



# Role of Inner Ear Macrophages and Autoimmune/Autoinflammatory Mechanisms in the Pathophysiology of Inner Ear Disease

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Macrophages play important roles in tissue homeostasis and inflammation. Recent studies have revealed that macrophages are dispersed in the inner ear and may play essential roles in eliciting an immune response. Autoinflammatory diseases comprise a family of immune-mediated diseases, some of which involve sensorineural hearing loss, indicating that similar mechanisms may underlie the pathogenesis of immune-mediated hearing loss. Autoimmune inner ear disease (AIED) is an idiopathic disorder characterized by unexpected hearing loss. Tissue macrophages in the inner ear represent a potential target for modulation of the local immune response in patients with AIED/autoinflammatory diseases. In this review, we describe the relationship between cochlear macrophages and the pathophysiology of AIED/autoinflammatory disease.

**Keywords: macrophages, monocytes, heterogeneity, autoimmune inner ear diseases, autoinflammatory diseases, colony-stimulating factor 1**

## INTRODUCTION

The functional mechanisms of resident macrophages (M $\phi$ s) in the inner ear remain largely unknown, in both the context of normal tissue physiology and disease development. Several recent reviews have discussed the importance of tissue-resident M $\phi$ s in the systemic and local regulation of inner ear homeostasis and disease pathology that improve our understanding of inner ear-resident M $\phi$ s (1–6).

In the United States, over 30 million adults, or approximately 15% of the entire population, are affected by hearing loss (7, 8). Research has indicated an expansion of the populations affected by sensorineural hearing loss, which impacts the conversion of mechanical sound to the neuroelectric indicators in the inner ear that relay signals to the auditory nerve (7, 8). Sensorineural hearing loss exerts a life-changing impact on affected patients; moreover, the current treatment modalities for sensorineural hearing loss are limited to the use of either cochlear implants or hearing aids. Cochlear implants directly stimulate the cochlear nerve by bypassing the damaged organ of Corti, which is most frequently affected by sensorineural hearing loss (9). Cochlear implants are among the artificial organs with the highest success rates; however, there is a social demand for more fundamental therapeutic options for sensorineural hearing loss.

Autoimmune inner ear disease (AIED) represents much fewer than 1% of all cases of sudden sensorineural hearing loss (10, 11), generally presenting as subacute, swiftly progressing, frequently fluctuating, bilateral, and asymmetrical sensorineural hearing loss (9–14). AIED can be labeled

as primary AIED, in which the inner ear is the most affected organ, or secondary AIED (15–30% of cases), which develops in association with a systemic autoimmune disease (12), such as autoimmune hepatitis (15), systemic lupus erythematosus (SLE) (16), multiple sclerosis (MS) (17), rheumatoid arthritis (18), inflammatory bowel disease (IBD) (19), or antiphospholipid syndrome (14, 20).

Collectively, current evidence indicates that aberrant events in the early innate immune response play critical roles in the development and manifestation of autoimmune hearing loss (10, 11). As with most autoimmune diseases, it has been postulated that a misdirected assault on the self-organs, mainly inner ear proteins in AIED, activates the pro-inflammatory T-cell response and autoantibody formation; this represents the basic pathophysiology of AIED and other autoimmune diseases. Autoinflammatory diseases fall within the family of immune-mediated diseases, many of which induce sensorineural hearing loss, suggesting that similar mechanisms are involved in the pathogenesis of AIED (21). In the autoinflammatory disorder-related hearing loss, genetic mutations or polymorphisms inherited in an autosomal dominant manner result in a gain-of-function mutation within the gene for nod-like receptor (NLR) family pyrin domain 3 (NLRP3), leading to excessive interleukin (IL)-1 $\beta$  release, sensorineural hearing loss, systemic amyloidosis, and/or transient skin rashes. Muckle–Wells syndrome (MWS) and neonatal-onset multisystem inflammatory sickness belong to a family of autoinflammatory diseases known as a cryopyrin-related periodic syndrome, which also involves sensorineural hearing loss (22, 23). However, the role of M $\phi$ s in AIED and autoinflammatory diseases has not been well-documented thus far.

Although 70% of patients with AIED initially respond to corticosteroids (11), understanding the role of M $\phi$ s in the pathophysiology of progressive hearing loss is critical for the development of improved therapies. In this review, we discuss recent findings related to the development of immune-competent cells within the inner ear (24, 25), thereby clarifying the role of inner ear-resident M $\phi$ s in inner ear homeostasis and pathological processes. We also cover a wide range of research areas involving tissue-resident M $\phi$ s that include those related to recent advances in antigen differentiation, gene expression patterns, and the clinical features and pathology of AIED/autoinflammatory diseases.

## ORIGINS AND THE DIVERSIFICATION OF TISSUE-RESIDENT MACROPHAGES—IDENTIFICATION THROUGH DIFFERENTIATION OF ANTIGENS, FATE-MAPPING, AND GENE EXPRESSION PATTERNS

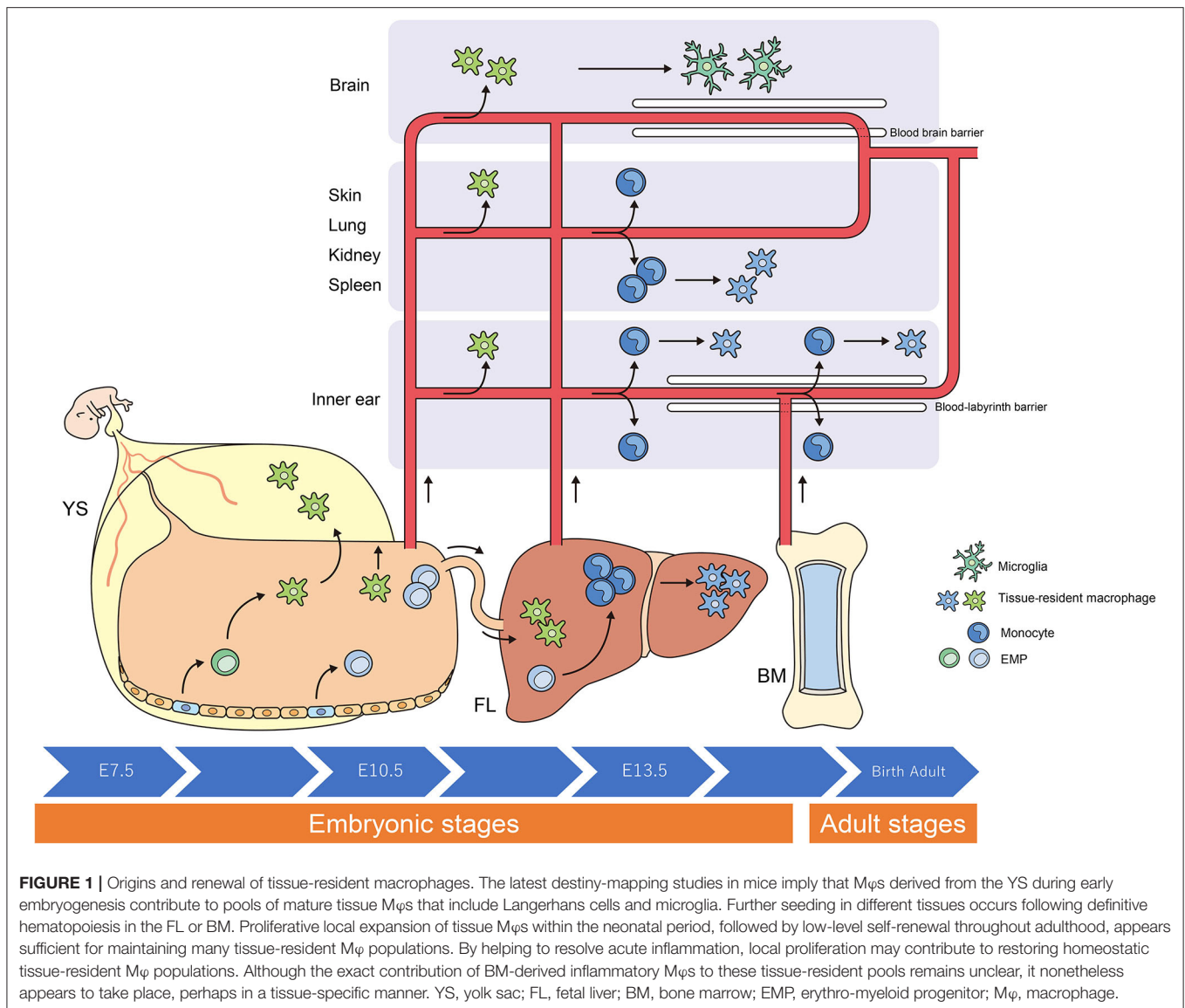
Macrophages are present in all vertebrate tissues, emerging earlier than any other blood cell type from mid-gestation and are distributed in almost every organ and tissue in the body throughout life (26, 27). In addition to their role in regulating

tissue development and regeneration, M $\phi$ s aid in maintaining local homeostasis by responding to internal and external stimuli, appearing as phagocytes that protect against microbes. Furthermore, they participate in the clearance of useless and senescent cells and act as sentinels with trophic, regulatory, and repair functions. Heterogeneous M $\phi$  phenotypes are observed in different tissue environments that highlight their organ-specific capabilities in developmental processes and normal physiology (28–30) (**Figure 1**). In addition, M $\phi$ s exhibit diverse tissue-specific functions, integrating cues from the external surroundings and their microenvironment. Hence, tissue-resident M $\phi$ s represent an appealing target for therapeutics given their implication in various pathological processes that include those related to atherosclerosis, autoimmune diseases, neurodegenerative and metabolic disorders, and tumor growth (13). Elucidating the developmental pathways and characteristics of M $\phi$ s may aid in the design of novel interventional strategies, which focused on the tissue-specific microenvironment.

Researchers have debated whether resident M $\phi$ s are constantly and predominantly repopulated *via* the delivery of blood-circulating monocytes, which derive from progenitors inside the bone marrow (BM). However, recent studies have demonstrated that specific M $\phi$  populations are independent of circulating monocytes and even adult BM hematopoiesis (1, 2, 24, 31). These tissue-resident M $\phi$ s are derived from the sequential seeding of tissues by means of various precursors during embryonic development. Primitive M $\phi$ s are generated from early erythro-myeloid progenitors (EMPs) inside the yolk sac (YS) that bypass monocytic intermediates and give rise to microglia *via* the transcription element *c-Myb*. Ultimately, fetal monocytes are generated from *c-Myb*+ EMPs that begin to seed the fetal liver (FL), giving rise to various types of mature M $\phi$ s. Hence, hematopoietic stem cell-impartial embryonic precursors transiently are present in the YS and FL represents the origin of long-lasting, self-renewing M $\phi$  populations with organ-specific functions (1, 26) (**Figure 1**).

The percentage of resident M $\phi$ s varies according to their origin, the developmental stage of the organism, and the tissue type. For instance, most of the microglia in the brain originate from YS-derived M $\phi$ s, whereas M $\phi$ s from the FL and BM provide a negligible contribution to microglia during all stages of life (6, 10). In contrast, resident M $\phi$ s in the gut are derived from the YS at some point during early embryonic development. Monocytes derived from the FL give rise to most of the resident M $\phi$ s in the intestine at birth; however, throughout adulthood, most resident M $\phi$ s originate from the BM (5, 27).

When compared with other tissue-resident populations of M $\phi$ s, the cellular expression profiles of cochlear M $\phi$ s and the markers that can be used to visualize these cells have been poorly documented. The dynamics of M $\phi$  populations in the developing cochlea have been characterized most appreciably in mice and are summarized in **Figure 2** (24, 31, 32). Colony-stimulating factor 1 (Csf1) signaling controls the seeding of the larger M $\phi$  population within the cochlea throughout development (24, 25). A second populace derived from the FL, which is Csf1 receptor-independent, is observed in the modiolus and the intraluminal surface of the perilymphatic

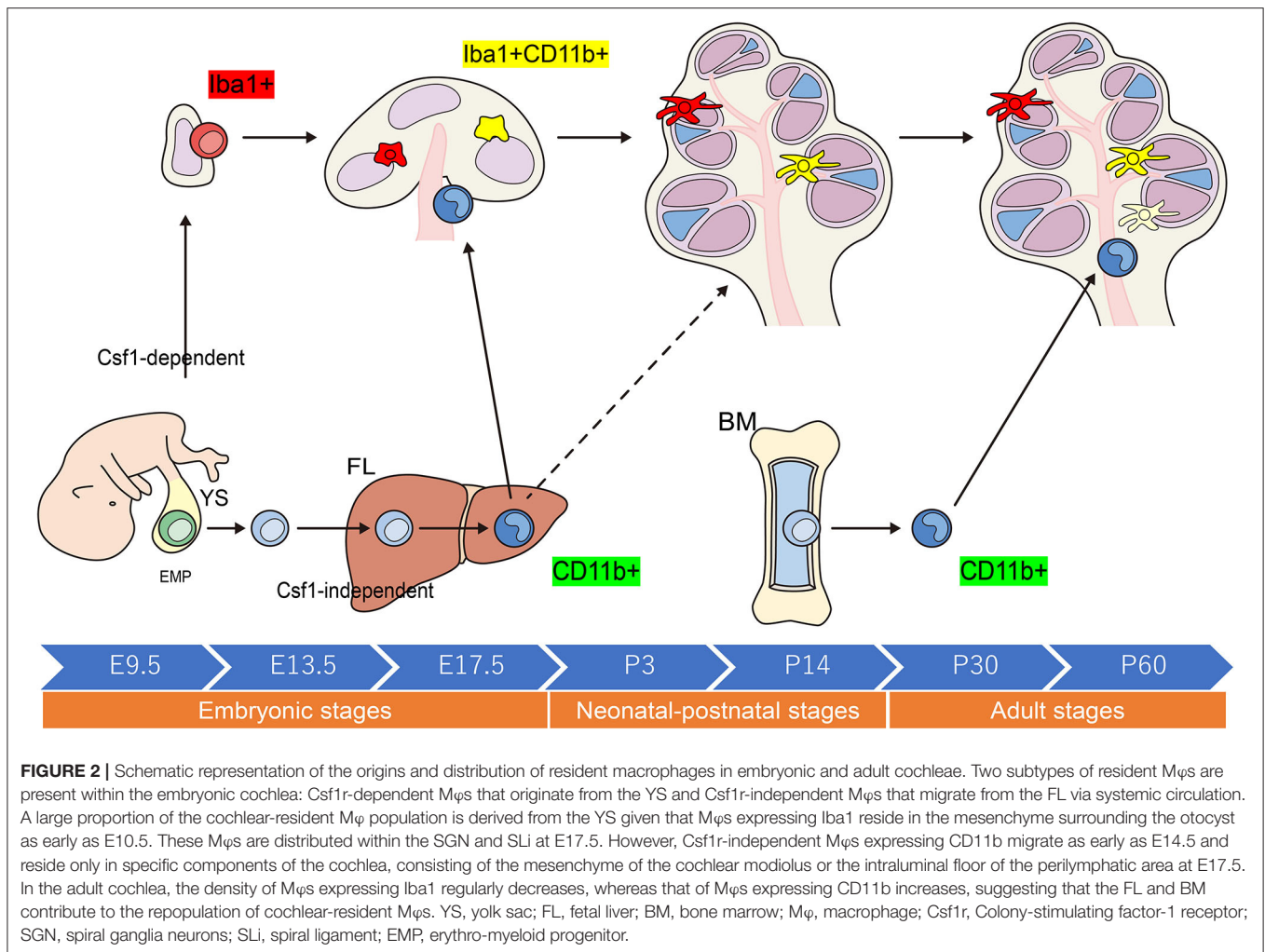


area inside the embryonic cochlea (24). Cochlear M $\phi$ s and perivascular macrophage-like melanocytes (PVM/Ms) lie close to blood vessels in the adult cochlea (33)—such as in the cochlear modiolus, supporting cells, spiral ganglion neurons (SGNs), stria vascularis (SV), and spiral ligament (SLi)—under normal conditions (4, 24, 25, 31, 32, 34–36) (Figure 3).

The inner ear is responsible for auditory sensation and the perception of acceleration/rotation, and it is difficult to restore the population of sensory cells in the inner ear after degeneration due to acute or chronic inner ear injuries, such as those related to Meniere's disease and sudden sensorineural hearing loss. This is partly because, in humans, hair cells in the inner ear are terminally differentiated, losing their potential for self-renewal following significant damage after birth (33). SGNs, which mediate synaptic connections among the hair cells and the neurons of the cochlear nucleus, also undergo damage and degeneration, while damage or atrophy of the SV and SLi disrupts

cochlear function. Repeated exposure of the auditory system to insults causes harm to these structures, resulting in functional impairments that lead to progressive hearing loss (7).

Cochlear M $\phi$ s persist from the early post-natal stages and renew or preserve their populace *via* the infiltration of circulating monocytes (34, 37, 38). PVM/Ms are found adjacent to the blood vessels in the SV and support cells in the cochlea (35, 39). PVM/Ms have a turnover time of several months in mice and are maintained *via* the migration of monocytes that originate from the BM into the cochlea (36). Functionally, PVM/Ms contribute to restoring the endocochlear potential, which is crucial for the activation of auditory hair cells (40, 41). Interestingly, M $\phi$  heterogeneity results in distinct phenotypes and, more importantly, completely exceptional organic functions in other tissues (28). Therefore, future studies should aim to elucidate the roles of tissue-resident and BM-derived M $\phi$ s in the initiation, progression, and termination of inner ear diseases.



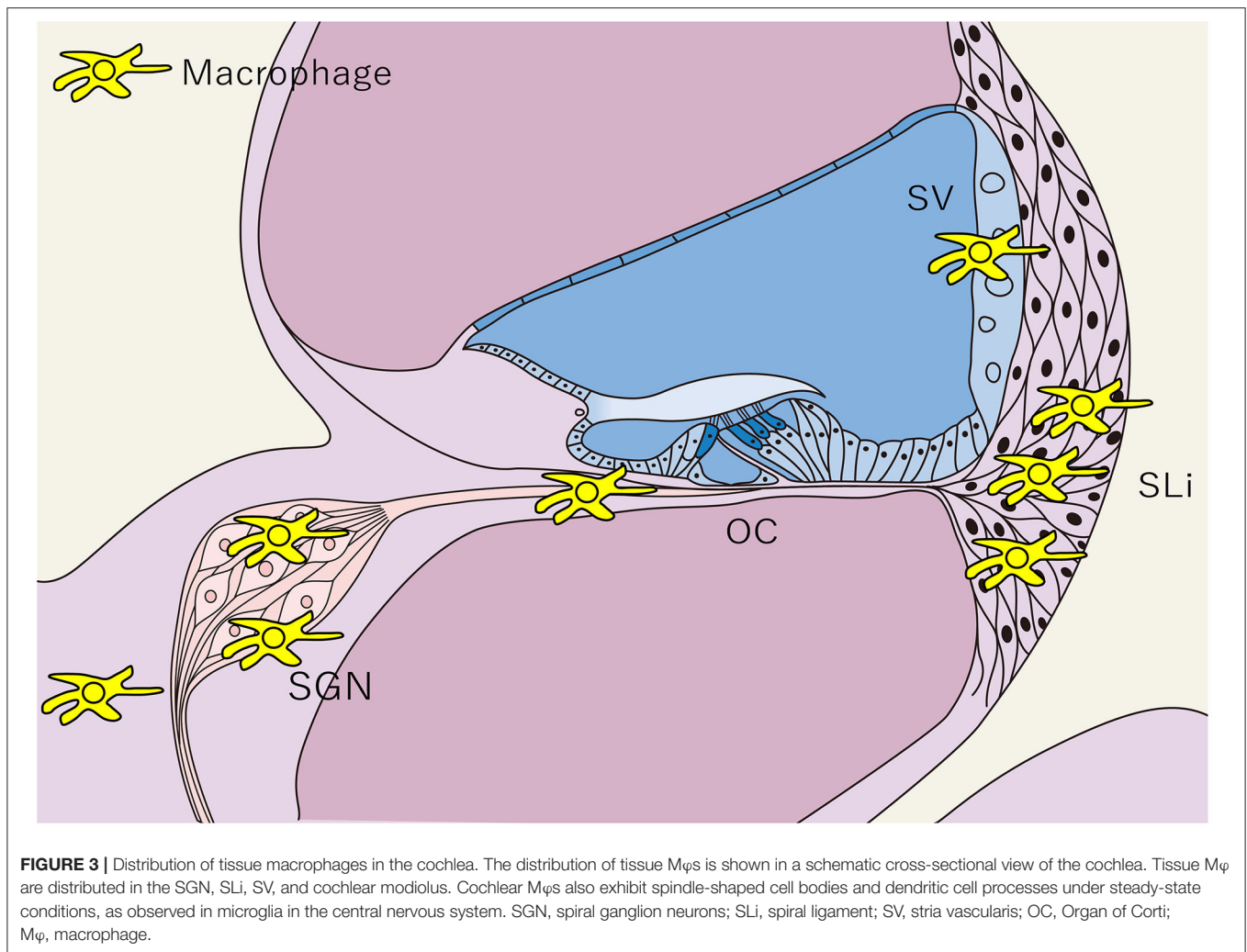
## MACROPHAGES AND AUTOIMMUNE DISEASES

Monocytes and M $\phi$ s can secrete a wealth of cytokines and chemokines, which further stimulate other forms of immune cells, thereby leading to inflammation (33, 42). The presence of autoantibodies and autoreactive B and T cells in most autoimmune diseases indicates that the adaptive immune system is essential for their pathogenesis; however, this cannot completely account for the resolution and development of those diseases, and studies have indicated that the innate immune response may also play necessary and irreplaceable roles in the pathogenesis of the autoimmune disease (33, 43, 44).

A monocyte or M $\phi$  infiltration is typically observed in most autoimmune diseases (33). The regulatory mechanisms that involve monocytes and/or M $\phi$ s in the development of the autoimmune disease have not been fully elucidated; nevertheless, the consensus appears to signify that their atypical activation plays a key role in the abovementioned mechanisms. M $\phi$ s exhibit shifts in polarization primarily based on diverse stimuli produced with the aid of cytokines, microbes, microbial products, and

other modulators *in vitro* (45). However, in an *in vivo* study, alterations in arginine metabolism following lipopolysaccharide (LPS) injection were found to elicit different phenotypes of M $\phi$ s in C57BL/6J and Balb/c mice (46). C57BL/6J peritoneal M $\phi$ s promoted inducible nitric oxide synthase (iNOS) activity, resulting in nitric oxide expression and a T-helper 1 (Th1) CD4+ T cell response. In contrast, M $\phi$ s from Balb/c mice triggered arginase activity, resulting in an ornithine and Th2 response. Analogous to Th1 and Th2, these M $\phi$ s have been termed M1 and M2 (46). Generally, M1-polarized M $\phi$ s are pro-inflammatory and secrete IL-12 and tumor necrosis factor (TNF)- $\alpha$ , which contribute to local irritation, while M2-polarized M $\phi$ s produce IL-4 and IL-10, which play roles in immunomodulation, wound repair, and tissue remodeling (43, 47).

Within tissues of the central nervous system (CNS), particularly in patients with progressive MS, infection is characterized by the massive activation of mononuclear phagocytes that include both monocyte-derived M $\phi$ s and resident microglia (48). The staging of MS lesions can be determined based totally on the presence of CD68-nice M $\phi$ s and human leukocyte antigens, together with the extent of myelin



loss (49). Findings obtained using the experimental autoimmune encephalomyelitis (EAE) model, an animal model of MS, have indicated that Mφs play crucial roles in triggering adaptive immune responses. For example, the Mφ NLRP3 inflammasome plays key role in inducing autoreactive T cell migration into the CNS in EAE (50). Mφs also produce several key cytokines (IL-1 $\beta$ , IL-6, and IL-23) that promote the generation and maintenance of Th17 cells, an important cell subset mediating CNS autoimmunity in EAE (51). For this reason, accumulating evidence suggests that Mφs play divergent roles in the pathogenesis of MS, exacerbating tissue damage despite their outstanding growth-promoting and neuroprotective effects (52). As predicted, this dual role of Mφs in MS may be defined by their polarization state. Indeed, both M1 and M2 subsets are found in MS lesions. The unexpected pro-inflammatory M1 reaction is maintained at sites of CNS damage, while the immunoregulatory M2 response is comparatively weaker and more transient (52). Yamasaki et al. demonstrated that resident macroglia are associated with particle clearance. In the context of MS, these cells exhibit global suppression of metabolism throughout disease initiation, whereas monocyte-derived Mφs

become exceptionally phagocytic and inflammatory, actively participating in the initiation of demyelination (53).

Monocytes/Mφs contribute to the pathogenesis of SLE by modulating the adaptive immune response in the kidney. Defective Mφ phagocytosis has also been thought to contribute to autoimmunity in SLE. The phagocytic potential of Mφs is vital for the clearance of dead cells and debris, which otherwise may be critical sources of autoantigens. Accumulating evidence from *in vitro* studies and murine models illustrates that ineffective clearance of apoptotic cells by Mφs may represent a critical trigger of the autoimmune response in SLE (33). In lupus-inclined NZB/W and NZW/BXSB mice, resident nephritic Mφs exhibit decreases in arginase and iNOS production despite treatment with M1- or M2 Mφ-inducing cytokines, regardless of their health status (54). Instead, these Mφs exhibit a combined pro- and anti-inflammatory phenotype throughout the course of lupus-related nephritis. The authors argued that monocyte-derived Mφs in these mice are poorly responsive to the cytokine stimulation that enables the transition to the corresponding M1 or M2 type (54). In addition to these phenotypic differences, functional analysis has confirmed that resident kidney Mφs

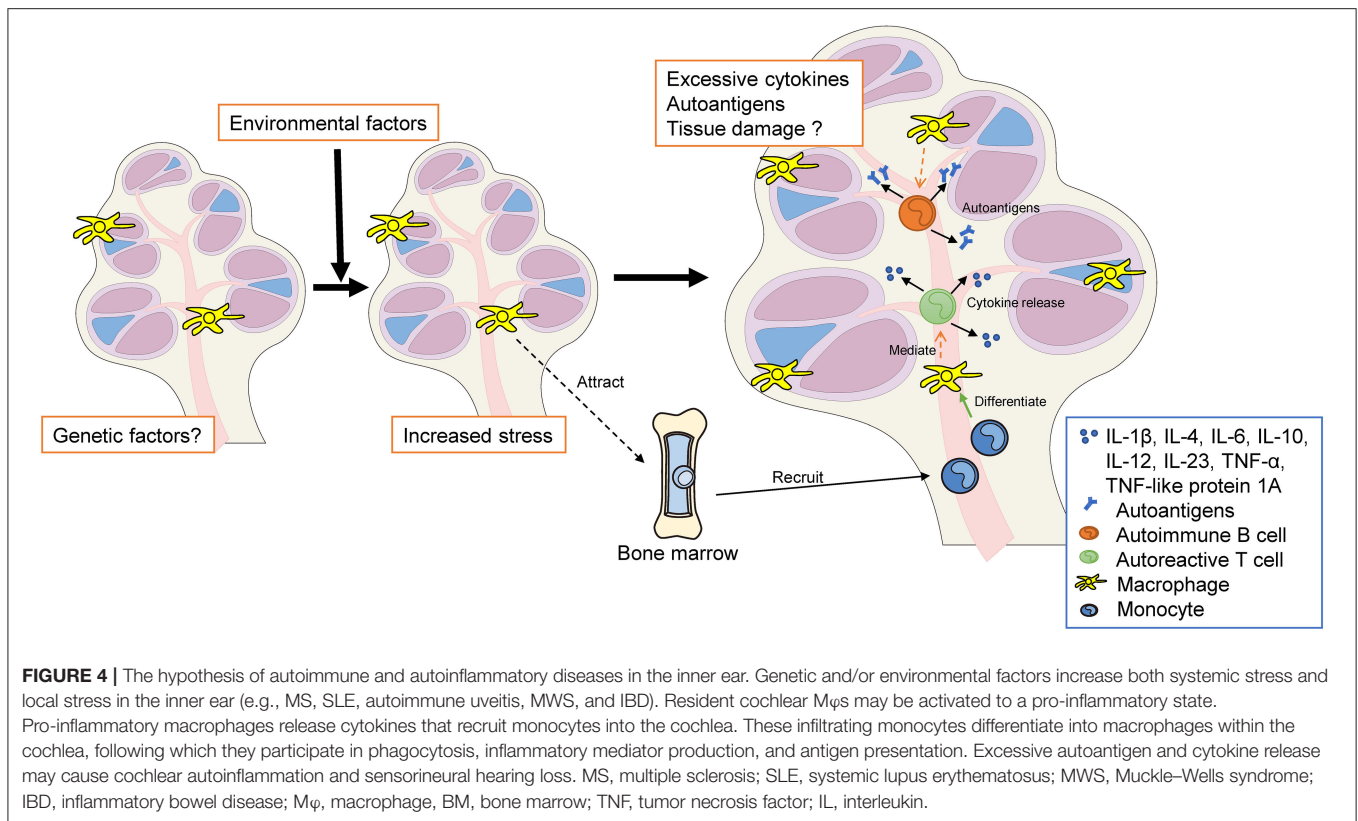


exhibit greater antigen-producing and phagocytotic effects than monocyte-derived kidney M $\phi$ s (33, 54).

Autoimmune uveitis, which occurs in several diseases that include Behçet's disease, sarcoidosis, and Vogt–Koyanagi–Harada disease, is a sight-threatening ocular inflammatory disorder (55). Immunization with interphotoreceptor retinoid-binding protein and extra adjuvants leads to the priming of autoreactive CD4<sup>+</sup> T cells in peripheral lymphoid organs and their polarization into pathogenic Th1 and Th17 cells. Once activated, Th cells in the eye induce the breakdown of the blood–retinal barrier, an immune barrier that protects the eyes from unfavorable inflammation through tight junctions between endothelial cells in blood vessels; these tight junctions block circulating leukocyte extravasation into the retina (56). Okunuki et al. suggested that retinal microglia constitute the essential cellular populace within the retina that enables entry of the autoreactive cells required for the initiation of autoimmune uveitis; however, systemic exposure to an autoantigen is in all likelihood the cause of autoimmunity in this disorder (55).

Taken together, these findings highlight the proposed relationship between monocytes/M $\phi$ s and the development of autoimmune diseases in the CNS, kidneys, and eyes. It is well-known that monocytes/M $\phi$ s are the key components of the innate immune system that underlie the amplification and suppression of inflammation (42). Increasing evidence indicates that these cells participate in the pathogenesis of autoimmune diseases mainly *via* their remarkably pro-inflammatory or fibrogenic functions (42, 57). As discussed

above, the heterogeneity of monocyte/M $\phi$  subpopulations varies dramatically in different autoimmune diseases, and their polarization profiles generally play key roles in diseases progression. However, for several autoimmune diseases, the phenotypic and functional characteristics of monocytes/M $\phi$ s remain poorly categorized, as many pro-inflammatory M1-polarized monocytes/M $\phi$ s concurrently express M2-associated markers or showcase immunomodulatory features (33).

## THE ROLE OF INNER EAR MACROPHAGES IN AIED

The inner ear is fully able to mount an immune response following the invasion of outside antigens. Consequently, numerous mechanisms have been proposed to underlie cochlear damage that include antibody–antigen reactions with autoantibody enhancement (type II immune responses), complement machine activation, immune-complicated depletion (type III immune responses), direct damage mediated *via* cytotoxic T-cells crossing the blood–labyrinth barrier and reaching the endolymphatic sac, vasculitis, micro-thrombosis, and electrochemical reactions (type IV immune responses) (10, 12, 14, 20, 58). Antigen recognition by the innate immune cells of the inner ear (neutrophils, M $\phi$ s, and dendritic cells) stimulates the release of IL-1 $\beta$ , which in turn triggers a series of adaptive immune responses. The recruitment of immunocompetent cells and the promotion of an adaptive

immune response occur in the presence of immune mediators, such as IL-1 $\beta$ , IL-2, and TNF $\alpha$  (13, 20). Studies have suggested an association between sudden sensorineural hearing loss and the presence of vestibulocochlear antibodies against inner ear antigens, such as heat shock protein 70, cochlin,  $\beta$ -tectorin, and types II and IX collagen (12, 20, 59–61).

Although the relationship between AIED/autoinflammatory diseases and cochlear monocytes/M $\phi$ s remains largely unknown, previous studies have indicated that cochlear M $\phi$ s play crucial roles in the onset and progression of infection after insults to the cochlear sensory epithelium. Such insults include noise or drug exposure and mechanical or surgical injury to the cochlea, such as that occurring during cochlear implantation (5, 31, 34, 62–72). These signals activate resident cochlear M $\phi$ s, switching them to a pro-inflammatory state and causing them to release cytokines that recruit monocytes into the cochlea (34, 62). Infiltrating monocytes then differentiate into macrophages within the cochlea, following which they exert phagocytotic functions (69, 73), produce inflammatory mediators, and play roles in antigen presentation (34). In some patients with Ménière's disease, high levels of IL-1 $\beta$  and TNF- $\alpha$  suggested that it was a chronic inflammatory disorder (74). In addition, several reports suggested an association between the immune responses caused by M $\phi$ s and Ménière's disease (75–80).

As described above, monocytes/M $\phi$ s are key components of the innate immune system in the pathogenesis of systemic autoimmune diseases and are involved in amplifying and suppressing inflammation (33, 42), mainly through their remarkably pro-inflammatory or fibrogenic properties (33, 42, 57). Nakanishi et al. suggested that monocytes are the primary regulators of IL-1 release in MWS, which is caused by a mutation in the *NLRP3* gene that leads to excessive IL-1 $\beta$  production (81). Gattorneo et al. also reported that monocytes from patients with MWS released a minute amount of IL-1 when compared with control monocytes, but that patients were extremely responsive to anakinra use (IL-1 inhibition) (82). Additionally, Nakanishi et al. indicated that LPS stimulation can activate the NLRP3 inflammasome in monocyte/M $\phi$ -like cells (CX3CR1-superb cells) in wild-type C57BL/6J mouse cochleae (81). These findings support the notion that local cochlear activation of the NLRP3 inflammasome in monocytes/M $\phi$ s can result in cochlear autoinflammation and sensorineural hearing loss (83). Vambutas et al. demonstrated that patients with steroid-resistant AIED are clinically sensitive to IL-1 inhibition; however, relative to those in individuals with steroid-sensitive AIED and controls, these monocytes synthesize greater but release much less IL-1 (84).

Previous studies have revealed that 46–57% of adult patients with IBD present with sensorineural hearing loss as an extraintestinal manifestation (85, 86); however, few reports have mentioned the roles of monocytes/M $\phi$ s. Dettmer et al. reported that the temporal bones of patients with IBD exhibited mild chronic inflammation, poorly defined granulomas, and CD68-positive M $\phi$  infiltration (87). IBD may also be associated with Cogan's syndrome, a rare disorder characterized by eye and inner ear inflammation manifesting as interstitial keratitis and audiovestibular dysfunction, respectively (88). The

mechanisms associated with eye and inner ear disorders in Cogan's syndrome are unknown; however, the authors of one autopsy case reported histopathologic evidence of vasculitis and an infiltration of CD45-positive inflammatory cells that include M $\phi$ s in both the cochlear and peripheral vestibular systems (89). Moreover, a few studies have suggested that the disease is a result of inner ear autoimmunity (90, 91). Aberrantly activated intestinal M $\phi$ s in patients with IBD produce diverse cytokines (IL-1 $\beta$ , IL-6, IL-23, TNF- $\alpha$ , and TNF-like protein 1A) required for T-cell differentiation, especially those related to the generation of Th1 and Th17 cells (92). Furthermore, in those with IBD, intestinal M $\phi$ s cause an abnormally fast breakdown of pro-inflammatory cytokines due to faster lysosomal degradation, whereas cytokine mRNA expression remains stable and within the normal range (93). This has been shown to elicit an impaired neutrophil response, leading to dysfunction in bacterial clearance and thereby boosting the formation of granulomas. Within the pathology of IBD, M $\phi$ s are hyperpolarized toward the M2 profile, as demonstrated in numerous studies. In various mouse models of IBD, inhibition of the pro-inflammatory activities of M1 M $\phi$ s or induction of tissue-repairing/immunomodulatory M2 M $\phi$ s results in attenuated experimental IBD (94, 95). Similar mechanisms are speculated to occur in the inner ear in patients with IBD.

In summary, cumulative and progressive sensory cell degeneration and death, caused by chronic inflammation, end in the activation of resident M $\phi$ s, with little infiltration of circulating monocytes (62), which parallels the innate immune response observed in chronic diseases. The activated resident M $\phi$ s adopt either a pro- or anti-inflammatory profile. Pro-inflammatory M $\phi$ s produce and release pro-inflammatory mediators—such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-6—which send signals to nearby cells, leading to further inflammation and cellular damage/apoptosis (34, 96, 97) (**Figure 4**). However, to date, no study has clarified which cells in the inner ear are targeted by M $\phi$ s, and the precise differences in phenotype and activity among newly recruited monocytes/M $\phi$ s and resident M $\phi$ s remain to be determined. Across autoimmune disorders, the heterogeneity of monocyte/M $\phi$  subpopulations varies dramatically; furthermore, their polarization profile usually plays a key role in disease development (33). Further research is required to elucidate the specific roles of cochlear monocytes/M $\phi$ s in the pathophysiology of autoimmune-mediated hearing loss.

## FUTURE DIRECTIONS

Numerous research groups have proposed M $\phi$ -targeted treatment options for inflammatory diseases. Among the most investigated strategies is the facilitation of M $\phi$  phagocytosis *via* nanoparticle targeting, which then passively targets the inflammatory site due to the mounting immune response (98, 99). The modulation and reprogramming of M $\phi$ s are also considered promising anti-tumor strategies (69–71). Using genetically modified monocytes or M $\phi$ s as vectors may aid

in the development of therapeutic strategies that promote regeneration or regrowth of particular structures inside the inner ear (6, 61, 100). This idea is especially well-suited for secreted paracrine or endocrine factors, such as hormones or growth factors. Because the inner ear includes three fluid-filled compartments, secreted elements derived from genetically modified M $\phi$ s may reach the central cells *via* diffusion through the inner ear without the involvement of the blood or lymphatic circulation. The transplantation of genetically engineered cells that can secrete particular metabolic or humoral cues may help to augment pharmacologic immune modulation inside the inner ear; however, the delivery of genetically modified cells into the inner ear may be challenging due to its anatomical characteristics. Given that monocytes and M $\phi$ s can migrate into the inner ear in both pathological and physiological states (6, 32, 61, 69), the human monocyte lineage can be extracted, cultured *ex vivo*, genetically manipulated, and reimplanted locally or systemically. Intravenous management of genetically modified monocytes should permit them to reach the inner ear despite challenges related to tissue or organ specificity.

Extending studies to identify and establish the set of markers expressed by cochlear M $\phi$ s to include multiplex and comparative transcriptomic studies may improve our ability to identify subpopulations and roles and to compare the profiles of resident M $\phi$ s in different organs. To better understand the roles of these cells, numerous processes that permit source- and area- (cochlear sub-structure) specific M $\phi$  analysis are required. Such techniques can also be used to identify remote cells or tissue indicators *in situ*. For example, in the brain, infiltrating monocytes have been shown to exhibit functional variations and contribute to disease pathology *via* multiple mechanisms following ischemic stroke and MS (53, 101). To develop therapeutic strategies for AIED and autoinflammation, it is first necessary to understand the effects of targeting cochlear M $\phi$ s. Furthermore, as hearing loss fluctuates in patients with AIED and autoinflammation, the timing of intravenous administration of genetically modified monocytes may represent a potential problem in clinical applications.

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## CONCLUSION

In this review, we discussed the latest advances and evidence regarding the connection between tissue-resident M $\phi$ s and AIED/autoinflammatory diseases. Three subtypes of cochlear-resident M $\phi$ s are found in exclusive components of the cochlea, and each subtype may play distinct roles in the abovementioned diseases. Furthermore, the dynamics and molecules expressed in tissue M $\phi$ s in the inner ear are gradually being elucidated. However, several aspects remain unclear. In particular, the role of tissue M $\phi$ s in the pathology of AIED is not well-understood, in part due to restrictions on the collection of human inner ear tissue. Moreover, additional research is required to compare the pathophysiology of such diseases in mouse models and humans. Despite the need for extensive research, the future of inner ear immunology and treatment for sensorineural hearing loss remains promising. Developing a greater understanding of monocyte/M $\phi$ -associated activities within the cochlea may be essential for developing new biological and therapeutic strategies for related diseases.

## AUTHOR CONTRIBUTIONS

TM designed and conducted the study and reported the findings. TO validated the study design, reviewed the manuscript, and supervised the study. Both authors contributed to the article and approved the submitted version.

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