Review

Prevention of Hearing Loss by Alteration of the Systemic Immune System

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Abstract

Although congenital sensorineural hearing loss (SHL) in the bilateral cochleae mainly results from genetic abnormalities, chronic SHL progressing in later life is often influenced by systemic immune disturbances, including autoimmunity, chronic inflammation, and immunosenescence.

We have investigated the relationship between the inner ear and systemic immunity and reviewed the possibilities to prevent SHL, including autoimmune SHL and age-related SHL. We also demonstrated two lymphocyte populations, interleukin 1 receptor type II (IL-1R2)-positive T cells (T1R2) and naturally occurring regulatory T cells (nTregs) in $CD4^+$ T cells, which increase with aging, suppress host immune function and promote organ degeneration. Alterations in systemic immunity by fewer microbial antigen challenges in the living environment, elimination of immune suppressive lymphocytes, or immune rejuvenation with a reconstituted thymus may contribute not only to renew the cochlear function in SHL, but also to extend the healthy life of functional organs in a vigorous and youthful body, one of humanity's greatest dreams.

Key words: autoimmune sensorineural hearing loss; age-related sensorineural hearing loss; inflammation, immune senescence; interleukin 1 receptor type II -positive T cells; naturally occurring regulatory T cells; immune rejuvenation; thymus.

1. Background

Although Sjögren's syndrome and Behcet's disease typically show oral lesions, it is well known that they are systemic symptoms beyond otolaryngology, and the head and neck area. Eosinophilic otitis media (EOM) and otitis media with antineutrophil cytoplasmic antibody (ANCA) show not only otitis media, but also a deterioration in systemic immunity [1,2].

Sensorineural hearing loss (SHL) in the inner ear, as opposed to conductive hearing loss in the middle ear including the ear drum, is also a partial manifestation in type 2 diabetes[3], cardiovascular disease, systematic lupus erythematosus (SLE)[4], and *granulomatosis with*

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polyangiitis (GPA)[5] . Age-related SHL, also known as presbycusis, connected with systemic aging develops due to mitochondrial DNA damage in the cochlea following oxidative stress [6] and shows a delay in progression with exercise or caloric restriction [7-9]. One of the authors previously demonstrated that food restriction upregulates interleukin 2 receptor (IL-2R) on T lymphocytes and activates cellular immunity in mice [10]. Thus, cochlear function and pathology are affected by, or coordinated with, the systemic environment including the immune system. We have also studied preventive treatments for progressive bilateral SHL caused by disturbances in systemic immunity with autoimmune diseases or aging, but not caused by genetic abnormalities or acoustic trauma [11-18].

In this review, we have chosen to focus on cochlear function and pathology related to the systemic immune system and the possibility of controlling the development of SHL.

2. Treatment of autoimmune SHL with allogeneic bone marrow transplantation

The transplantation of hemopoietic stem cells provides an opportunity to provoke a “reset” of the immune system in patients with autoimmune diseases [19] and has been utilized in the treatment of a whole spectrum of severe autoimmune diseases refractory to conventional therapy [20,21].

The MRL/Mp-lpr/lpr (MRL/lpr) mouse strain, a murine model of autoimmune SHL and SLE, shows progressive SHL by 20 weeks of age [22,23] and lupus nephritis at 12-16 weeks [24]. This strain has reduced Fas messenger RNA (mRNA) production and decreased negative selection of self-reactive T cells, followed by the production of autoantibodies (anti-single-stranded DNA [ssDNA] antibody, rheumatoid factor [RF], etc.) by B cells or by the deposition of an IgG (autoantibody)-containing immune complex in the lesions of the stria vascularis [22,23], as well as the basement membranes of the glomeruli [25] This vascularis is known to function in the maintenance of the blood-labyrinth barrier and auditory functions [26], and has been identified as the most likely site of disease-causing autoimmune SHL [25,27].

We performed allogeneic bone marrow transplantation (BMT) in which MRL/lpr recipient mice received bone marrow cells from young C57BL/6 mice which are non-autoimmune prone and show slow manifestation of presbycusis [12,13]. The BMT procedures consist of systemic irradiation with 9-10 Gy to delete immunocompetent cells, including bone marrow cells, in recipients and then inoculating bone marrow cells from C57BL/6 donor mice.

The results have indicated that BMT can be used to treat SHL as well as SLE; cochlear pathology, serum autoantibodies and lupus nephritis were all ameliorated. Therefore, it is conceivable that the autoimmune SHL in the MRL/lpr mice results not from defects in the cochlea, including the stria vascularis, but from defects in the systemic immune system constituted by bone marrow cells [13]. BMT could therefore provide a curative effect on inner ear autoimmune dysfunction associated with systemic autoimmune diseases including not only SLE, but also RA [28-30], ulcerative colitis [31,32],

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relapsing polychondritis [33], steroid-responsive sensorineural hearing loss [34].

3. Retardation of age-related SHL by restraint of chronic inflammation due to bacterial infection

The causes of chronic bilateral SHL mainly include genetic factors, noise exposure, ototoxic drugs, oxygenic stress, and excessive intake of calorie [7,8,35,36]. On the other hand, these factors alone cannot explain progression of age-related SHL, which is rapidly increasing in incidence, affecting about half of the population over 75 years old [37,38] and that to date has been an incurable disease.

Recent research in gerontology has shown that inflammaging, a state of chronic systematic inflammation associated with age, is a consequence of immunosenescence, the aging of the immune system, that contributes to the aging process and the development of age-related disabilities and diseases including age-related SHL [39,40]. Local inner ear immunity is part of the overall systemic response and can induce cochlear degeneration and SHL [16,41-43]. Type II diabetes and cardiovascular disease associated with inflammaging have been identified as being linked to age-related SHL severity [44]. Verschuur et al. [38] indicated that chronic inflammation represented by the white blood cell count was strongly associated with a worsening of age-related SHL among community-dwelling adults aged over 75 years.

A senescent immune system is characterized by continuous reshaping and shrinkage of the immune repertoire by persistent antigenic challenges. These changes lead to a poor response to newly encountered microbial antigens, as well as to a shift in the immune system towards an inflammatory or autoimmune profile [39]. Laboratory animals show longer lifespans in immunologically clean environments because of the absence of immune stress, which is mainly due to chronic infections due to pathogenic invaders [45]. The time onset of these age-related diseases and the mean survival time also depend on the environment, which can consist of specific pathogen-free (SPF) conditions or conventional (CV) conditions [46].

Therefore, we examined audiological, pathological and immunological differences between breeding conditions of SPF and CV in the senescence-associated mouse type 1 (SAMP1), a murine inbred strain with a genetic background of AKR mice [47,48], which shows the early occurrence of thyme involution and accelerated dysfunction of immunocompetent cells, particularly T cells, followed by acceleration of age-related SHL with the degeneration of spiral ganglion (SG) neurons in the cochlea [44,47]. The results indicated the retardation of age-related SHL and degeneration of SG neurons, as well as prevention of immunosenescence, in the SPF mice [15].

These findings raise the question as to why systemic immune functions affect cochlear function. One reason is oxygenic stress produced in the body as inflammaging, with immune senescence influencing the inner ear through blood flow [48]. Another reason is systemic immunity itself: We have previously demonstrated that T cells in the systemic circulation infiltrate the inner ear and proliferate locally as a consequence of the immune response in a mouse model of graft-versus-host

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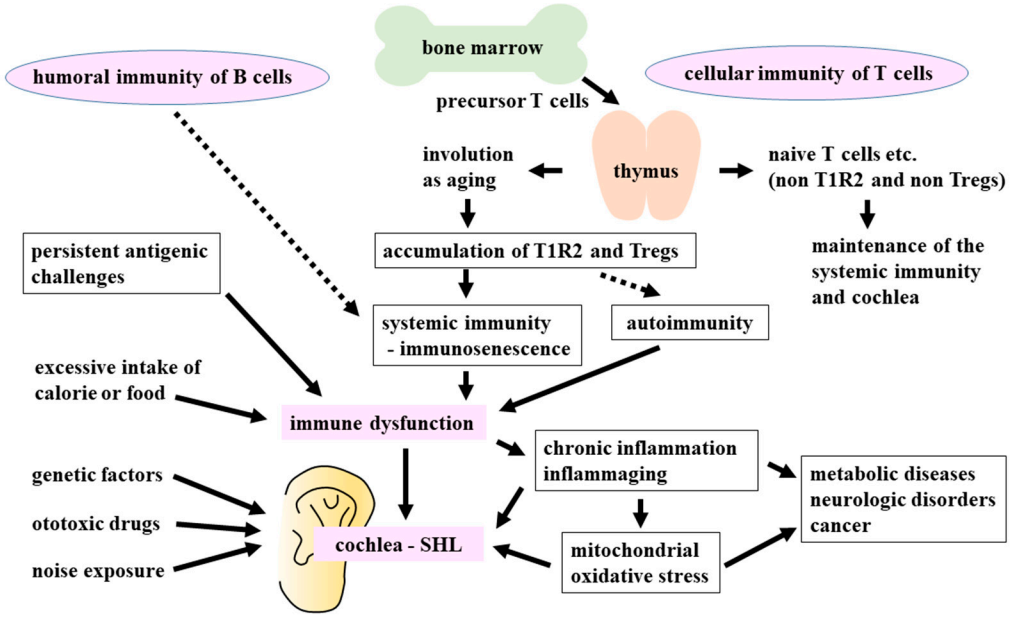
disease using BALB/c and C57BL/6 mice [11]. Subramanian et al. [49] demonstrated that activated T cells enter the central nervous system and modulate the development and function of bone marrow-derived macrophages as antigen-presenting cells in SCID mice with transferred rat T cells and/or bone marrow cells. It has been shown that macrophages support the regeneration of the central and peripheral nervous system [50,51]; the cells secrete Interleukin-1 (IL-1) [52] and mediate the release of nerve growth factor (NGF) in a variety of cells such as Schwann cells [53-55]. NGF leads to increased neural survival and regeneration [55-57] and is involved in age-related neuro-degeneration diseases such as Alzheimer's disease [56,58]. Komeda et al. [59] indicated that the blockage of IL-1 activity in the cochlea induces SG degeneration.

Therefore, it is conceivable that when immune functions are preserved under clean environments, T cells improve the neuro-degeneration system in the inner ear, thereby delaying both accelerated degeneration of the SG cells and age-related SHL in SAMP1 mice (Figure 1).

Figure 1



4. Prevention of age-related SHL by immune rejuvenation

The profound atrophy of thyme tissue is central to immunosenescence [60] and leads to perturbed output of new T cells extended from hematopoietic stem cells (HSCs), as well as lymphoid progenitors and increased memory lymphocytes with accumulation of dysfunctional senescent cells [61-64].

Age-associated immunodeficiency and cognitive deterioration are two predominant features of the aging process. Disordered immune reactions are closely related to brain impairments including Alzheimer's disease, resulting in the deterioration of central cognitive functions [65-67]. It is widely accepted that immune surveillance of the CNS occurs, and that immune and inflammatory responses

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can take place in the brain, including neurons, by infiltration of circulating immune cells and activation of resident cells [68]. Thymectomy induces an imbalance between lymphocytes, macrophages, and cytokines, which induces neurotransmitter and neuroendocrine changes, and subsequent memory disturbance [69]. The inner ear is also regulated by systemic immunocompetent cells, including T cells and macrophages, which are supplied through the blood-inner ear barrier, similar to the blood-brain barrier [11,70], and these are associated with local inflammation and restoration [40,41,71].

We have previously demonstrated that age-related SHL is prevented in SAMP1 by rejuvenation of recipient immunity by syngeneic inoculation of $CD4^+$ T cells from young donors, while the inoculation of $CD8^+$ T cells or B cells had no preventive effect on age-related SHL [17].

Because rejuvenation of the thymus leads to reconstitution of cellular immunity with function as good as young cells and better than those of aged mice and humans [69], we grafted syngeneic fetal thymi to SAMP1 recipients. Results indicated that the populations of interleukin 1 receptor type II (IL-1R2)-positive T cells (T1R2) and naturally occurring regulatory T cells (nTregs) in $CD4^+$ T cells increased with aging and that the grafts led to down regulation of T1R2 and nTregs in $CD4^+$ T cells, reducing the population, age-related SHL, and degeneration of SG in SAMP1 mice [17,18] (Figure 1). Inoculation of $CD4^+$ T cells by deleting T1R2 and nTreg also had the same effects on age-related SHL and SG (manuscript in preparation).

Interleukin (IL)-1 has been particularly implicated in neurodegeneration [68] and is controlled mainly by interleukin-1 receptor type 1 (IL-1R1) to transduce signals, especially IL-1β and interleukin 1 receptor type 2 (IL-1R2), to diminish IL-1 without any transduction of IL-1 binding signals [52,68]. IL-1 receptors interact with IL-1 to modulate the functions of leukocytes including $CD4^+$ T cells, all cell types of the brain [52], and spiral ganglion (SG) neurons [59]. nTregs accumulate with advanced age, despite thyme involution, leading to a dwindling thyme T-cell population and inducible regulatory T cells (iTregs), and promoting tissue degeneration and senescence-associated inflammation, as well as disturbances in immune activation against tumors and pathogens [72]. Depletion of Tregs was shown to significantly improve neural survival after mechanical injury in an animal model [73].

5. Clinical tactics to prevent SHL by immune alteration

It is not feasible to renew the immune system in autoimmune SHL patients with BMT because of the stressful treatment. Caloric restriction, which limits eating habits, may be impractical or impair the quality of life for people, especially in industrialized countries. On the other hand, current findings suggest at least three immunological strategies to prevent age-related SHL: i) A clean living environment with few pathogens causing inflammation may maintain recipient immunity and cochlear function. ii) Elimination of T1R2 and nTreg from $CD4^+$ T cells with antibodies may contribute to immune rejuvenation and prevention of neurosenescence in the cochleas recipients. iii) Use thyme epithelial cells differentiated from autologous pluripotent stem cells [74] or iPS cells. Grafting of these

 doi:10.20944/preprints201901.0039.v1

cells may lead to immune rejuvenation and prevention of age-related SHL as an anti-aging activity. This is a major objective and the center of much research attention globally. Further studies must be promptly performed to develop this concept in industrialized countries facing expansions in their elderly populations.

6. Conclusions

Although Age-related SHL is rapidly increasing in incidence, affecting about half of the population over 75 years old [37], no strategy has been developed for the prevention and treatment of this neurodegenerative disease.

This chronic deterioration progressing in later life is often influenced by systemic immune disturbances, including autoimmunity, chronic inflammation, and immunosenescence. Alteration of systemic immunity by fewer challenges from microbial antigens in the living environment, elimination of immune suppressive lymphocytes like T1R2 and nTregs or immune rejuvenation with reconstituted thymi may contribute not only to renew the cochlear function in SHL, but also to extend a healthy life with functional organs in a vigorous and youthful body, one of humanity's greatest dreams.

Competing Interests

The authors declare that they have no competing interests.

Authors' contributions

HI: Study design and writing the manuscript. MI: critical reading and discussion of the manuscript. Both authors have read and approved the final manuscript.

Acknowledgements

This study was supported by grants-in-aid for scientific research (08671994, 11671712, 18591895, 21592170, and 16K11202) from the Ministry of Education, Science and Culture, a grant from the Millennium program of the Ministry of Education, Culture, Sports, Science and Technology, a grant from the Science Frontier program of the Ministry of Education, Culture, Sports, Science and Technology, a grant from the 21st Century Center of Excellence (COE) program of the Ministry of Education, Culture, Sports, Science and Technology, the Katano and the Shiozaki Yasuko prizes of Kansai Medical University and funding from the Academic Society for Research in Otolaryngology, Kansai Medical University in Japan.

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Figure legend

Figure 1. SHL and immune dysfunction