need to carefully take into account their dosage to avoid worsening the hearing loss, and replacement therapy of miRNA-183 would also be suitable to use if the hearing loss is the result of too low expression of said miRNA.[27]

Biosafety Aspects of miRNA

In the last few decades, miRNA-based therapy has continued to develop. However, less than twenty drugs based on miRNAs have undergone clinical trials and none have succeeded in reaching phase three clinical trials.[28] There are several possible causes for this to occur, on of them being the ability of miRNAs to act as "master regulators" in cellular level networks.[29] This means that one miRNA can target tens to hundreds of genes by reducing gene stability and inhibiting the translation process, resulting in adverse effects that would be difficult to predict unless complete information about gene interactions are known.[30] miRNAs can target not only mRNA but also interact with lncRNAs, pseudogenes, and circular RNAs (circRNAs), further amplifying the effect it can potentially trigger.[31]

The large number of targets available to a single miRNA is a limitation in developing miRNA therapy. This limitation can be overcome by chemically modifying these molecules. The modifications made are to increase the specificity of binding between miRNA and target genes. Other methods that can be done to overcome the limitations of miRNA development are further identification of the miRNAs involved in each biological disease condition, efficient delivery of miRNA modulators to target cells or target tissues, regulation of expression of target genes, and minimizing the occurrence of non-specific interactions.[28] The use of thermodynamics-based tools can be one way to overcome limitations in the development of miRNA therapy.[32] Selecting a miRNA design that has a small melting temperature (Tm) to reduce seed-dependent off-target effects and prevent the use of endosomal transport-based therapeutic agent delivery methods can also be used as an effort to mitigate these various obstacles. Not only that, efforts are needed to identify any potential complications and close supervision of subjects

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taking part in the trial at every stage before, during and after the clinical trial. In particularly, the dosage of miRNA when used in therapies needs to be carefully calculated to prevent over suppression which can lead to complete silencing of genes, which would have unwanted effects.

CONCLUSION

SNHL is a common hearing loss that can cause physical and psychological comorbidities. Early diagnosis and therapeutic agents need to be developed because those currently available are considered less than optimal in disease diagnosis and therapy as they are not specific to their etiopathologies. This literature review suggests that miRNA-34a, miRNA-29b, and miRNA-183 have the potential to be specific biomarkers as well as therapeutic agents for SNHL. Research has shown that increasing the expression of these three miRNAs causes a decrease in the number of inner hair cells which results in a decrease in hearing ability. Hence it can be concluded that these three miRNAs have the potential to be specific biomarkers of SNHL and when used simultaneously can increase the specificity, sensitivity and effectiveness of detecting SNHL disease. When the expressions of miRNA-34a, miRNA-29b, and miRNA-183 are suppressed, the number of inner hair cells can be maintained and hearing improves. However, the dosage of suppressing the expression of these three miRNAs must be carefully considered as to prevent further hearing loss. The main challenge facing miRNA therapy is that it can target many different genes, so it must be addressed in a variety of ways, such as increasing the molecules' specificity. Hence, research regarding practical applications miRNA as personalized SNHL theragnostics should be used to determine the correct protocols for each.

ETHICAL APPROVAL

There is no ethical approval.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Authorship contributions as follows: conceptualization, AHF, GVPH and ADAK; methodology, GVPH; validation, AHF, GVPH and ADAK; formal analysis, AHF, GVPH and ADAK; investigation, AHF, GVPH and ADAK; resources, AHF; data curation, ADAK; writing—original draft preparation, AHF, GVPH and ADAK; writing—review and editing, AHF, GVPH and ADAK; visualization, AHF, GVPH and ADAK; project administration, GVPH.

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