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Review Article

The emerging roles and therapeutic implications of immunosenescence-mediated inflammaging in age-related hearing loss

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Abstract: Age-related hearing loss (ARHL) represents one of the most prevalent chronic sensory deficits experienced by the elderly, significantly diminishing their quality of life and correlating with various medical and psychological morbidities. This condition arises from the cumulative effects of aging on the auditory system, implicating intricate interactions between genetic predispositions and environmental factors. Aging entails a progressive decline in immune system functionality, termed immunosenescence, leading to a chronic low-grade inflammation known as inflammaging. This phenomenon potentially serves as a common mechanism underlying ARHL and other age-related pathologies. Recent research suggests that rejuvenating immunosenescence could mitigate inflammaging and ameliorate age-related functional declines, offering promising insights into anti-aging therapies. Consequently, this review endeavors to elucidate the role of immunosenescence-mediated inflammaging in ARHL progression and discuss its therapeutic implications.

Keywords: Age-related hearing loss (ARHL), immunosenescence and inflammaging

Introduction

Age-related hearing loss (ARHL) stands as a prevalent chronic sensory deficit commonly experienced by the elderly, characterized by bilateral and progressive sensorineural hearing loss [1]. This condition ensues from the cumulative effects of aging on the auditory system, involving complex interactions between genetic predisposition and environmental factors [2]. According to estimates by the World Health Organization (WHO), by 2050, approximately 2.5 billion individuals over the age of 60 will encounter some degree of hearing loss, imposing a significant burden on medical insurance [3]. While ARHL is not life-threatening, it is associated with various medical and psychological morbidities, including cognitive decline, social isolation, depression, and loss of self-esteem [4-6]. Presently, effective preventative and treatment strategies beyond prosthetic devices are scarce [7], underscoring the necessity for a deeper understanding of the mechanisms driving ARHL progression.

Aging is marked by a progressive dysfunction of the immune system, referred to as immunosenescence, which encompasses lymphoid organ remodeling and a diminished ability to regulate inflammation [8]. Consequently, immunosenescence can give rise to chronic low-grade inflammation and associated damage in various aging tissues, a process often termed inflammaging. Dysregulated immune function and elevated serum levels of pro-inflammatory cytokines have been linked to age-related morbidities, suggesting that immunosenescence-mediated inflammaging may represent a common mechanism underlying ARHL and other age-related pathologies, providing new clues for the development of anti-aging therapy [9-12]. Therefore, this review examines the role of immunosenescence in age-related cochlear inflammaging and discusses its therapeutic implications for ARHL.

The cellular pathology of ARHL

Prior research has established that the primary etiology of ARHL lies in irreversible damage to

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the sensorineural tissues within the cochlea, with the gradual loss of cochlear hair cells (HCs) serving as an early indication of cochlear function decline [13-16]. Additionally, histological investigations have confirmed extensive age-related degenerative changes in the cochlea, encompassing HCs and spiral ganglion neurons (SGNs) loss, diminished vascularization, stria vascularis (SV) atrophy, and impaired function of supporting cells (SCs) [17-21]. Moreover, recent studies have highlighted aging's detrimental effects on auditory pathways, resulting in the loss of auditory nerve afferent fibers and synapses [22, 23].

Numerous studies have delved into the cellular mechanisms underlying age-related hearing loss (ARHL) at the single-cell level. Shrestha et al. conducted a systematic investigation into the effects of aging on different subpopulations of type I spiral ganglion neurons (SGNs), revealing that type IC SGNs were particularly susceptible to aging [24]. Besides, Liu et al. performed molecular and cytological profiling of murine hair cells (HCs), uncovering an age-related upregulation of genes associated with DNA damage, oxidative stress, and autophagy. This suggests that functional impairment precedes HC loss and contributes to ARHL [25]. Furthermore, Sun et al. recently presented the first dynamic single-cell landscape of aging cochlear tissue in mice, identifying aging-associated transcriptomic changes in 27 types of cochlear cells. Intriguingly, this study revealed unexpected age-related transcriptional fluctuations in intermediate cells localized in the stria vascularis (SV). Moreover, it demonstrated that upregulation of the endoplasmic reticulum (ER) chaperone protein HSP90AA1 could alleviate ER stress-induced damage associated with aging, offering a potential therapeutic target for preventing ARHL [26].

In summary, the cellular pathology of ARHL reveals an age-related increase in inflammatory responses within the cochlea, suggesting that inflammaging may significantly contribute to the onset and progression of ARHL.

Inflammaging as an important underlying mechanism of ARHL

The cochlea was previously considered an immune-privileged organ; however, recent research has demonstrated the significant impact of systemic inflammation on cochlear function [27-29]. Accumulating evidence suggests that inflammaging serves as a crucial pathophysiological mechanism underlying the onset and advancement of ARHL [30]. Verschuur et al. systematically examined the relationship between serum inflammatory markers and ARHL using data from the British cohort study. They identified IL-6, C-reactive protein, white blood cell, and neutrophil counts as precise predictors of hearing loss severity in older individuals over a 10-year period, indicating a progressive decline in auditory function alongside systemic inflammation during aging [31, 32]. This finding was corroborated by Lassale et al., who observed a significant correlation between white blood cell count and ARHL [33]. Furthermore, macrophage migration inhibitory factor (MIF), a key innate immunity regulator, was previously noted to play a critical role in maintaining normal auditory function but was found to be downregulated in older adults [34]. Additionally, several studies have highlighted the influence of individual genetic variations on ARHL development, with significant associations observed between ARHL susceptibility and polymorphisms of TNF-α, TNF-α receptors, and IL-1 receptors [35-37]. In light of these findings, Lowthian et al. initiated a large-scale Australian-based clinical trial to investigate the potential therapeutic effects of aspirin, a mild anti-inflammatory agent, on ARHL progression. Upon completion, this trial may furnish further evidence supporting the benefits of mitigating inflammaging in preventing ARHL.

Furthermore, preclinical investigations have provided substantial evidence supporting the link between inflammaging and ARHL. Utilizing next-generation sequencing technology, Su et al. verified the upregulation of multiple inflammatory genes during cochlear aging, notably enriched in pro-inflammatory pathways such as the toll-like receptor signaling pathway and TNF signaling pathway [38]. Additionally, Sun et al. elucidated a dynamic single-cell transcriptomic profile of aging mouse cochlea, identifying a significant accumulation of infiltrated neutrophils and a gradual increase in expression of senescence-associated secretory phenotype (SASP)-related genes, suggesting heightened inflammatory responses in the aging cochlea [26]. Concurrently, Noble et al. extensively documented age-related morphological and functional changes in cochlear macrophages,

revealing a notable increase in activated macrophages within the aging cochlea, which exhibited enhanced interactions with glia, potentially contributing to cochlear inflammaging and consequent ARHL [39]. Furthermore, NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3), a pivotal initiator of inflammation, has been implicated in aberrant macrophage-glia interactions, thereby contributing to ARHL [40]. NLRP3 has been shown to promote the expression of pro-inflammatory factors in aging tissues, including IL-1β and caspase, thereby exacerbating inflammaging [41, 42].

Collectively, these findings underscore an interconnected and interdependent relationship between inflammaging and the development of ARHL.

Inflammaging as the central pillar of immunosenescence

Immunosenescence is traditionally perceived as deleterious, attributed to its association with low-grade chronic inflammation and progressive functional impairment in mounting effective immune responses against infections and neoplasms [11, 43]. Immunosenescence-mediated inflammaging arises from the accumulation of various immune cell subsets with impaired functionality. Both the innate and adaptive immune systems are impacted by immunosenescence, with certain immune cell subsets exhibiting notable alterations [44]. Overall, immunosenescence diminishes the capacity for antigen processing and presentation in the innate immune system, leading to impaired memory formation and a narrowed T cell receptor (TCR) repertoire in the adaptive immune system. Specifically, compared to younger individuals, macrophages in elderly individuals downregulate the expression of MHC class II molecules and Toll-like receptors (TLRs) and display reduced phagocytic activity [45-47]. Additionally, immunosuppressive macrophages (M2 phenotype) show a significant increase in elderly lymphoid tissues and muscle [48, 49]. A previous study has also indicated a gradual downregulation of activating receptors, including NKp30, NKp46, and DNAM-1, in natural killer (NK) cells from elderly individuals, compromising their cytotoxicity [50]. Meanwhile, although immunosenescence was thought not to affect the absolute number of T cells, substantial changes in T cell phenotypes have been observed [51, 52]. Firstly, thymic involution impairs the production of naive T cells and reduces the diversity of the TCR repertoire, thereby increasing susceptibility to infection, neoplasms, and autoimmunity [53]. Secondly, lifelong exposure to antigens further contributes to the shrinkage of the TCR repertoire, characterized by the transition from naive T cells to highly differentiated memory T cells or senescent cells with upregulated pro-inflammatory molecules [54, 55]. Furthermore, immunosenescence has been reported to diminish the output of B cells and remodel the B cell compartment, hindering the efficacy of humoral immunity against infection [56-58].

While a comprehensive understanding of the pathophysiological processes of immunosenescence remains elusive, current research has identified its associations with several characteristic changes, including thymic involution, inflammaging, impaired immune responses, and oxidative stress [59-61]. Inflammaging is considered as the central pillar of immunosenescence, characterized by the systemic upregulation of inflammatory factors [62, 63]. The accumulation of cell debris related to cellular senescence is accountable for inflammaging [64]. During this process, senescent cells acquire a distinctive SASP, marked by the secretion of various inflammatory markers, including interleukin-1 (IL-1), IL-6, IL-8, IL-13, IL-18, and tumor necrosis factor (TNF), leading to the persistence of unresolved inflammatory processes. Simultaneously, the excessive production and accumulation of reactive oxygen species (ROS) can induce DNA damage and disrupt cellular structures, resulting in cell apoptosis and subsequent chronic tissue damage. Consequently, inflammaging can contribute to a spectrum of age-related diseases, such as Alzheimer's disease, cardiovascular diseases and ARHL [9-12].

Therapeutic implications of immunosenescence-mediated inflammaging in ARHL

Iwa and colleagues have long been dedicated to demonstrating the importance of maintaining systemic immune function in preventing ARHL, confirming that immunosenescence and related inflammaging are major contributors to accelerated ARHL [65, 66]. Utilizing a strain of senescence-accelerated mouse (SAMP1), they initially observed a reduction in lymphocyte

numbers and age-related impairment of T cell function concomitant with age-related auditory dysfunction, suggesting a synergistic effect of genetic background and systemic immune function in ARHL development [65]. To delineate the individual contributions of genetic and environmental factors to ARHL, Iwa et al. investigated the effects of allogeneic bone marrow transplantation (BMT) in preventing ARHL in SAMP1 mice. As anticipated, mice receiving BMT experienced significant relief from ARHL, spiral ganglion cell (SGC) degeneration, and T cell dysfunction, demonstrating a delayed onset of immunosenescence. Notably, no donor cells were found to infiltrate the spiral ganglia, emphasizing that BMT's rationale lies in its modulation of systemic immune function rather than direct maintenance of SGCs by locally infiltrated donor cells [66]. They also showed that inoculation of young $CD4^+$ T cells or fetal thymus exhibited similar effects on ARHL as BMT, downregulating IL-1R2 expression in splenic and lymph nodal $CD4^+$ T cells, reducing naturally occurring regulatory T cell (nTreg) numbers, partially restoring their proliferative potential, and preventing SGC degeneration, resulting in improved responses to diverse auditory stimuli [67, 68]. Furthermore, recent studies focused on elucidating the specific fractions of $CD4^+$ T cells critical in preventing ARHL. Results indicated that inoculation of non-Treg non-IL1R2 (nTnI) cells, including Treg and IL1R2-deleted $CD4^+$ T cells, inhibited serum nitric oxide (NO) release, thereby preventing SGC degeneration and ARHL development [69]. Additionally, a recent study by Mitani et al. further validated that inoculation of both fresh and cryopreserved lymphocytes reduced cellular immunosenescence, suppressed serum NO production, prevented spiral ganglion degeneration, and alleviated cochlear inflammaging, offering novel approaches for clinical prevention of ARHL [70]. Collectively, these therapies aim to rejuvenate systemic immunity, reduce inflammaging levels, and ultimately prevent age-related functional impairments (**Figure 1**).

Recent studies have indicated that platelet factor 4 (PF4) holds promise as a rejuvenating agent for immunosenescence, offering a new avenue for preventing ARHL [71-73]. As a member of the CXC chemokine family, PF4 is primarily synthesized by the megakaryocytic lineage and serves diverse functions in coagulation, immune modulation, and angiogenesis [74, 75]. Despite mounting evidence implicating PF4 in thrombocytopenia and atherosclerosis, its association with immunosenescence and inflammaging remains poorly understood. Tandem mass tags-based proteomics analysis of plasma from the Bama longevity group and a control group identified PF4 as one of the most significantly downregulated proteins in the elderly, suggesting its potential as a clinically useful biomarker for aging [76]. This finding was corroborated by a subsequent study, which revealed significantly reduced circulating levels of PF4 in blood plasma preparations of elderly mice and humans compared to younger counterparts [73]. Schroer et al. demonstrated that systemic administration of PF4 markedly reduced the expression of pro-inflammatory factors, complement factors, and microglia activation markers in the hippocampus, thereby attenuating neuroinflammation and restoring cognitive decline in aged mice. Notably, these effects were not mediated by a direct central mechanism of PF4, as it cannot cross the blood-brain barrier (BBB). Instead, PF4 rejuvenated the aging peripheral immune system in a CXCR3-dependent manner, leading to reduced proportions of age-related T effector memory cells, a shift toward a youthful gene signature with a more naive T cell phenotype, and decreased inflammatory signals, subsequently lowering serum levels of pro-aging immune factors, including CCL2, CyPA, and TNF. Collectively, PF4 targets immunosenescence to attenuate inflammaging and alleviate age-related cognitive decline [73]. Similarly, Leiter et al. demonstrated that elevating systemic PF4 levels could ameliorate age-related regenerative and cognitive impairments in a hippocampal neurogenesis-dependent manner, while Park et al. showed that PF4-induced cognitive restoration occurred through NMDAR signaling-mediated synaptic plasticity [71, 72]. These findings strongly suggest a potential role for PF4 in mitigating age-related functional impairments, positioning it as a promising therapeutic target for preventing ARHL.

Summary and perspectives

In summary, aging is characterized by progressive immune system dysfunction, known as immunosenescence, which triggers the secretion of pro-inflammatory cytokines such as IL-1, IL-6, and TNF, leading to unresolved inflammatory processes in the cochlea. Consequently,

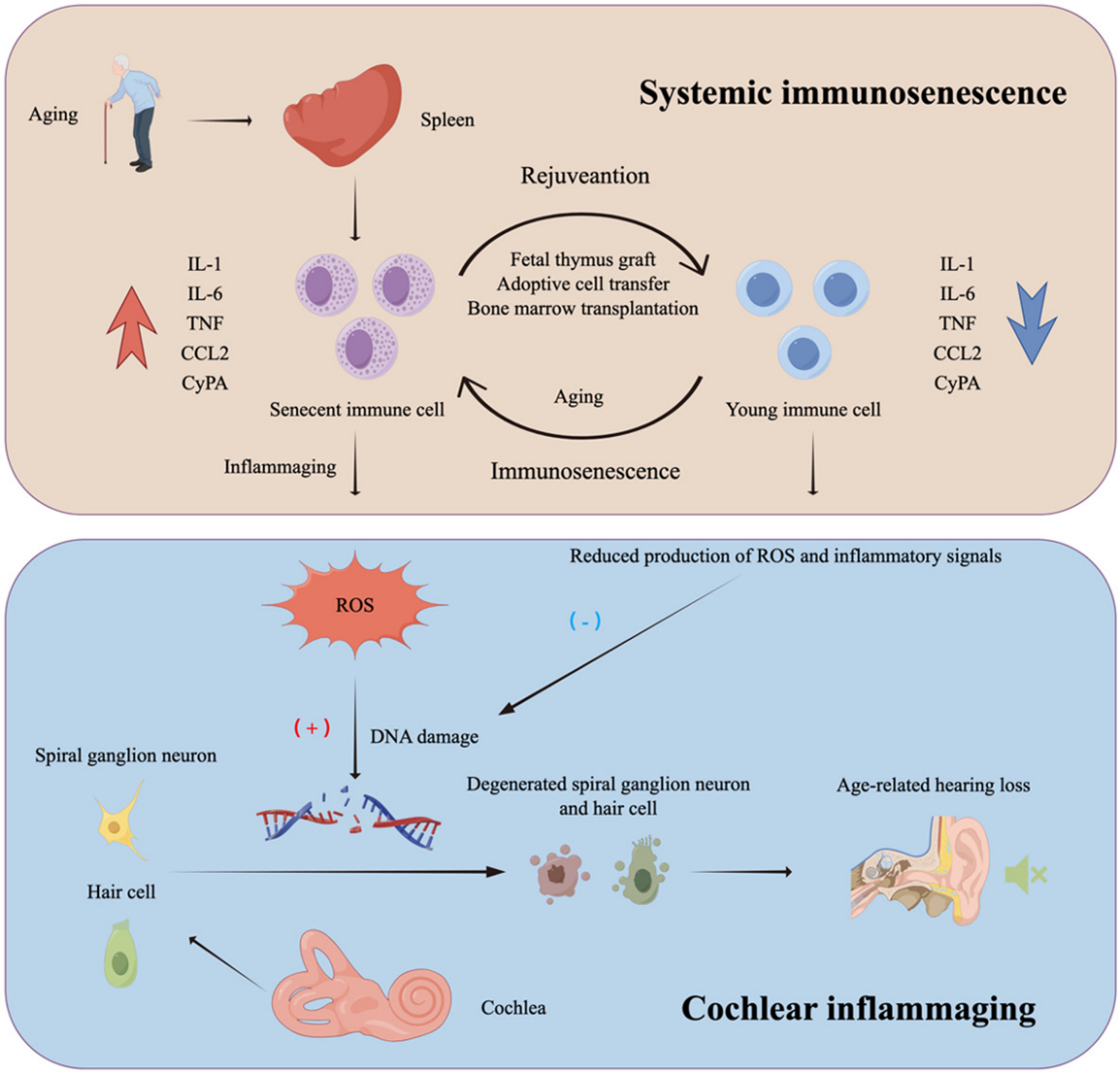

Figure 1. Schematic diagram of the interconnections between immunosenescence-mediated inflammaging and age-related hearing loss (ARHL). Aging is characterized by progressive immune system dysfunction, termed immunosenescence, which culminates in chronic low-grade inflammation known as inflammaging. Promising approaches, such as fetal thymus grafting, adoptive cell transfer, and bone marrow transplantation, rejuvenate the aging peripheral immune system. These interventions notably shift age-related senescent immune cells towards a youthful gene signature with diminished inflammatory signals. Consequently, this leads to a reduction in reactive oxygen species (ROS)-mediated DNA damage and the restoration of degenerated spiral ganglion neurons and hair cells, thereby offering protective effects against ARHL.

cochlear inflammation induces the overproduction and accumulation of reactive oxygen species (ROS), resulting in apoptosis and degeneration of spiral ganglion neurons and hair cells due to DNA impairment and cellular breakdown, thereby contributing to the onset of ARHL. Promising interventions, including fetal thymus grafts, adoptive cell transfer, and bone marrow transplantation, rejuvenate the aging peripheral immune system, shifting age-related senescent immune cells towards a youthful gene signature with reduced inflammatory signals. This subsequently mitigates ROS-mediated DNA damage and facilitates the restoration of degenerated spiral ganglion neurons and hair cells, offering protective effects against ARHL.

In the past decade, mounting evidence has established immunosenescence-mediated inflammaging as a pivotal mechanism contributing to age-related pathologies. It is plausible that insights gained from the study of these

diverse diseases could be applicable to ARHL. Currently, several preclinical studies provide evidence that rejuvenating immunosenescence delays the onset of ARHL, implying that novel agents capable of reversing immunosenescence-mediated inflammaging may offer a promising therapeutic avenue for preventing ARHL in future research endeavors.

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Disclosure of conflict of interest

Figure 1 was created using Figdraw (www.figdraw.com, ID: ISAOTb200a).

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