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Review article

Novel insights into mechanisms and therapeutics for presbycusis

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ABSTRACT

Presbycusis, also referred to as age-related hearing loss, poses a substantial burden on both individuals and society. The hallmark of presbycusis is a progressive decrease in auditory sensitivity. Irreversible hearing loss occurs due to the limited regenerative capacity of spiral neurons and peripheral cochlear hair cells (HCs). Although hearing aids and cochlear implantations (CIs) are established approaches for alleviating symptoms of presbycusis, there are currently no preventive or curative measures available. This article provides a comprehensive discussion on the research progress pertaining to the classification, molecular mechanism, genetic susceptibility, as well as the applications and prospects of diverse therapeutic interventions of presbycusis. Building upon these discussions, promising interventions like gene therapy and stem cell (SC) therapy are proposed for their potential value in restoring cochlear function; thus aiming to pave new avenues for prevention and cure of presbycusis.

1. Introduction

Presbycusis, also known as age-related hearing loss, refers to a gradually progressive, irreversible, symmetrical sensorineural high-frequency hearing impairment that occurs with advancing age [1]. By 2025, the global population aged 60 and above is projected to reach approximately 1.2 billion individuals, including over 500 million people affected by presbycusis [2]. The elderly population in China is projected to rise from 284 million in 2025 to 400 million by 2040, with an estimated prevalence of hearing impairment reaching up to 11.04 % [3]. In addition, among the elderly hearing-impaired individuals, approximately 66.78 % suffer from presbycusis.

The high prevalence of presbycusis exacerbates economic and social challenges by imposing a multitude of health burdens. Individuals with presbycusis often experience the "cocktail party effect", accompanied by symptoms like tinnitus, vertigo, imbalance, and falls [4]. Untreated moderate or severe presbycusis can greatly affect communication skills and may result in social isolation, depression, and possibly dementia [5]. Therefore, there is an urgent need for proactive and effective approaches to prevent and treat presbycusis.

Risk factors for presbycusis can be categorized into four groups: cochlear aging, environmental factors (such as occupational noise exposure, ototoxic medication exposure, hormone influences, alcohol, and tobacco intake), genetic factors (including race, family history, biological sex, and specific genes), and diseases (such as obesity, hypertension, and diabetes) [6,7].

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Presbycusis can be induced by the impairment of peripheral auditory organs (peripheral presbycusis) and the disorder of the central auditory pathway (central presbycusis). Peripheral presbycusis primarily involves the progressive degeneration of the cochlear sensory epithelium, cochlear nerve, stria vascularis (SVs), and basement membrane [8,9]. Central presbycusis is attributed to the dysfunction of the central auditory nervous system [10]. At the molecular level, with the process of aging, elevated oxidative stress, augmented DNA damage, deterioration of mitochondrial function, heightened chronic inflammation, and other cellular senescence, as well as reduced protection of the autophagy pathway, collectively contribute to the onset of presbycusis [11].

Currently, there is a lack of FDA-approved pharmacotherapy for presbycusis, necessitating the reliance on electronic devices such as hearing aids and cochlear implants to enhance sensory input [12]. Although electronic devices have improved speech comprehension for many people, the perceived sound quality remains imperfect and their ability to recognize natural sounds in noisy environments is limited, and these devices treat the symptoms rather than the root causes [13,14]. Hence, researchers are actively exploring novel strategies to optimize the prevention and treatment of presbycusis. With the discovery of cochlear progenitor cells and their potential for regenerating into hair cells (HCs) or neurons following damage, there is a promising opportunity to develop stem cell (SC) therapies aimed at reversing hearing loss [15]. Following the rapid advancements in sequencing technology, candidate genes associated with presbycusis have been identified, and several pathogenic mutations have been validated in animal models [16,17]. Gene therapy has effectively reversed hearing loss in animal models by introducing normal genes into target cells or repairing damaged genes using gene editing techniques [18,19]. The emergence of novel technologies like gene therapy and SC therapy instills hope for the potential cure of presbycusis.

This review offers an updated overview of the mechanisms of presbycusis and clarifies the potential associations of candidate biomarkers with various pathological types of presbycusis. The objective is to deepen the comprehension of the mechanisms of different types of presbycusis, thereby facilitating the formulation of more individualized treatment strategies. By summarizing the most recent research advancements of various therapies, especially the outcomes from fundamental and clinical trials related to gene therapy and SC therapy, the intention is to guide efforts toward finding a cure for presbycusis.

2. Classification of presbycusis

The histopathological findings of presbycusis in the inner ear involve a reduction in both inner and outer HCs, accompanied by a decrease in supporting cells, atrophy of spiral ganglion neurons (SGNs), degeneration of cochlear nerve fibers, as well as thickening, calcification, and hyalinosis of the basement membrane [8,9]. Furthermore, presbycusis also be attributed to degenerative changes within the central auditory nervous system [10]. Different types of presbycusis are defined based on distinct pathological features. Table 1 summarizes the pathological characteristics and hearing impairment features associated with various types of presbycusis.

2.1. Sensory presbycusis

Sensory presbycusis is characterized by age-related atrophy and degeneration of HCs, primarily affecting the organ of Corti located at the cochlear base [20]. Initial pathological alteration in patients with sensory presbycusis involves stereocilium loss, followed by slight distortion and flattening of the organ of Corti, subsequent loss of support and sensory cells, ultimately leaving only the ciliary membrane intact [21]. Individuals with sensory presbycusis experience an abrupt decline in high-frequency auditory perception while maintaining relatively preserved speech recognition function [22].

2.2. Metabolic presbycusis

Metabolic presbycusis is recognized by speckle-like atrophy and cystic changes of the cochlear SVs, which are particularly severe in the apex of the cochlea [23]. And due to impaired endolymphatic circulation in the cochlea, all three layers of SV cells undergo atrophy and degeneration, leading to an inability to perceive sounds across all frequencies. Consequently, the audiogram of metabolic presbycusis predominantly exhibits a flat configuration [24].

2.3. Neural presbycusis

Neural presbycusis is marked by a progressive decline in the population of SGNs, primarily affecting the basal and apical regions [25]. Patients with neural presbycusis exhibit elevated pure-tone thresholds across all frequencies, particularly at high frequencies, accompanied by disproportionate word discrimination ability loss relative to the pure-tone threshold [26].

2.4. Mechanical presbycusis

Mechanical presbycusis is attributed to conduction disorders in the inner ear which are caused by basement membrane calcification, widening, thickening, and decreased elasticity, and does not involve cochlear or auditory neuropathy [27]. Mechanical presbycusis initially appears in middle age as a progressive decrease in pure tone hearing unrelated to pathology [8].

2.5. Mixed presbycusis

The distinct subtypes of presbycusis can be differentiated by explicit clinical and/or pathological characteristics. However, the

Table 1
Classification and characteristics of presbycusis.

Classification		Pathologic characteristics	Characteristics of hearing impairment
Sensory presbycusis		Atrophy and degeneration of HCs [20].	An abrupt high-tone hearing loss [22].
Metabolic presbycusis		Speckle-like atrophy and cystic changes of SVs [23].	A flat audiogram and almost normal word discrimination [24].
Neural presbycusis		Regressive deterioration of SGNs [25,26].	The decline in word discrimination was disproportionate to the increase in pure-tone hearing thresholds [21].
Mechanical presbycusis		Conduction disorders in the inner ear, without cochlear pathological damage [27].	A slowly descending audiogram is mainly characterized by high-frequency hearing loss [8].
Mixed presbycusis		A combination of two or more pathological types mentioned above [21].	No specific audiogram pattern was observed [28].
Other presbycusis	Indeterminate presbycusis	No correlation was observed between audiometric patterns and cochlear pathological changes [29].	
	Central presbycusis	The auditory segment of the central nervous system exhibits age-related modifications [30].	

majority of presbycusis patients exhibit a combination of two or more pathological types, known as mixed presbycusis [21]. There is no specific audiogram pattern for patients with mixed presbycusis [28].

2.6. Other presbycusis

Presbycusis is categorized as indeterminate presbycusis when there is no observed correlation between audiometric patterns and pathological changes within the cochlea [29]. Additionally, in cases where age-related alterations manifest in the auditory segment of the central nervous system, leading to a decline in sound perception or communication abilities, it is referred to as central presbycusis [30].

3. Recent advances in the main mechanisms of presbycusis

3.1. Cellular senescence accelerates presbycusis

The process of presbycusis is primarily driven by oxidative stress, wherein reactive oxygen species (ROS) can damage the crucial intracellular components such as nucleic acids, lipids, and proteins [31]. Mitochondria is the organelle that governs homeostasis and serves as the primary target for free radicals [32]. Excessive ROS can damage crucial mitochondrial components, including mitigate mitochondrial DNA (mtDNA), mitochondrial membrane, respiratory chain proteins, and nuclear DNA. This may lead to disruptions to energy metabolism and facilitating cochlear senescence [33,34]. Long-term oxidative stress and mitochondrial dysfunction will trigger a series of chronic inflammatory responses, further aggravate ROS, and subsequently initiate a positive feedback effect resulting in chronic inflammatory damage [11]. Collectively, these series of responses give rise to the gradual and varying degrees of apoptosis of HC, SGN, and neurons in the primary auditory cortex, thereby impeding sound conduction and facilitating the progression of presbycusis [35].

The involvement of certain genes or proteins in the pathogenesis of presbycusis has been confirmed through their regulation of oxidative stress. The antioxidant system, comprising a diverse array of antioxidant enzymes and molecules, is indispensable in safeguarding against cochlear damage associated with oxidative stress [36]. It has been suggested that inhibition of the mTOR complex 1 (mTORC1), a component of serine/threonine kinases, delays cochlear aging caused by oxidative damage [18]. Conversely, the depletion of *Tsc1* (a negative regulator of *mTORC1*) resulted in the early-onset death of HCs and thereby accelerated hearing loss. Glucose-6-phosphate dehydrogenase attenuated cochlear aging by upregulating antioxidant enzymes and modulating apoptosis pathways [37]. Glutamyl transferase 1 (GGT1)-deficient mice exhibited elevated oxidative stress, along with extensive degeneration of cochlear and vestibular HCs, leading to presbycusis and impaired balance [38]. The transcription factor NF-E2-related factor (Nrf2) protects against presbycusis by up-regulating antioxidant enzymes and detoxifying proteins to mtDNA damage in neurons [39]. Sirtuins (SIRTs), a group of NAD + -dependent histone deacetylases comprising the seven members SIRT1-SIRT7, play a pivotal role in aging [40]. SIRT1 knockout resulted in a delayed onset of hearing loss in mice and protected cochlear HCs and SGNs against ROS [41]. Reduced levels of SIRT3 may contribute to central presbycusis by enhancing the acetylation of superoxide dismutase 2, thereby impairing its ability to scavenge ROS [17]. Another study demonstrated that SIRT3 enhanced resistance to ROS by promoting the augmentation of mitochondrial NADPH levels and the ratio of glutathione to oxidized (GSH/GSSG) via stimulating isocitrate dehydrogenase 2 [42]. $p22^{phox}$, a crucial subunit of NADPH oxidases (NOX), contributes to auditory nerve damage and presbycusis by facilitating NOX-dependent ROS generation, thereby, activating the calcium/glutamate signaling pathway-mediated toxic effect in auditory neurons [43]. The reduction of thioredoxin 2 (Trx2), an antioxidant protein, drove central presbycusis by diminishing ability of the auditory cortex to withstand oxidative stress [44]. lncRNA H19 resisted presbycusis via regulating the miR-653-5p/SIRT1 axis and thereby suppressing oxidative stress-induced apoptosis in HCs [45]. Heat shock factor 1 maintained auditory function via preserving HCs by effectively mitigated endoplasmic reticulum stress and cell apoptosis [46]. Certain drugs' inhibitory or delaying effects on presbycusis induced by oxidative stress have been demonstrated. β-Lapachone (β-lap), a potent substrate of quinone oxidoreductase 1, effectively inhibited the progression of presbycusis by augmenting cellular NAD levels and mitigating oxidative stress [47]. Oral supplementation with N-acetylcysteine (NAC), an antioxidant, can stimulate de novo GSH and prevent oxidative damage to the cochlea [38].

The dysregulation of mitochondrial-related genes and proteins, along with mtDNA mutations, significantly contribute to cochlear cell senescence [33,34]. Mice deficient in P43, the mitochondrial triiodothyronine receptor, exhibited accelerated HCs and SGNs loss, resulting in more severe hearing defects [33]. In H_2O_2-induced aging cochlear explants, the expression of dynamic protein-related protein 1 (DRP-1) gene was downregulated. However, overexpressing *DRP-1* in aging cochlear cells HEI-OC1 activated mitophagy and alleviated oxidative damage accumulation-induced mitochondrial dysfunction [34]. Knocking out *Fus1* gene, encoding a mitochondrial protein, led to heightened oxidative stress, impaired mitochondrial function, and inhibited autophagy [48]. Consequently, this resulted in severe degeneration of the cochlear mitochondrial SVs, causing early-onset and rapidly progressive hearing loss in mice. Mice harboring a mutation in mtDNA polymer γ (Polg A D257A/D257A) exhibited an accumulation of mtDNA mutations and a premature aging phenotype that led to the loss of crucial cochlear cells (HCs and SGNs) and acceleration of presbycusis [49]. In senescent cochlear, the protein levels of proliferator-activated receptor-γ coactivator-1α (PGC-1α) and mitochondrial transcription factor A (TFAM), which are key transcription factors involved in mitochondrial biogenesis, were found to be decreased [50]. Furthermore, Transcriptome sequencing analysis revealed a significant up-regulation of the long non-coding RNA AW112010 (lncRNA AW112010) gene in the cochlea of an early-onset presbycusis mouse model, and the up-regulation of lncRNA AW112010 promoted mitochondrial biogenesis and rescued cochlear HCs. In addition, senescent stria marginal cells (SMCs) exhibited a significant increase in the deletion

of mtDNA 4834 bp (equivalent to 4977 bp in humans) and mtDNA 3860 bp [16]. The inhibition of *Bak*, a mitochondrial pro-apoptotic gene, provided robust protection against presbycusis by preventing the age-related degeneration of SGNs and HCs [51]. Upregulation of uncoupling protein 2 exacerbated presbycusis by promoting apoptosis in IHCs through inducing aberrant energy metabolism and mitochondrial dysfunction [52].

Chronic inflammation accelerates cochlear cell degeneration related to presbycusis. The heightened auditory threshold observed in older individuals was closely linked to augmented levels of inflammatory cytokines (interleukin-6 and C-reactive protein) as well as an increased presence of inflammatory cells (leukocytes and neutrophils) [53]. Elevated levels of the pro-inflammatory cytokines tumor necrosis factor-alpha and interleukin-1 beta were detected in the cochlea of senescence-accelerated mouse-prone 8 (SAMP8) mice, a rapid aging mouse model, indicating that inflammation may underlie the pathogenesis of premature presbycusis in SAMP8 mice [54]. Shi et al. [55] also observed an increase in caspase-1, interleukin-1 beta, interleukin-8, and nod-like receptor protein 3 inflammasome expression in the cochlear tissue of aged rats, suggesting that the activation of nod-like receptor protein 3 may be the underlying cause of presbycusis. Furthermore, Lowthian et al. [56] investigated the potential therapeutic benefits of anti-inflammatory agents, for treating presbycusis. Pyroptosis, a pro-inflammatory form of programmed cell death, is dependent on inflammatory caspases (primarily caspase-1, 3, 4, 5, and 11) [57]. The ensuing inflammatory cascade triggered by pyroptosis has implications for the pathogenesis of presbycusis. Following cleavage by caspase-3, Gasdermin E (GSDME) induced cochlear pyroptosis and inflammation, thereby accelerating the progression of hearing loss [58]. Yang et al. [59] demonstrated that piceatannol delayed the progression of presbycusis by protecting HCs from inflammation and pyroptosis through modulating the Caspase11-GSDMD pathway.

3.2. Noise exposure-induced presbycusis

Noise exposure in the environment is a prominent etiological factor contributing to global hearing impairment, with industrialization exacerbating the duration and intensity of such exposure. Previous studies have demonstrated that early exposure to noise, short-term exposure to high-intensity noise, or long-term exposure to low-intensity noise can expedite the progression of presbycusis [60–62]. The therapy of an augmented acoustic environment holds promise for mitigating cochlear cell and neuronal damage, thereby improving presbycusis [63].

In animal models of aging, significant advancements have been achieved in elucidating the molecular mechanisms underlying the exacerbation of cochlear aging and the development of presbycusis due to noise exposure. Noise exposure also disrupted membrane surface expression of various potassium channels and reduced conductance through the potassium ion channel KV7.4 in the cochlea, representing an early event in noise-induced presbycusis [64]. Besides, the calcium-activated channels BK and SK2 protected presbycusis by counteracting noise-induced outer hair cell (OHC) hyperpolarization. Deficiency of human insulin-like growth factor 1 in mice resulted in accelerated presbycusis dependent on noise exposure, which was associated with heightened inflammation, oxidative stress, and apoptosis [65].

3.3. Autophagy prevents presbycusis

Autophagy, also called mitophagy, eliminates detrimental substances and preserves metabolic equilibrium alongside cellular homeostasis by using lysosomes as the degradative machinery to effectively eliminate cytoplasmic proteins and damaged organelles [66]. The protective role of autophagy has been substantiated in diverse age-related diseases, including atherosclerosis, Parkinson's disease, cataracts, and presbycusis [67].

Autophagy in the auditory cortex of mice exhibited a biphasic pattern, increasing during youth and adulthood, but declining in old age [68]. Furthermore, decreased mitophagy and abnormal mitochondrial morphology are also observed in the cochlear cells of aging mice, contributing to the exacerbation of presbycusis [69]. The downregulation of SIRTI hampered autophagy by suppressing acetylation process of endoplasmic reticulum stress receptor ATG9A, thereby contributing to the death of HCs and accelerating deafness in aged mice [70]. The up-regulation of *miR-34a* significantly triggered apoptosis of HCs by inhibiting autophagic flux in the aged cochlea [71]. The age-related decline of mitochondrial outer membrane-localized mitotic receptor BNIP3L/NIX in the cochlea resulted in insufficient induction of autophagy, contributing to presbycusis [69]. The level of the transcriptional repressor FOXG1 protein in the auditory system initially increased and subsequently declined during cochlear aging [72]. Additionally, reducing FOXG1 protein accelerated cochlear aging by suppressing autophagy while promoting ROS generation and cochlear cell apoptosis. The mutations in the thyroid hormone receptor alpha (*THRA*) gene were associated with an upregulation of oxidative stress and autophagy in the cochlea, resulting in abnormalities in OHCs and subsequent hearing impairment in mice [73]. Autophagy activation can inhibit aging, but excessive activation may also accelerate aging [74]. Studies have shown a decrease in the protein level of Peptidyl-prolyl cis/trans isomerase (PIN1) in HCs and SGNs of aged mice, leading to induced autophagy in cochlear cells, thereby aggravating presbycusis [74,75].

Resveratrol, a SIRT1 agonist, had the potential to delay presbycusis by restoring autophagic function in mouse Corti organs through revering HC death and hearing damage [70]. Ursodeoxycholic acid, a miR-34a inhibitor, enhanced autophagic activity to significantly rescued miR-34a-induced HC death [71]. Rapamycin, an autophagy inducer, activated OHC and SGN autophagy to effectively mitigated presbycusis [76]. Thymoquinone, an antioxidant, reversed HC apoptosis by activating the autophagy-positive regulator *SIRT1* and suppressing *Bak1* mRNA expression in the cochlea [77]. Aspirin treatment enhanced the survival of HCs in aging mice by upregulating the FOXG1 protein level and increasing autophagy [72]. Urolithin A (UA) delayed presbycusis by reducing auditory cell senescence and inducing mitochondrial autophagy [78].

Presbycusis encompasses a multitude of molecular mechanisms, with numerous genes and proteins assuming pivotal regulatory

roles. Table 2 provides an overview of the key genes and proteins implicated in presbycusis. The alterations in these factors within the aging auditory system (either increased or decreased), their impact on presbycusis progression (inhibition or facilitation), as well as the specific structures affected by these factors, including HCs, supporting cells, SGNs, and auditory cortex, along with the types of presbycusis associated with these factors are comprehensively documented.

4. Research progress on genetic susceptibility of presbycusis

Genetic susceptibility studies of presbycusis encompass linkage analysis and genome-wide association studies (GWAS). Linkage analysis is effective in investigating the association between familial diseases and gene loci, and GWAS provides a more comprehensive examination of the entire genome by identifying genetic variants associated with disease or phenotype in populations [79]. Garringer et al. [80] conducted linkage analysis on 56 pairs of male veteran twins and identified the DFNA18 locus in the chromosome 3q22 region as a potential genetic factor associated with presbycusis. Furthermore, Huyghe et al. [81] performed genome-wide SNP linkage analysis on 1126 samples from 204 families and discovered that the locus at 8q24.13-q24.22 is significantly associated with

Table 2
Genes/proteins associated with presbycusis.

Effect on presbycusis	Mechanisms	Genes/Proteins	Levels in the aging auditory system	The affected cochlear tissue/central auditory tissues	Possible associated presbycusis	Reference
Inhibition	Oxidative stress	GGT1	/	IHCs	Sensory presbycusis	[38]
		Nrf2	/	HCs, SGNs	Sensory presbycusis, neural presbycusis	[39]
		SIRT3	/	HCs, SGNs	Sensory presbycusis, neural presbycusis	[42]
	Oxidative stress and autophagy	PIN1	Decrease	HCs, SGNs	Sensory presbycusis, neural presbycusis	[74,75]
		THRA	/	OHCs	Sensory presbycusis	[73]
	Oxidative stress, autophagy, and apoptosis	FOXG1	Increase in 12-month-old mice, while decrease in 24-month-old mice	HCs	Sensory presbycusis	[72]
		Trx2	Decrease	Auditory cortex	Central presbycusis	[44]
	Oxidative stress, mitochondrial dysfunction, and autophagy	DRP-1	Decrease	HCs	Sensory presbycusis	[34]
		Fus1	/	SVs	Mechanical presbycusis	[48]
		P43	/	HCs, SGNs	Sensory presbycusis, neural presbycusis	[33]
	Oxidative stress, mitochondrial dysfunction, and inflammation	NAD	Decrease	/	/	[47]
	Mitochondrial dysfunction.	*lncRNA AW112010*	Increase	HCs	Sensory presbycusis	[50]
		PGC-1α	Decrease	HCs	Sensory presbycusis	[50]
	Autophagy	BNIP3L/NIX	Decrease	HCs, SCs, and SGNs	Sensory presbycusis, neural presbycusis	[69]
		SIRT1	Decrease	HCs	Sensory presbycusis	[70]
Facilitation	Oxidative stress	NOX	/	OHCs and SGNs	Sensory presbycusis, neural presbycusis	[43]
		SIRT1	/	HCs and SGNs	Sensory presbycusis, neural presbycusis	[41]
	Oxidative stress and apoptosis	Bak	Increase	HCs and SGNs	Sensory presbycusis, neural presbycusis	[51]
	Oxidative stress and autophagy	mTORC1	Increase	HCs and SGNs	Sensory presbycusis, neural presbycusis	[18]
	Oxidative stress, mitochondrial dysfunction, and apoptosis	mtDNA 3860 bp deletion	Increase	SMCs	Metabolic presbycusis	[16]
	Autophagy	miR-34a	Increase	HCs	Sensory presbycusis	[71]
	Mitochondrial dysfunction and apoptosis	mtDNA 4834/ 4977 bp deletion	Increase	SMCs	Metabolic presbycusis	[16]
/	Oxidative stress	SIRT3	Decrease	Auditory cortex	Central presbycusis	[17]

presbycusis. Friedman et al. [82] and Van et al. [83] used GWAS to report significant associations between presbycusis with SNPs, namely rs11928865 and rs161927, in the metabotropic glutamate receptor 7 (*mGluR7*) gene. Additionally, Van et al. identified a significant association between presbycusis and SNP rs5011436, which is located within an intron of the IQ motif containing GTPase activating protein 2 (*IQGAP2*) gene.

Genetic variation exerts a profound influence on the occurrence and progression of presbycusis. The variants within mitochondrial genes and other candidate genes may elevate an individual's susceptibility to presbycusis. mtDNA mutations at positions 4977 bp exhibit high mutation rates in human patients with presbycusis [84]. In a rat model, a mtDNA mutation at position 4834 bp is linked to an increased incidence of presbycusis [84]. The mutations of the N-acetyltransferase 2*6A (*NAT2*6A*) allele can enhance genetic vulnerability to presbycusis and individuals carrying *NAT2*6A* mutant alleles face a greater risk of hearing loss compared to those with *NAT2*6A* heterozygous mutations [85]. A study conducted in Japan demonstrated the association of *CDH23* variants with diverse phenotypes of hearing loss, including presbycusis [86]. A study in the Caucasian population identified the causative variant within a 13-kb genomic region of the candidate susceptibility gene *KCNQ4*, which is associated with presbycusis [87]. Several population-based studies have provided support for the protective effect of the *APOE* allele on hearing and its role as a common molecular driver of presbycusis and Alzheimer's disease [88]. Previous studies have found that in the elderly population, individuals with non-syndromic sensorineural hearing loss exhibit a lower frequency of *APOE ε4* alleles compared to those with normal hearing, suggesting that their allelic mutations may predispose them to cochlear sensorineural hearing loss-induced by atherosclerosis and ischemic damage [89]. Additionally, another research found a significant association between the *UCP2* Ala55Val polymorphism and hearing impairment in elderly Japanese individuals [90].

In addition, there were ethnic disparities in the significance of some genes' association with presbycusis. While *GSTM1* and *GSTTI* polymorphisms exhibited significant associations with presbycusis in the Finnish population, these associations were not observed in the European and Chinese populations [91,92]. Similarly, *GRHL2* was found to be significantly associated with presbycusis in the European population [93], but not in the Han population [94]. The *GRHL2* rs10955255 polymorphism was identified as being associated with an increased risk of presbycusis, particularly in individuals of Caucasian descent, while the rs1981361 polymorphism was recognized as a potential risk factor for presbycusis among Asians [95] These findings underscore the significance of gene-environment interactions in the pathogenesis of presbycusis, emphasizing the need for a comprehensive understanding across diverse ethnic groups and populations.

5. Therapies of presbycusis

5.1. Hearing aids therapy

Amplification of speech through hearing aids, the most prevalent therapeutic approach for presbycusis, benefits individuals with this condition by enhancing auditory perception [96]. These devices are primarily utilized for individuals experiencing mild to moderate hearing loss [97]. Empirical studies have unequivocally demonstrated that using hearing aids can augment auditory experiences, enhance cognitive competence, and improve working memory by bolstering the cortical neuroplasticity of individuals afflicted with presbycusis [96]. The findings of a systematic review with meta-analysis indicated that hearing aids could alleviate the detrimental psychological, social, and emotional consequences associated with hearing impairment and improve health-related quality of life, which could be attributed to the enhanced capacity for communication [98]. Previous researches have suggested wearing hearing aids may be insufficient in alleviating depression in individuals with presbycusis [99,100] while a latest investigation has shown significant improvement in depressive symptoms during the initial year of hearing aid usage [101]. The inconsistencies in the outcomes of the abovementioned studies exploring the potential of hearing aids to alleviate depression could be attributed to several factors. Firstly, discrepancies in research methodologies and sample populations may have contributed to the variations in results. Secondly, the varying performance of hearing aids could also be a factor. For instance, early hearing aids amplified background noise, which potentially diminished presbycusis individuals' social activities and thereby failed to improve their depression. With the advancements in hearing aid technology, noise reduction capabilities have been significantly enhanced, leading to an improved usage experience and emotional well-being for presbycusis patients, and ultimately contributing to a reduction in depression. Furthermore, factors such as social and familial support, and the subjects' psychological therapy, which may not have been adequately controlled and considered in the studies, could have potentially impacted the consistency of the findings.

Despite being the most prevalent treatment for presbycusis, the utilization of hearing aids is limited due to their cost and less-than-ideal user experience. The average cost of a hearing aid is $4700 (range: $3300-6000) [102]. Patients must undergo a prolonged adaptation period to acclimate to the new sound signal, and some individuals opt to discontinue using hearing aids due to perceived suboptimal sound quality [102]. Furthermore, hearing aids are limited to sound amplification and cannot facilitate the repair of damaged auditory nerves or inner ear structures, thus incapable of fully restoring hearing. The future advancements in hearing aid technology, if further enhancing technical performance, optimizing wearing comfort, and reducing costs, will facilitate their broader application in alleviating mild and moderate hearing loss as well as serving as an adjunctive treatment for severe cases.

5.2. Cochlear implantation (CI) therapy

In addition to hearing aids, cochlear implants are the sole remaining efficacious modality for hearing rehabilitation in elderly aged 70 and above with severe to profound hearing impairment. As an electronic bionic device, cochlear implants consist of two main components: an external device (including a microphone, speech processor, and transmitter) and an implant (comprising a receiver

and electrode system) [103]. The microphone captures sound, the speech processor converts it into an electrical signal, the transmitter transmits the signal to the receiver, and the electrode system directly stimulates the auditory nerve, thereby restoring or reconstructing hearing function in the profoundly deaf [103]. Multiple studies have consistently demonstrated that CIs significantly enhanced speech recognition, cognitive function, mental well-being, and health-related quality of life for patients suffering from presbycusis [104,105]. This intervention also provides substantial economic benefits [106].

The prognostic factors of CI surgery are multifaceted. In general, higher age at implantation, more severe hearing loss, and longer duration of hearing loss were associated with inferior outcomes and a prolonged postoperative recovery period [107–109]. Furthermore, the duration of profound hearing loss and residual speech recognition ratio exhibited a higher predictive value than the age at which individuals undergo CIs, indicating that age should not serve as a limiting factor for cochlear transplantation in elderly patients [108]. The poor prognosis in elderly individuals may be attributed to the overall aging of the auditory system, damage to spiral ganglion cells, reduced central cortical plasticity, and consequently decreased auditory processing capabilities [110]. Additionally, the relatively weaker cognitive abilities, adaptability, and learning capacity in older adults could also limit their understanding and processing of auditory information, thereby affecting surgical outcomes [109].

The implementation of cochlear implants in elderly patients often leads to certain complications. The primary serious complications identified are device removal and device failure, while the most prevalent minor complications found are imbalance, infection, dysgeusia, and transient facial palsy [111,112]. Furthermore, serious complications also encompass wound disruption and flap dehiscence, while minor complications may manifest as delayed transient facial palsy, facial nerve stimulation, tinnitus, and vertigo. Age should not be a limiting factor for CI complications in the elderly, as these complications are comparable to those observed in young individuals and children; however, patients with severe hearing damage, complete cochlear loss, suppurative otitis media, psychosis, and contraindications to CIs should be excluded from consideration for CIs [112].

Although certain complications may arise following cochlear surgery, the numerous advantages of this procedure far outweigh the rare postoperative adverse outcomes. Less than 1 % of the global population has benefited from cochlear implantation, indicating the considerable potential for the dissemination and uptake of CIs [112]. Limited public awareness, and the absence of diagnostic centers, professional equipment, and personnel, coupled with financial constraints faced by patients, have impeded the widespread utilization of this technology [113]. Consequently, the government should develop corresponding policies and strategies to address the availability, accessibility, and affordability of cochlear implants in the future.

5.3. Drug therapy

Drug therapy offers several advantages in treating presbycusis, including enhanced auditory function, reduced tinnitus symptoms, and improved quality of life through mechanisms such as promoting ear microcirculation, nourishing nerves, exerting anti-inflammatory effects, and combating free radicals [114]. However, it is important to note that drug interventions can only decelerate the progression of presbycusis rather than reverse the irreversible degenerative changes occurring in the auditory system.

Due to the significant role of oxidative stress in presbycusis, antioxidants have been extensively investigated in presbycusis pharmacognosis, with some demonstrating potential benefits. Several studies have revealed that augmenting the intake of vitamin A, vitamin C (VC), vitamin E (VE), folic acid, riboflavin, magnesium, and lycopene can effectively reduce the prevalence of presbycusis and improve hearing in older individuals, thereby advocating for appropriate dietary counseling to prevent hearing loss [115–117]. Moreover, antioxidants (beta-carotene and VC) demonstrated a synergistic effect with magnesium in reducing the risk of hearing loss [118]. However, a six-month study found no significant difference in hearing threshold between the antioxidant VC and VE and placebo groups [119]. Apart from human studies, animal models are valuable tools for investigating the therapeutic potential of antioxidant drugs in presbycusis. For instance, oral supplementation of β-lap has demonstrated its ability to mitigate oxidative stress-induced damage to HCs, SVs, and SGNs in aged mice, which holds promise for treating sensory presbycusis, metabolic presbycusis, and neural presbycusis [47]. Similarly, oral administration of NAC or intraperitoneal injection of rapamycin exhibited efficacy in rescuing HC damage caused by ROS in mice, suggesting that these antioxidants may be effective in the treatment of sensory presbycusis [18,38]. Long-term administration of Selegiline, a monoamine oxidase B inhibitor, could mitigate the progression of presbycusis in BALB/c mice through its antioxidative properties [120]. Additionally, melatonin-treated mice exhibited higher distortion product otoacoustic emission amplitude and signal-to-noise ratio along with reduced HC damage and delayed onset of presbycusis, suggesting melatonin could be considered as a potential pharmacological intervention for sensory presbycusis [121].

Based on the diverse mechanisms of cochlear damage, various therapeutic strategies have emerged, including statins, teprenone as a heat-shock protein inducer, cochlear vasodilators, salicylic acid, 1-methyl nicotinamide, cocoa flavonoids, and steroids [122–128]. Additionally, traditional Chinese medicine preparations like ErLong ZuoCi have shown promising results in animal experiments and clinical trials for presbycusis [129]. Recently, a study from Switzerland utilized bulk RNA sequencing to identify 27 potential FDA/EMA-approved drugs that target neuronal processes, inflammation, oxidative stress, cell signaling, and other biological processes associated with presbycusis by analyzing transcriptomes from cochlear substructures [130].

Previous studies have indicated that drug treatment is primarily suitable for various types of presbycusis, including sensory, metabolic, and neural presbycusis. Furthermore, pharmacotherapy has been investigated as a potential preventive strategy to reduce the risk of presbycusis. However, for established cases of presbycusis, monotherapy with drugs may yield limited effects and a combination approach involving other treatments like hearing aids or cochlear implants might prove more effective. Overall, pharmacotherapy has demonstrated certain advantages in treating presbycusis; however, most studies have been confined to animal models, necessitating high-quality clinical trials to extrapolate these findings to humans and ascertain the safety and efficacy of such drugs in human subjects.

5.4. SC therapy

HCs and auditory neurons of mammals exhibit limited regenerative capacity, resulting in irreversible hearing impairment. However, SC-based regeneration therapy offers a promising avenue for ameliorating permanent inner ear damage. Recent advancements in research have instilled renewed optimism for harnessing the potential of SCs to treat hearing loss. Li et al. [131] successfully isolated inner-ear vestibule-derived SCs with pluripotent differentiation capacity from adult mice and subsequently transplanted them into chicken embryos in vitro, where they effectively differentiated into HCs within the developing inner-ear capsule. This study elucidated the possible source of regeneration for inner ear HCs, suggesting the promise of cell transplantation for auditory reconstruction in individuals with hearing impairment. Corrales et al. [132] demonstrated that transplanting neural progenitor cells into denervated gerbils' cochlea resulted in their survival and subsequent nerve regeneration within the sensory epithelium of the organ of Corti. Additionally, Ren et al. [133] showed that neural SC transplantation significantly attenuated neuronal apoptosis, reduced auditory brainstem response (ABR) thresholds, and improved hearing in aged deaf mice. Furthermore, introducing exogenous SCs and embryonic neurons into the inner ear of adult mammals may serve as a compensatory measure for the degenerative loss of sensory and neuronal cells [134]. These findings suggest that regenerative therapies hold promise for replacing apoptotic cochlear cells and neurons to restore hearing function.

A phase 1 clinical trial in the US utilized intravenous infusion of Autologous Umbilical Cord Blood to treat children with acquired sensorineural hearing loss [135]. Notably, 45 % of the patients demonstrated significant improvement in ABR following the infusion, and no adverse events were encountered. In another phase I clinical trial in Germany, extracellular vesicles (EVs) derived from human mesenchymal stromal cells (MSC) were transplanted into the inner ear of patients with Meniere's disease, thereby alleviating the inflammatory response of cochlear transplantation, being safe, and holding the potential to enhance cochlear health and speech perception [136]. These phase I clinical trials have initially attested to the safety and benefits of SC therapy in treating deafness. Although these studies are not particularly aimed at presbycusis, the mechanism of SC regeneration is comparable, and it can offer valuable references for SC therapy for presbycusis. Furthermore, larger-scale phase 2/3 clinical trials are requisite to provide more support for SC therapy in treating deafness.

SC transplantation holds great promise as a treatment approach for initiating HC regeneration and restoring hearing loss in mammals affected by presbycusis, yet numerous limitations and challenges persist. The current research primarily focuses on mouse models; however, further investigation and validation are necessary to extrapolate findings from mouse to humans due to significant interspecies variations. In order to meet the demands of large-scale clinical applications, it is necessary to develop novel SC expansion technologies that can ensure a stable and abundant supply of cells [137]. Preserving the long-term activity and differentiation potential of SCs poses a significant constraint on the advancement of SC therapy technology [138]. Furthermore, to advance the clinical applications of SC therapy in treating presbycusis, it is imperative to optimize cost-effectiveness for enhanced accessibility and ensure the safety of SC therapy by mitigating potential immune response or adverse reactions induced by SC administration.

5.5. Gene therapy

Genetic factors can influence the susceptibility and severity of presbycusis. Although hearing aids and CIs are the primary interventions for presbycusis, they cannot fully restore auditory function to its original state. Furthermore, even if HCs regenerate successfully through SC therapy, their subsequent loss due to congenital mutations remains inevitable. Therefore, gene therapy appears to be a fundamental approach to addressing hereditary hearing loss. The United States Food and Drug Administration defines gene therapy as "a technique that modifies an individual's genes (by replacing, suppressing or editing faulty genes) to treat or cure diseases [139]. The presence of the blood-labyrinth barrier in the inner ear effectively attenuates systemic immune responses, making it an ideal target for gene therapy [140]. Moreover, the existence of endolymphatic and perilymph fluid within the inner ear facilitates the efficient transfection of vector-carried genes into cochlear cells, ensuring precise targeting for gene therapy [141].

Gene therapy for restoring hearing in individuals with presbycusis has been investigated using mouse models. The activity of *mTORC1* in cochlear NSE gradually increases with age, and the inhibition of *mTORC1* activity by knocking out the key component of *mTORC1*, Raptor, can promoted the survival of HCs and SGNs in the aging inner ear, thereby restoring hearing in mice with presbycusis [18]. Similarly, Han et al. [41] demonstrated that the deletion of *Sirt1* protected cochlear HCs and SGNs, resulting in a delayed onset of presbycusis through the use of *Sirt1* knockout mouse models. Moreover, *Bak* knockout mice exhibited reduced damage to HCs and SGNs, leading to a postponed occurrence of presbycusis [51]. These findings present a novel potential for the prevention and treatment of sensory presbycusis as well as neural presbycusis. In addition, the targeted deletion of the *Foxg1* gene in HCs in mice resulted in an expedited process of HC apoptosis and the development of presbycusis, thereby suggesting that therapeutic interventions aimed at *Foxg1* gene deletion could potentially serve as a preventive and curative approach for sensory presbycusis [72]. Based on the presbycusis animal models, certain genes have been identified as potential contributors to the pathogenesis of this condition. These candidate genes may influence hearing by modulating cochlear cells and auditory nerves. However, it should be noted that these mutated genes do not necessarily directly induce the onset of presbycusis; instead, they may solely enhance the susceptibility to this condition. Additionally, other factors such as environmental influences and genetic background are also likely to play a pivotal role in presbycusis development. Therefore, conducting a comprehensive investigation and exploration into these candidate genes is crucial for elucidating their contribution to presbycusis pathogenesis. Future research should focus on delving deeper into the specific roles and regulatory mechanisms of these genes within the human inner ear. This entails examining their involvement in maintaining inner ear homeostasis, facilitating HC regeneration, and modulating neuronal function.

Initial advancements have been achieved in clinical trials of gene therapy for the treatment of deafness. The study conducted by Shu

et al. [142,143] demonstrated significant improvement in auditory function for 83 % (5/6) of children diagnosed with autosomal recessive deafness 9 (DFNB9) caused by *OTOF* gene mutation through the utilization of adeno-associated virus (AAV) serotype 1 -carrying human *OTOF* transgene (AAVI-hOTOF) gene therapy, without observed dose-limiting toxicity. The researchers are conducting larger sample sizes and longer follow-up trials in order to substantiate the efficacy and safety of AAVI-hOTOF gene therapy. Although significant advancements have been achieved in the treatment of hereditary hearing loss caused by mutations in the *OTOF* gene, clinical trials for gene therapy targeting the more prevalent inherited hearing loss resulting from mutations in *GJB2*, *SLC26A4*, and mitochondrial *12S rRNA* [144] have not yielded successful outcomes. Therefore, future research should focus on developing therapeutic strategies targeting these deafness-associated genes to benefit more patients.

The successful application of gene therapy in treating hereditary hearing loss patients can serve as a valuable reference for assessing the efficacy and safety of gene therapy for presbycusis resulting from genetic mutations. Despite disparities in the age of onset and underlying mechanisms between hereditary hearing loss and presbycusis, the fundamental principle of gene therapy remains consistent, involving the repair or replacement of mutated genes to restore normal physiological functions. Therefore, considering the patient's age, health status, and potential adverse effects comprehensively, patients with presbycusis may also derive benefits from gene therapy as it continues to advance.

6. Conclusions and future prospects

Presbycusis is a prevalent affliction affecting elderly individuals, characterized by a progressive auditory decline that significantly impacts their overall well-being. This article offers a comprehensive exploration of the pathological and clinical features associated with different forms of presbycusis, along with advancements in scientific investigations of its molecular mechanisms and therapeutic interventions.

The pathological manifestations of presbycusis primarily encompass damage and loss of HCs, degeneration of the SVs, loss of SGNs, basement membrane damage, and central auditory cortex impairment, resulting in elevated hearing thresholds while also impacting sound recognition and language comprehension abilities [8,9]. Based on distinct pathological changes, presbycusis can be categorized into different types. Table 1 summarizes the pathological characteristics and hearing impairment features associated with various types of presbycusis.

Certain genes and proteins play a pivotal role in the onset and progression of presbycusis, with their expression and regulation exerting either promotive or inhibitory effects on the advancement of this condition. Based on distinct cochlear pathological changes, presbycusis can be classified into various subtypes, potentially associated with different genes and proteins. By investigating the impact of these factors on cochlear lesions, we can infer a presbycusis classification linked to them. The genes/proteins associated with presbycusis are presented in Table 2, along with their alterations in the aging auditory system, their impact on the progression of presbycusis, and the specific structures affected by these factors. Additionally, Table 2 provides insights into potential associations between these genes/proteins and different types of presbycusis. It is crucial for future investigations to further elucidate the precise mechanisms and interrelationships among these genes/proteins, thereby enhancing our comprehension of the pathogenesis underlying presbycusis. Simultaneously, additional clinical studies are warranted to validate the applicability of these molecular mechanisms in diagnosing and treating presbycusis.

Significant advancements have been achieved in the prevention and treatment of presbycusis. For older individuals suffering from presbycusis, a three-tiered therapeutic approach can be implemented. Firstly, in the initial stages of presbycusis, primary preventive measures can be implemented to slow down the rate of auditory decline. Older adults should prioritize maintaining a healthy lifestyle that includes a well-balanced diet, moderate exercise routine, optimal sleep patterns, and avoidance of excessive fatigue. Additionally, supplementation with antioxidants such as vitamin C, E, and A may help mitigate oxidative stress reactions while safeguarding auditory function [115–117]. Secondary intervention strategies involve using hearing aids to amplify sound for individuals with mild to moderate presbycusis, and tertiary treatment interventions include cochlear implant surgery for those with severe or profound presbycusis, aimed at enhancing their auditory capabilities.

Hearing aids is the most prevalent therapy for mild to moderate presbycusis, conferring benefits to individuals by enhancing auditory perception, cognitive ability, and alleviating depression associated with hearing impairment [96–98,101]. Nevertheless, it's high price, lack of clarity, sound distortion, poor personalization, and insufficient listening efficacy in noisy environments and close listening scenarios is unsatisfactory [13,14]. As a result, the role of hearing aids can only be regarded as compensation rather than treatment. Compared with hearing aids, CIs necessitate surgical implantation, which adds a process of adaptation and rehabilitation. Moreover, the external device of the CIs bears disability tags and is prone to being lost, resulting in a poor experience for the wearer and restricting the popularity of CIs to a certain extent. However, for individuals with severe to profound or total hearing loss who are dissatisfied with the outcomes of hearing aids, CIs still need to be considered. CIs restore or reconstruct hearing by stimulating the auditory nerve [103]. Besides enhancing auditory perception, they have more advantages regarding sound clarity, speech perception in noisy environments, and speech comprehension [104,105]. Furthermore, the development of fully implanted cochlear implants is anticipated to promote the broader application of this therapy. Drug therapy is predominantly employed in patients with early and moderate presbycusis. Through effects such as enhancing the microcirculation of the inner ear, nourishing nerves, and exerting anti-inflammatory actions, it can alleviate the symptoms of deafness and enhance the patient's quality of life [114]. Given the complex etiology of presbycusis, it is challenging to achieve a cure through single-drug therapy. A combination with other treatment modalities, such as hearing aids and cochlear implantation, is necessary to formulate a comprehensive treatment strategy and enhance the therapeutic outcome.

Although current interventions, such as hearing aids and CIs, can mitigate hearing loss by enhancing speech input, none of them

offer a definitive cure for presbycusis. Whole-genome and whole-exome sequencing enable comprehensive detection of all existing variations, facilitating the identification of multiple rare variants associated with susceptibility genes for presbycusis. Innovative approaches such as gene therapy or gene editing techniques have demonstrated successful application in the restoration of damaged genes in presbycusis animals. Furthermore, gene therapy has achieved success in restoring auditory function among patients with hereditary hearing loss, providing clinical references for its efficacy and safety in treating presbycusis [142,143]. After taking into some factors such as the patient's age, health status, and potential side effects, it is promising to implement gene therapy for treating presbycusis caused by genetic mutations, aiming to achieve a fundamental cure for this condition. The efficacy of SC and drug therapies has been demonstrated in animal models of presbycusis. In particular, SC therapy has shown significant progress in regenerating the essential components of inner ear function, such as HCs or SGNs, thereby promoting the recovery of auditory function and presenting a promising therapeutic option for individuals with presbycusis. In order to improve the efficacy of drug therapy and reduce systemic side effects, researchers are currently investigating methods for targeted drug delivery to the cochlea that bypass the blood-labyrinth barrier. This includes utilizing sophisticated drug delivery systems like nanocarriers to achieve accurate and efficient direct drug delivery to the cochlea. However, significant challenges remain in the transition from animal models to clinical applications, including inter-species variations, technical difficulties in SC research (such as differentiation, proliferation, and transplantation), as well as safety and ethical concerns. These crucial factors need to be meticulously consideration and resolution as we advance these innovative treatments. Nevertheless, there have been phase I clinical trials of SCs in children with acquired sensorineural hearing loss [135]. As technology continues to improve and challenges are addressed, these approaches hold promise for becoming effective treatments for presbycusis. in the future.

Moreover, the aging process leads to changes in both the peripheral and central auditory systems. While much attention has been given to therapeutic approaches for peripheral presbycusis, these methods have not been sufficient in addressing the challenges presented by central presbycusis. Central presbycusis is commonly viewed as the consequence of peripheral presbycusis, marked by simultaneous declines in both hearing and cognitive function [145]. The intricate nature of this condition complicates clinical diagnosis and the development of successful rehabilitation plans. Presently, the prevailing methods for addressing central presbycusis involve the use of hearing aids to address peripheral hearing loss, accompanied by customized auditory and cognitive training aimed at improving sensory input and lessening cognitive strain, potentially slowing the advancement of central presbycusis. However, some studies suggested that central presbycusis may independent from peripheral presbycusis in certain aspects, indicating that despite enhancements in peripheral hearing with hearing aids, assistance for central presbycusis may be limited [10]. Future research on central presbycusis should focus on gaining a more thorough understanding of the internal relationship between central presbycusis and peripheral presbycusis. This clarification is crucial for improving rehabilitation strategies for central presbycusis. Tailored interventions, including psychoacoustic testing and monitoring of specific auditory markers, should be utilized to enhance management outcomes for older adults with cognitive impairment. These interventions should be accompanied by a high-quality audiological evaluation system to ensure a comprehensive and accurate diagnosis of auditory function. Moreover, the utilization of neuroimaging technology has the potential to assist in the identification of both structural and functional alterations within the central auditory system. The active investigation of artificial intelligence technology is imperative for its incorporation into the development and utilization of cochlear implants, ultimately allowing for the creation of individualized treatment strategies aimed at enhancing auditory function and overall quality of life for patients.

In conclusion, the etiology of presbycusis is complex, with ongoing research remaining limited and treatment modalities in a in a maturation stage. In light of the demographic shift towards an aging population, it is crucial to engage in thorough investigations of age-related hearing impairment to develop more targeted and efficacious therapeutic interventions for affected individuals.

CRediT authorship contribution statement

Xiaoying Lin: Writing – original draft, Visualization, Investigation, Data curation. **Yiyuan Xu:** Writing – review & editing, Validation, Supervision, Conceptualization. **Chunmei Fan:** Writing – original draft, Visualization, Validation. **Guanbin Zhang:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Data availability statement

Not applicable. This is a descriptive review that relies primarily on the analysis and synthesis of existing literature. No original data were generated or analyzed during the course of this study.

Ethics statement

Review or approval by an ethics committee was not needed for this study because no data on patients or experimental animals was used in the article. Informed consent was not required for this study because no clinical data was produced in the review article.

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