Review

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Mechanisms of Inflammation and Divergent Immune Response in Meniere Disease

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Meniere Disease (MD) is a chronic inner ear disorder marked by recurrent episodes of vertigo, sensorineural hearing loss, tinnitus, and aural fullness. Approximately 60–70% of MD cases are sporadic, and increasing evidence supports a significant role for immune-mediated mechanisms in their pathogenesis. This review provides a comprehensive analysis of current evidence on the immunological underpinnings of sporadic MD and explores how these processes give rise to distinct immunophenotypes. Furthermore, in this review, we propose an immunological framework to complement existing clinical diagnostic criteria, enabling more precise classification and personalized management of MD based on immune phenotypes. Research support the concept that MD represents a spectrum of disorders rather than a single disease, comprising at least three distinct immune phenotypes: (1) a T helper 2 (Th2) cytokine–mediated subtype with an allergic-like inflammation; (2) an autoinflammatory subtype characterized by elevated levels of interleukin (IL)-1β; and (3) a subtype associated with autoimmune and/or autoinflammatory comorbidities involving other organs beyond the inner ear. Understanding these phenotypes holds promise for improving diagnostic accuracy and guiding targeted therapeutic strategies in MD. A better understanding of the immune phenotypes in sporadic MD can elucidate promising biomarkers for drug discovery and clinical interventions.

Keywords: Meniere Disease; genetics; hearing loss; autoimmune; RNA-sequencing; inflammation

Introduction

Meniere Disease (MD) is a debilitating inner ear disorder characterized by sensorineural hearing loss (SNHL), recurrent episodes of vertigo, and tinnitus or aural fullness [1]. It has a broad geographic distribution across Eurasia, with a prevalence ranging from 39 to 154 cases per 100,000 individuals; the highest prevalence has been observed in Finland (539 cases per 100,000), while the lowest rates are reported in Taiwan and Japan, with 2 and 3 cases per 100,000 inhabitants, respectively [2,3].

The condition is associated with the accumulation of endolymphatic fluid within the scala media, a phenomenon known as "Endolymphatic hydrops" (EH) [4]. This increase in pressure can damage the organ of Corti and Reissner's as well as the basilar membranes. However, EH has also been observed in other forms of SNHL that lack episodic vertigo, suggesting that EH alone may not fully account for MD episodic symptoms [5].

Meniere Disease shows considerable clinical heterogeneity, with five distinct clinical phenotypes identified based on predictive factors [6,7]. These phenotypes, found in both unilateral and bilateral forms of the disease, include sporadic MD (SMD), MD without migraine, familial MD (FMD), MD with migraine, and MD associated with autoimmune disorders [6,7].

Familial clustering exists in approximately 10% of MD cases, with observed inheritance patterns including autosomal dominant and autosomal recessive modes involving biallelic variants. To date, ~15 genes have been identified in MD pathogenesis [8], among them, *OTOG* [9,10], *MYO7A* [11,12] and *TECTA* [13] encode essential proteins crucial for maintaining the structural integrity of the organ of Corti. Recently, a rare haplotype in the gene *GJD3* has been reported across several unrelated families [14]. Many patients with MD exhibit persistent systemic inflammation characterized by distinct cytokine profiles [15].

This review aims to summarize the immunological landscape of MD by integrating the up-to-date evidence on its epigenomic, genomic, and transcriptomic features that contribute to the emergence of distinct immunophenotypes.

Sporadic Meniere Disease

Approximately 80%–90% of MD cases occur sporadically. Evidence from cytokine profiling and sequencing studies has demonstrated that most sporadic cases show dysregulated immune responses; these patients can be clustered based on their distinct cytokine profiles and levels of systemic inflammation [15,16].

Historical Perspective

The potential link between immune dysfunction and MD-like symptoms was initially reported in 1923, when two patients with tinnitus, vertigo, hearing loss and nausea were found to have a chronic history of food allergy [17]. Later, in 1986, a study reported significantly high levels of circulating immune complexes (CIC) in 54% of MD cases (36 out of 66), compared to only 2.9% (1 out of 36) in the control group. The immunological profile in these patients revealed elevated levels of various immunoglobulin (Ig) proteins: one patient exhibited high levels of IgM, IgG, and IgA; five patients had elevated levels of IgG; ten showed high levels of both IgM and IgE, and twenty patients had elevated levels of IgM [18].

By 1991, a study involving 30 MD patients, some of whom reported comorbid allergies or autoimmune disease, revealed that 96% of patients (29 out of 30) exhibited elevated levels of CIC compared to controls. The findings suggested that IgM and IgG antibodies may trigger the release of chemotactic factors, leading to granulocyte and macrophage migration to affected regions [19].

Furthermore, epidemiological evidence from independent studies in Spain [20] and the United Kingdom [21] supports associations between MD, autoimmune diseases, and allergic conditions. These findings were later confirmed in population-based analyses in South Korea [22], essential to shape the concept of distinct MD immunophenotypes.

MD Association With Autoimmune and/or Autoinflammatory Diseases

Although it is generally accepted that the adaptive immune system mediates autoimmunity, and the innate immune system mediates autoinflammation, both types of immune responses are closely interconnected through multiple cytokine-related pathways [23]. Therefore, the immunophenotypes observed in MD are shaped by both adaptive and innate responses to a different extent, influenced by each individual's genetic background and environmental factors.

Epidemiological evidence supports that MD is associated with various autoimmune and autoinflammatory disorders (Fig. 1A). In a 2011 study involving a cohort of 575 MD patients, approximately 3% of cases were reported to have a recurrent autoimmune disorder, with rheumatoid arthritis (RA) being the most frequently found [20].

A study published in 2014 reported that individuals with MD were more likely to have either allergies or autoimmune conditions compared to healthy controls. The most frequently reported comorbid conditions included psoriasis, drug allergies, and a physician-diagnosed combination of hay fever, rhinitis, and eczema. However, psoriasis is a mixed autoimmune and autoinflammatory disease and a paradigmatic example of the broad inflammatory spectrum observed in MD [24]. Several arthritis phenotypes were also reported, including all major types combined, with specific subtypes such as spinal arthritis, osteoarthritis, and rheumatoid arthritis being particularly observed [21].

Furthermore, evidence from a 2015 proteomic study indicated a potential autoimmune component in the etiopathogenesis of MD [25]. This study identified 17 immune-related proteins, including *IGHG1*, *RGS10*, *C2orf34*, *SH3GLB1*, *ACY1*, *CAMK4*, *GSG1L*, *NEK7*, *B3GALT4*, *MCCD1*, *NCMA2*, *NPY2R*, *HNRPH3*, *C12orf48*, *DLG3*, *ANXA11*, and *PCLO*, that were significantly upregulated in MD patients compared to controls. Additionally, analysis of endolymphatic sac luminal fluid revealed enrichment of nine proteins in MD individuals, including eight immunoglobulin variants and one interferon regulatory factor 7.

The diagnostic criteria for MD were revised in 2015 by the Barany Society International Classification Committee for Vestibular Disorders [1]. After this update, several efforts were made to classify MD cases into clinical subgroups based on symptoms and associated comorbidities. Hence, five clinical subgroups were found applicable to both unilateral and bilateral MD, with subgroup 3, an autoimmune MD (AIMD), characterized by the coexistence of MD with an autoimmune disorder [6,7].

In a two-year long longitudinal study, 19.7% of MD cases (14 out of 71 cases) were classified as AIMD, with comorbid conditions such as hypothyroidism, psoriasis, and rheumatoid arthritis [15]. Although overall clinical differences between AIMD and non-autoimmune MD were limited, the AIMD subgroup exhibited significantly elevated levels of interleukin (IL)-8 and tumor necrosis factor (TNF)-α. Additionally, 14% of AIMD patients met the classification criteria for FMD.

Notably, MD patients with comorbid autoimmune disease, including autoimmune or autoinflammatory disorders, such as autoimmune thyroiditis or psoriasis, are often classified under the broad category of "autoimmune MD". Nevertheless, since both types of immune responses (adaptive and innate) can be active in psoriasis and given the low prevalence of autoantibodies [26] along with high levels of T cell cytokines [27], these cases may be better categorized as a distinct subgroup, such as autoinflammatory-linked MD (Fig. 1B) [28].

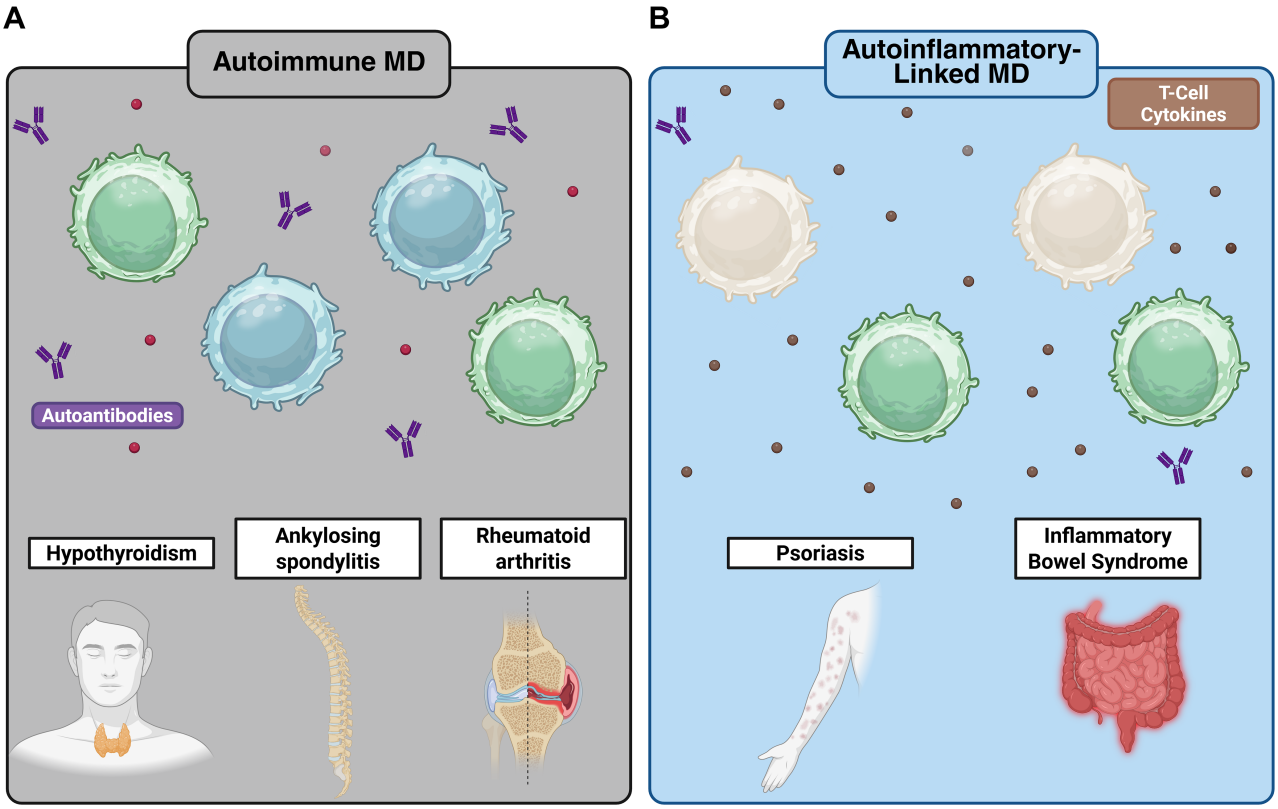

Fig. 1. Common disorders found in Autoimmune and Autoinflammatory-Linked MD Phenotypes. (A) Characterization of autoimmune MD (AIMD). Common comorbid autoimmune disorders associated with MD include hypothyroidism, ankylosing spondylitis, and rheumatoid arthritis. Autoantibodies are frequently observed in AIMD. (B) Characterization of autoinflammatory-like MD. Common comorbid autoinflammatory disorders associated with MD include psoriasis and autoinflammatory bowel syndrome. Autoinflammatory-like MD exhibits lower levels of autoantibodies. MD, Meniere Disease. Created in BioRender. https://BioRender.com/iblstyx.

Classification of MD Patients According to the Immunophenotype

Besides fulfilling the clinical criteria established by the Bárány Society International Classification Committee for Vestibular Disorders in 2015 (Table 1, Ref. [1]), we propose the following criteria to differentiate the 3 distinct MD immunophenotypes (Table 2, Ref. [15,28]).

A flowchart depicting the diagnostic process and identification of immunophenotype in MD is illustrated in Fig. 2.

Autoinflammatory MD Phenotype

The NOD-like receptor pyrin domain-containing (NLRP) inflammasomes are part of the innate immune system that play an essential role in detecting and responding to damage-associated molecular patterns (DAMPs) released from stressed or dying cells, and pathogen-associated molecular patterns (PAMPs) derived from infections [29].

In 2017, a study identified a p.Arg918Gln mutation in the *NLRP3* gene, encoding the NLR family pyrin domain-containing 3 protein [30]. This mutation was found to cause autosomal-dominant SNHL (DFNA34) in two unrelated families. Affected individuals exhibited progressive bilateral hearing loss without vestibular symptoms. In one family, affected individuals exhibited cochlear autoinflammation accompanied by systemic inflammatory symptoms, while in the other family, hearing loss occurred without systemic inflammatory manifestations. The study further demonstrated that resident macrophages and monocytes in the mouse cochlea could express and activate the NLRP3 inflammasome, leading to IL-1β secretion.

Recently, a 2024 study on age-related hearing loss found that mitochondrial dysfunction caused by altered dynamin-like GTPase OPA1 (*OPA1* gene) resulted in a high expression of *NLRP1*, *NLRP3*, caspase 1, IL-1β, IL-18, and TNF-α in HEI-OC1 cells. The results suggest that mitochondrial dysfunction may trigger the pyroptosis-associated proinflammatory axis, contributing to the aging of cochlear hair cells [31].

Although NLRP12 is less extensively studied than NLRP3, recent evidence has associated NLRP2 variants with familial cold autoinflammatory syndrome 2 (FACS2). A study conducted in 2008 reported two 10-year-old monozygotic twin brothers with FACS2 who also developed bilateral SNHL, despite demonstrating normal serum

Table 1. Diagnostic criteria of definite and probable MD according to the Bárány Society [1].

Definite MD
A. Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours.
B. Audiometrically documented low-to medium frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo.
C. Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear.
D. Not better accounted for by another vestibular diagnosis.
Probable MD
A. Two or more episodes of vertigo or dizziness, each lasting 20 minutes to 24 hours.
B. Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear.
C. Not better accounted for by another vestibular diagnosis.

Table 2. Criteria for MD immunophenotypes based on cytokine profile and cellular count [15].

A. Th2-Mediated MD
a. Systemic elevation of >2 Th2 cytokines – IL-4, IL-5, IL-13 – and granulocyte-macrophage colony stimulating factor (GM-CSF).
b. High granulocyte count.
c. No better accounted for by another autoimmune or autoinflammatory comorbid disorder.
d. Absence of autoantibodies.
B. Autoinflammatory MD
a. Systemic elevation of IL-1β, TNF-α, IL-10, or hepatocyte growth factor (HGF) levels.
b. High monocyte and macrophage count.
c. No better accounted for by another autoimmune or autoinflammatory comorbid disorder.
d. Absence of autoantibodies.
C. MD Associated with Autoimmune and/or Autoinflammatory Diseases [28].
MD individuals who meet the clinical diagnostic criteria and present with an autoimmune/autoinflammatory comorbid disorder that affects organs other than the inner ear (e.g., psoriasis, rheumatoid arthritis, or ankylosing spondylitis).

IgD levels [32]. Furthermore, another study in 2020 reported that patients of East Asian origin with NLRP12-associated autoinflammatory disorders commonly presented with SNHL, with an increased prevalence observed among individuals carrying the p.R284X variant in the *NLRP12* gene [33].

In 2018, a study investigated the expression of IL-1β and other proinflammatory cytokines in a cohort of 113 MD patients and 54 healthy controls [34]. MD patients exhibited a 2.6- to 7.1-fold increase in the expression of IL-1β, IL-1RA, IL-6, and TNF-α compared to controls. The study identified two distinct clusters based on IL-1β and IL-1RA levels: MD Low (MDL) and MD High (MDH). Upon stimulation of peripheral blood mononuclear cells (PBMCs) with *Penicillium spp.* and *Aspergillus spp.*, the MDH subgroup showed significantly higher levels of IL-6 and TNF-α compared to MDL patients [34].

A study analyzed proinflammatory cytokines in a cohort consisting of 7 MD patients (4 MDL and 3 MDH) and 6 patients with vestibular migraine (VM) [35]. As expected, the MDL group exhibited the least number of differentially expressed cytokines compared with controls, whereas the MDH group showed significantly increased levels of nearly all cytokines evaluated, except CCL22 and CXCL10, which were more highly expressed in VM patients. Importantly, the combined assessment of IL-1β, CCL3, CCL22, and CXCL1 achieved 93.8% sensitivity and 95.8% specificity in distinguishing MD from VM, underscoring their potential diagnostic utility.

A 2021 study investigated the DNA methylation profiles in MDH and MDL patients, which revealed substantial epigenetic heterogeneity between the groups [36]. MDH patients exhibited over 10,000 differentially methylated CpG sites (DMCs) and 140 differentially methylated regions (DMRs), in contrast to fewer than 400 DMCs and 40 DMRs in MDL patients. Moreover, the number of significantly annotated genes was markedly higher in MDH (>1750 genes) compared to MDL (<50 genes). Notably, among the differentially methylated genes in MDH were *H3Y1*, *ACSBG1*, and *IL32*, implicating epigenetic modulation of inflammatory and immune-related pathways in this MD subgroup.

A recent study classified MD patients into two subgroups—MDH and MDL—based on their plasma IL-1β levels. Bulk RNA sequencing of samples from 42 patients was performed to investigate transcriptomic differences between the two subgroups [37]. Gene expression analysis identified *IL6* and *INHBA* as significantly differentially expressed genes (DEGs). Notably, *IL1B* and its receptors showed no differential expression, even when compared with controls.

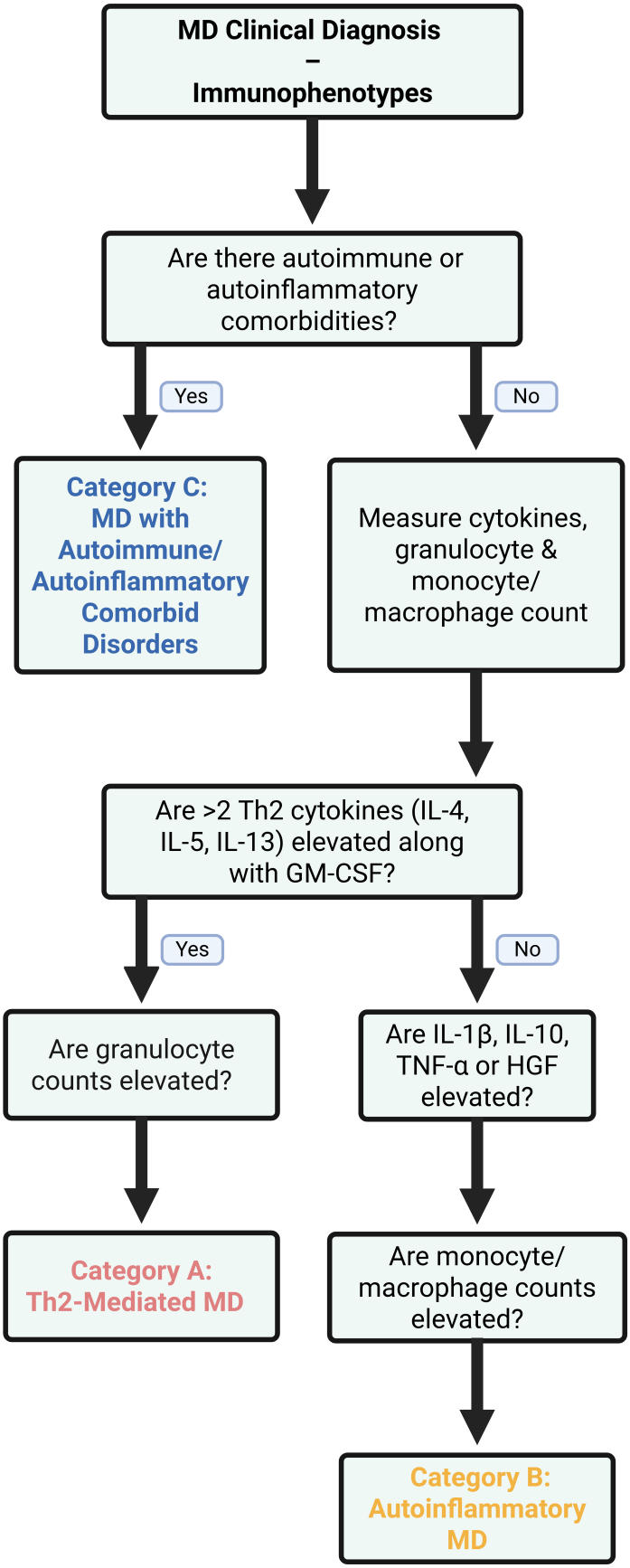

Fig. 2. A flowchart outlining MD immunophenotyping based on cytokine testing. Created in BioRender. https://BioRender.com/iblstyx.

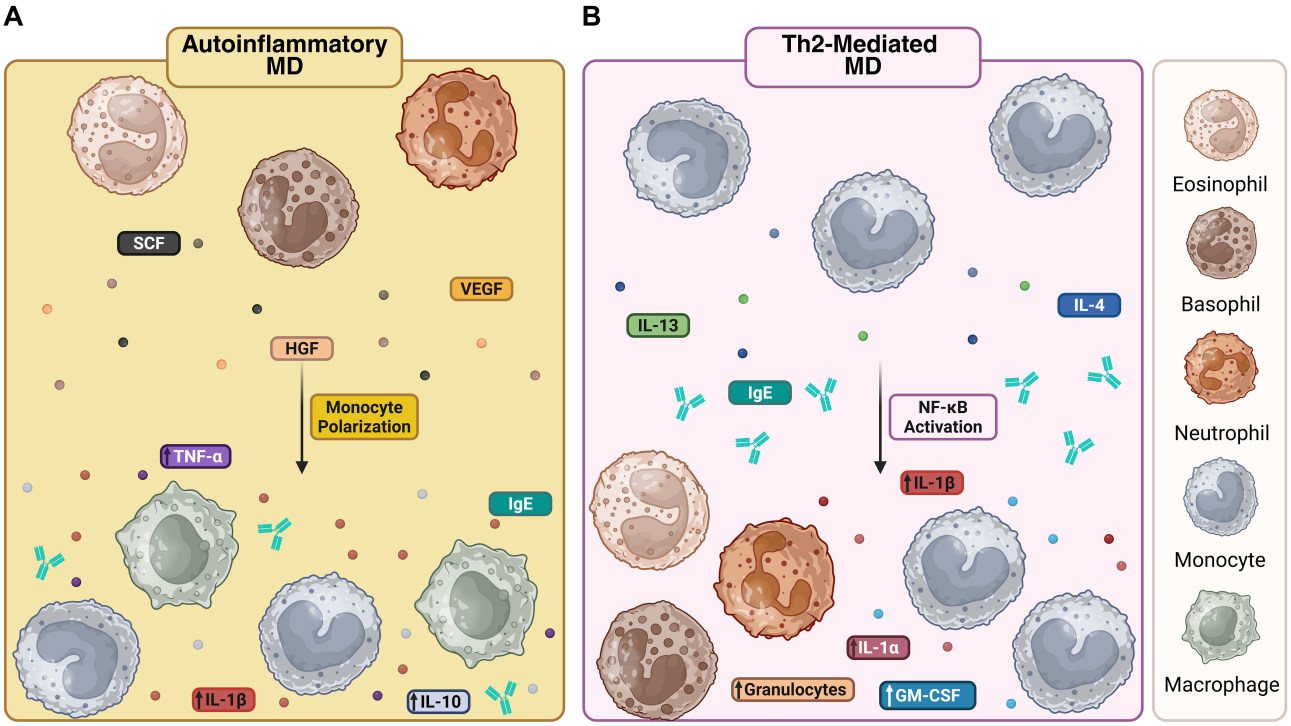

Fig. 3. Mechanisms of Action in Autoinflammatory and Th2-Mediated MD Phenotypes. (A) Autoinflammatory MD phenotype mechanisms of action. Granulocytes polarize monocytes with stem cell factors, hepatocyte growth factor, and vascular endothelial growth factor. Upregulation of interleukin (IL)-1β and IL-10 leads to systemic inflammation. (B) T helper 2 (Th2)-Mediated MD phenotype mechanisms of action. IL-4, IL-13, and free IgE activated NF-κB. The Th2-Mediated MD phenotype is characterized by high granulocyte count, high granulocyte-macrophage colony stimulating factor (GM-CSF) expression, and 2< Th2 cytokines. Created in BioRender. https://BioRender.com/iblstyx.

Single-cell RNA sequencing (scRNA-seq) of peripheral blood mononuclear cells revealed that autoinflammatory MD is driven by polarized monocytes [16]. The study identified two transcriptionally distinct MD clusters: an inactive cluster, showing minimal deviation from controls, and a monocyte-driven cluster (MDMc) characterized by an inflammatory gene expression profile. In MDMc, monocytes showed upregulation of pro-inflammatory genes, including *IL1R1*, *IL1R2*, *IL1RN*, *CXCL8*, *IL3RA*, and *CSF3R*. The study also revealed that monocyte polarization appeared to be induced by the release of vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and stem cell factor (SCF) (Fig. 3A). The same study also examined transcriptomic profiles between patients with migraine (MI) and VM. No significant transcriptional differences were found between MI and VM; however, gene set enrichment analysis revealed that the combined MI+VM group demonstrated distinct immune response pathways compared with MD.

In a subsequent study published in 2024, *in vitro* evidence demonstrated that upregulated IL-1β levels increased glutamate levels by promoting glutaminase expression in HEI-OC1 cells. This mechanism may contribute to the audiovestibular phenotype observed in MD patients [38].

Furthermore, Frejo *et al.* (2025) [15] conducted a longitudinal study and identified autoinflammatory MD in 12.7% of patients (9 out of 71 cases). In this subgroup, IL-1β levels remained consistently upregulated across at least two measurements recorded six months apart. Compared to MD patients exhibiting low IL-1β expression, those with the autoinflammatory phenotype also demonstrated increased levels of IL-10, IL-4, and IL-5 [15].

Th2-Mediated MD Phenotype

Immune dysregulation leads to allergic responses, characterized by the production of IL-3, IL-4, IL-5, and IL-13 cytokines from T helper 2 (Th2) cells, and the secretion of IgE by plasma cells [39]. Th2 cytokines (IL-4, IL-5, IL-10, and IL-13) were found to be significantly upregulated in a cohort of 103 MD patients compared to controls, with serum IgE levels differing considerably between the two groups. Notably, the study also identified CD23 expression in cochlear hair cells, suggesting the presence of a specific bidirectional IgE transport system regulated by IL-4 [40].

Further investigation of allergy-like MD phenotype demonstrated a reduction in lymphocytes, monocytes, and basophils, alongside an increased abundance of granulocytes (Fig. 3B). These patients also exhibited substantially

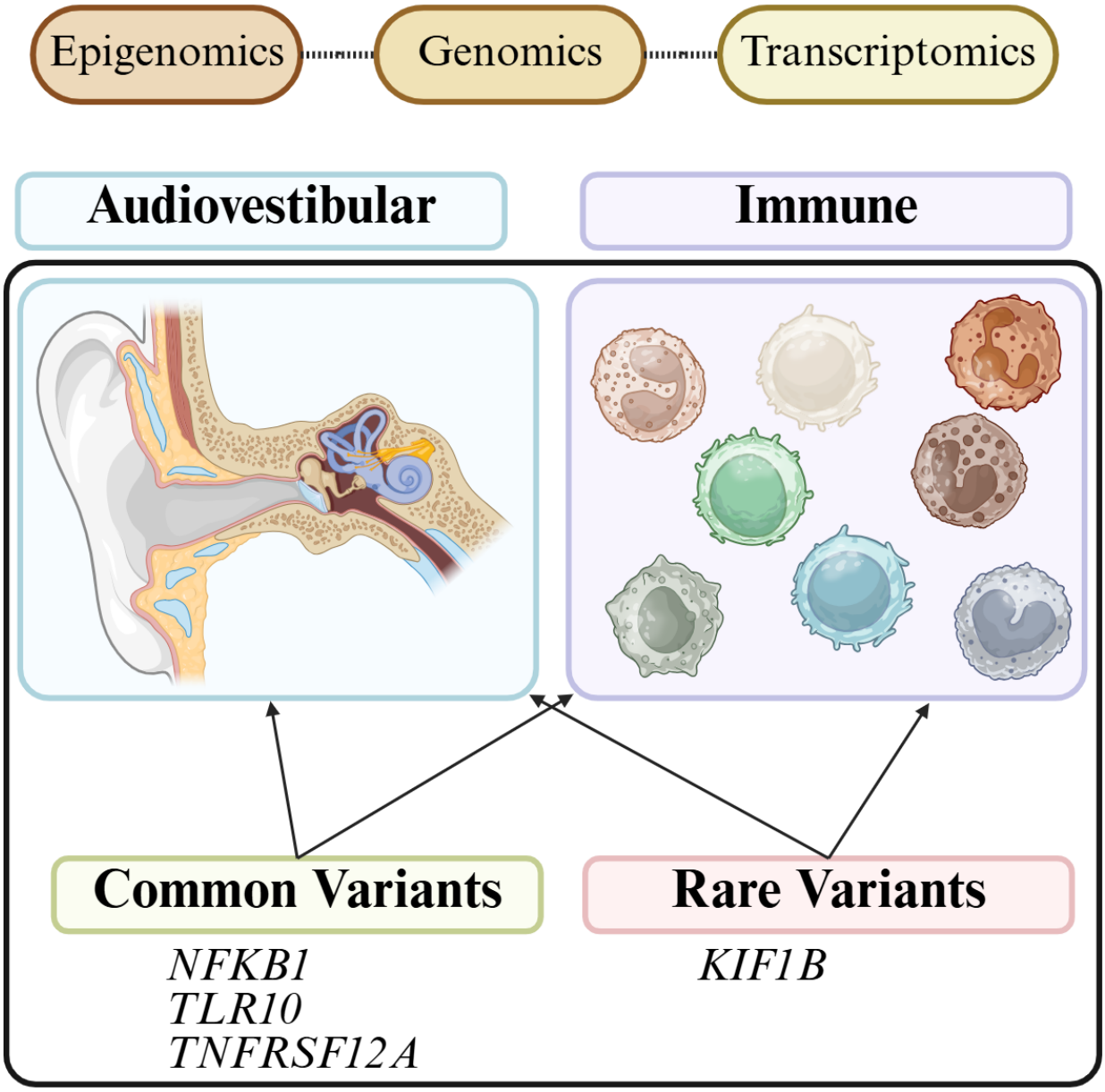

Fig. 4. Role of genetic variation in the immune response in MD. Common variants in *NFKB1* and *TLR10* are associated with the progression of hearing loss but have modest effects. A regulatory variant, rs4947296 (chr6:31014645T>C), acts as a trans-expression quantitative trait locus (eQTL) influencing the expression of immune-related genes, including *NFKB1* and *TNFRSF12A*, via the TNF-like weak inducer of apoptosis (TWEAK)/NF-κB inflammatory pathway. Additionally, a rare variant in *KIF1B* has been linked to the autoinflammatory MD phenotype, potentially playing a crucial role in mitochondrial dysfunction. Created in BioRender. https://BioRender.com/iblstyx.

increased levels of IL-4, IL-6, and IgE compared to controls [41]. A recent longitudinal study reported the allergy-like immunophenotype in 24.5% of MD cases (18 out of 71 cases) [15]. As expected, these patients showed high IgE levels and upregulation of IL-4, IL-5, IL-6, IL-8, IL-10, and IL-13 compared to the other immunophenotypes. Notably, none of the patients in this group reported previous environmental or food allergies, although 3 patients had allergic rhinitis or asthma.

Jiang *et al.* (2025) [42] validated the classification of MD immunophenotypes using flow cytometry and cytokine profiling in a Chinese cohort. The study identified three distinct $CD4^+$ T cell-defined immune phenotypes: (1) autoinflammatory, (2) type 2-skewed, and (3) inactive; each phenotype accounting for about one-third of the patient cohort. Notably, the type 2-skewed phenotype was characterized by increased proportions of Treg and TGF-β^+ $CD4^+$T cells, along with partial upregulation of IL-4 and IL-13, aligning with previous findings of Th2-mediated MD. Contrary to

classic allergic profiles, serum levels of IgE in this cluster were not significantly elevated, suggesting that MD Th2-mediated phenotype follows a non-atopic type 2 immune response. Furthermore, the study reported reduced levels of Th2 and Th17 cells across all MD patients when compared to controls, along with elevated TGF-β^+ cells and chemokines such as CCL3 and CCL4.

Genetic Regulation of Inflammation and Immune Response in MD

Genetic variation plays a critical role in modulating inflammatory and immune responses in MD. Although common variants (allelic frequency >0.05) exert modest effects on the phenotype, they are usually located upstream of the transcription start site, near promoter regions, and regulate gene expression [43]. Conversely, rare variants often have a greater phenotypic impact, as they occur within the coding region, leading to frameshift mutations and loss-of-function proteins [44–47].

Several common variants have been associated with immune response genes and SNHL progression in MD. A study assessing functional variants in nitric oxide synthase genes, *NOS1* and *NOS2A*, observed no significant association with MD pathogenesis [48]. However, a subsequent study involving 302 MD patients and 420 controls assessed short tandem repeats (STRs) in the MICA gene (Major Histocompatibility Complex Class I Chain-Related A) and reported a protective impact of variants located in exon 5, as they appeared to reduce the progression of hearing loss in MD [49].

Two independent studies conducted in 2013 and 2014 reported a substantial association between genetic variants in *TLR10* and *NFKB1* genes and the progression of bilateral and unilateral SNHL, respectively, in MD cases [50,51] (Fig. 4). NF-κB is a central transcription factor activated by IL-1β and TNF-α, promoting inflammatory responses by modulating the expression of numerous genes involved in the immune response, including those encoding pro-inflammatory cytokines [52]. Persistent activation of NF-κB promotes chronic inflammation, contributing to the development and progression of bilateral MD [53].

This mechanism was further demonstrated by Frejo *et al.* (2017) [53] in a genome-wide association screening of immune-related genes in 420 individuals with bilateral MD, and identified a regulatory variant (rs4947296, chr6:31014645T>C), located less than 1 Mb from the major histocompatibility complex (MHC), which was associated with bilateral MD. This variant acts as a *trans*-expression quantitative trait locus (eQTL) in mononuclear cells. The transcriptomic comparison between MD patients carrying the rs4947296 CC genotype (risk variant) and those with the TT genotype (protective variant) showed 973 DEGs, including *NFKB1* and *TNFRSF12A*. Additionally, functional analysis revealed that lymphocytes carrying the risk genotype did not show increased *TNFRSF12A* expression after stimulation with TNF-like Weak inducer of apoptosis (TWEAK), whereas those with the protective genotype showed elevated *NFKB1* levels. These findings suggest that this variant regulates the TWEAK-NF-κB pathway, thereby influencing inflammatory responses in MD patients [53]. Supporting these observations, a recent scRNAseq study of the stria vascularis demonstrated that TWEAK is released by intermediate cells and acts on marginal and spindle cells expressing *TNFRSF12A* [54].

Another study published in 2025 investigated rare variants in immune response genes associated with the autoinflammatory MD phenotype [55]. By integrating scRNAseq data from the autoinflammatory phenotype with whole exome sequencing from MD patients, the study identified *KIF1B* as upregulated in monocytes from the autoinflammatory phenotype, carrying a rare variant chr1:10374335C>T in 3 unrelated individuals. These carrier individuals exhibited overexpression of transcript ENST00000622724.3 in PBMCs, which was absent in controls. Kinesin-like protein KIF1B (*KIF1B* gene) is upregulated in patients with septic shock [56,57] and is known to induce mitochondrial apoptosis under stressful conditions [58]. Furthermore, *KIF1B* expression was found to be enriched in the stria vascularis in both FMD and SMD [59].

Treatment of MD With Immunomodulators

Over the years, several immunotherapeutic approaches have been developed to combat systemic inflammation [60]. However, only limited studies have specifically evaluated their application in MD patients with immune dysregulation [61]. IL-1β and Th2 cytokine blockers may help reduce systemic inflammation and potentially alleviate specific symptoms associated with MD (Table 3).

Table 3. Proposed immunomodulators for MD treatment based on IL-1β, NF-κB, IL-6 and IL-14/IL-13.

Cytokine	Immunomodulator
IL-1β	*Anakinra*
	Rilonacept
	Canakinumab
NF-κB	*Sulfasalazine*
IL-6	*Tocilizumab*
IL-4/IL-13	*Dupilumab*
	Pitrakinra

IL-1β

IL-1β is a key pro-inflammatory cytokine with diverse biological effects, playing a critical role in both acute and chronic inflammatory responses as well as in autoimmune diseases [62]. Monocytes synthesize IL-1β as an inactive precursor, pro-IL-1β (31 kDa), which is cleaved by the protease caspase-1 to produce its active, mature form

(17 kDa) [63,64]. While the role of IL-1β in hearing disorders remains largely undefined, evidence from animal models of autoimmune inner ear disease (AIED) and clinical cases of autoinflammatory syndromes associated with SNHL suggests a possible involvement. Notably, IL-1β has been implicated in certain types of hearing loss, such as Muckle-Wells syndrome (MWS) [65], DFNA34 [30], and corticosteroid-resistant AIED [66]. Furthermore, the International Mouse Phenotyping Consortium reported that *IL1R2*-knocout mice show low frequency HL [67]. However, none of these disorders exhibit the vestibular phenotype commonly observed in MD.

Autoinflammatory IED and MWS have been treated with Food and Drug Administration (FDA)-approved IL-1β blockers such as *Anakinra* and *Canakinumab*, with improvement of hearing function [68–71]. *Anakinra* is a recombinant human IL-1RA that inhibits IL-1 activity by competitively binding to interleukin-1 receptor type I (IL-1R1), thereby preventing recruitment of the IL-1 receptor accessory protein (IL-1RAP) and subsequent downstream signaling. It is FDA-approved for the treatment of RA [72] (Fig. 5A). In contrast, *Canakinumab* is a fully human monoclonal antibody that selectively binds to IL-1β, blocking its interaction with the IL-1R1/IL-1RAcP receptor complex [73]. Another FDA-approved IL-1 blocker, *Rilonacept*, is a soluble decoy receptor fusion protein that neutralizes IL-1α, IL-1β, and IL-1RA, and is approved for the treatment of MWS and other cryopyrin-associated periodic syndromes (CAPS) [74].

A recent study identified a novel 28-kDa IL-1β fragment in PBMCs from patients with AIED following lipopolysaccharide (LPS) stimulation, which was absent or downregulated in controls [75]. This IL-1β isoform, generated uniquely by caspase-7 cleavage, induced a strong pro-inflammatory response characterized by elevated IL-6, TNF-α, and CCL3 expression, indicating a crucial role in AIED pathogenesis. In a retrospective study, 49 AIED patients treated with *Anakinra* showed promising clinical outcomes: 46% of corticosteroid-resistant patients, 73% of corticosteroid-dependent patients, and 78% of relapsed patients responded to treatment [76]. Hearing improvement averaged 14 decibels in pure-tone thresholds and a 22% in word recognition score, both exceeding outcomes typically achieved with corticosteroids. Notably, elevated C-reactive protein (CRP) was found to be correlated with elevated IL-6 levels in AIED [77]; however, an increase in C-reactive protein was observed in only 15% of patients and showed no correlation with treatment response, suggesting CRP is not a reliable indicator for treatment outcomes.

These findings reinforce the role of IL-1β–driven inflammation in AIED and support the use of IL-1 antagonism as a therapeutic approach, particularly for patients unresponsive or dependent on corticosteroids. Although data on immunomodulation in MD remains limited, a study using a mouse model of EH reported that *Anakinra* alleviated LPS-induced EH and associated audiovestibular dysfunction [78]. This provides potential evidence that IL-1 inhibition may offer therapeutic benefits in MD patients with an autoinflammatory phenotype, warranting further investigation of anakinra as a targeted immunomodulatory therapy in inner ear disorders.

NF-κB

NF-κB is a family of transcription factors that play a key role in regulating immune and inflammatory responses [52]. The family comprises RelA (protein [p] 65), RelB, c-Rel, NF-κB1 (p50), and NF-κB2 (p52), which can form various homo- or heterodimer complexes [79].

The canonical NF-κB pathway is primarily mediated by the RelA (p65)/NF-κB1 heterodimer and is activated through the IκB kinase (IKK) complex, consisting of IKKα, IKKβ, and the regulatory subunit NEMO (NF-κB essential modulator) (Fig. 6). Upon stimulation by pro-inflammatory signals, the IKK complex phosphorylates IκBα at specific serine residues at Ser32 and Ser36 near its N-terminus, targeting it for ubiquitination and subsequent proteasomal degradation. This degradation releases NF-κB dimers, which then translocate into the nucleus to regulate the transcription of target genes involved in inflammation, immunity, and cell survival [80]. In contrast, the non-canonical NF-κB pathway is primarily mediated by the RelB/NF-κB2 heterodimer and activated by specific members of the TNF superfamily, including TWEAK, lymphotoxin-α, BAFF, and RANKL [81].

NF-κB signaling has been implicated in various hearing loss disorders, including noise-induced hearing loss (NIHL) and MD. A study published in 2006 demonstrated that NF-κB1-deficient mice exhibited heightened vulnerability to acoustic overstimulation, accelerated age-related hearing loss, and auditory nerve degeneration. Notably, these changes occurred without significant hair cell loss or reductions in endocochlear potential. The findings indicated that NF-κB activity may play a neuroprotective role, helping maintain auditory neurons' integrity by mitigating excitotoxic damage and promoting neuronal resilience during aging [82].

As of 2025, no targeted therapies have been explored to block NF-κB signaling in hearing-related disorders. However, *Sulfasalazine,* a drug widely used to treat autoimmune conditions such as rheumatoid arthritis or inflammatory bowel disease [83,84], has been reported to modulate this signaling axis. Several mechanisms of action for *sulfasalazine* and its metabolites have been suggested to explain its anti-inflammatory effects [85]. *Sulfasalazine* has been known to inhibit NF-κB activation, thereby reducing the expression of pro-inflammatory cytokines like TNF-α [86], and promoting caspase-8-dependent apoptosis in macrophages [87]. It also blocks osteoclast formation by downregulating RANKL while upregulating osteoprotegerin [88].

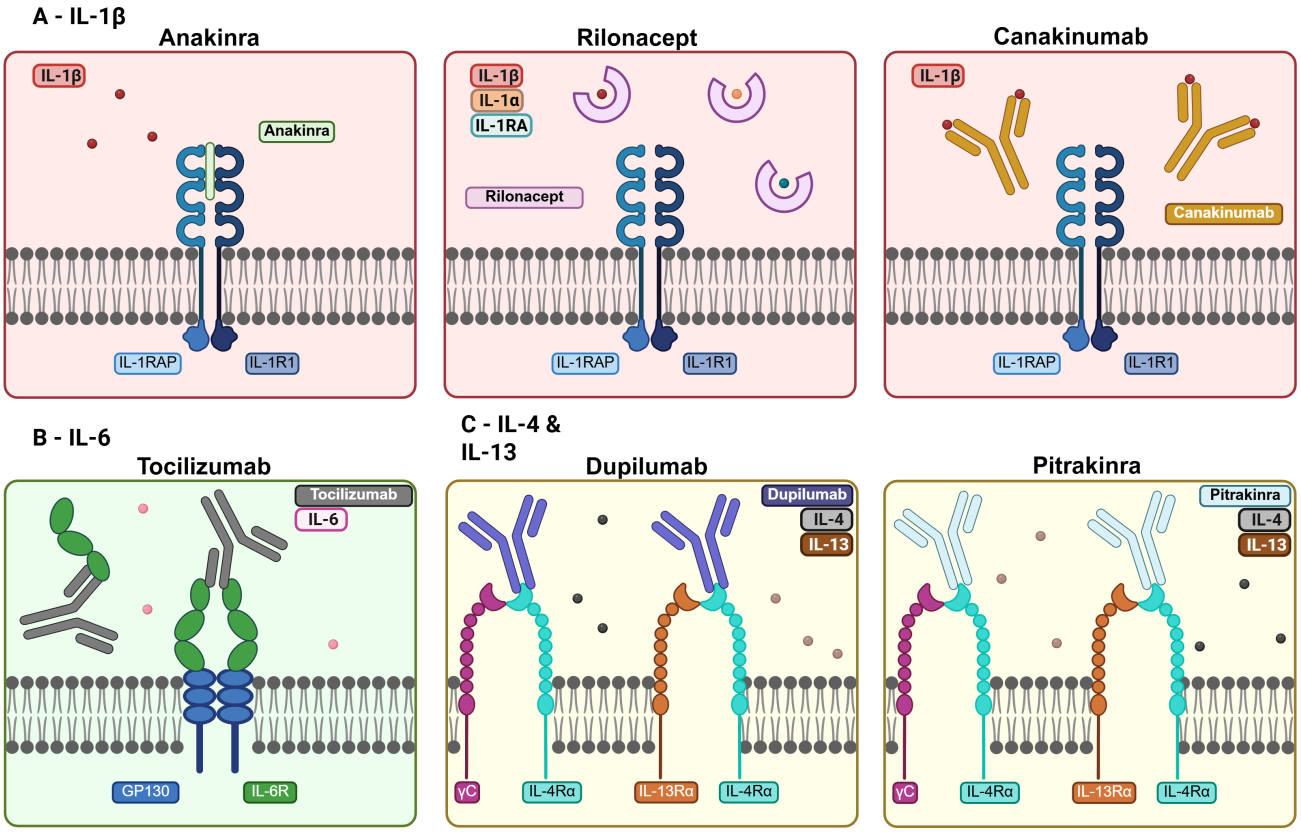

Fig. 5. Potential immunomodulators block inflammatory cytokines. (A) IL-1β blockers *Anakinra*, *Rilonacept,* and *Canakinumab*. (B) IL-6 blocker *Tocilizumab*. (C) IL-4 and IL-13 blockers *Dupilumab* and *Pitrakinra*. Created in BioRender. https://BioRender.com/iblstyx.

Additionally, Sulfasalazine increases adenosine production through ecto-5'-nucleotidase, exerting anti-inflammatory effects mediated by adenosine [89]. Both sulfasalazine and salicylates reduce leukocyte accumulation via an adenosine-dependent pathway, independent of NF-κB and prostaglandins [90]. Furthermore, sulfasalazine and its metabolites inhibit B-cell activity, lowering IgM and IgG levels [91], while sulfapyridine reduces chemokine secretion [92]. Finally, 5-aminosalicylic acid activates AMPK signaling, thereby counteracting NF-κB-mediated axis [93].

IL-6

Interleukin-6 is a 21 kDa pro-inflammatory cytokine secreted by macrophages that plays a crucial role in modulating immune responses [94,95]. Elevated IL-6 levels have been observed in various autoimmune and autoinflammatory conditions, such as rheumatoid arthritis [96], and have also been implicated in hearing-related disorders. A 2010 study demonstrated IL-6 expression in the cochlea as early as six hours following noise exposure [97]. Notably, treatment with an anti-IL-6 receptor antibody (MR16-1) substantially improved auditory thresholds at 4 kHz in mice, whereas no significant improvement was observed in the control group. In another study, alterations in TNF-α, IL-6, IL-2, and IL-8 levels were assessed before and after therapeutic intervention [98]. Reductions in TNF-α and IL-6 levels were significantly associated with positive therapeutic outcomes, whereas changes in IL-2 and IL-8 levels showed no correlation with treatment efficacy.

Tocilizumab, an FDA-approved monoclonal antibody targeting IL-6, is indicated for the treatment of rheumatoid arthritis, giant cell arteritis, cytokine release syndrome, and other inflammatory conditions (Fig. 5B). It exerts its therapeutic effect by inhibiting IL-6 signaling through binding to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) [99]. In 2024, *Tocilizumab* showed therapeutic success in patients with Cogan's syndrome—a rare autoimmune vasculitis characterized by non-syphilitic interstitial keratitis and audiovestibular dysfunction [100,101].

IL-4 and IL-13

Interleukin-4 is primarily secreted by mast cells, Th2 cells, eosinophils, and basophils. It plays a central role in Th2 cell-mediated immunity [102], promotes IgE class switching in B cells [103], and induces alternatively activated macrophages (AAMΦs) [104]. Similarly, IL-13, also secreted by Th2 cells, has a different amino acid sequence but shares functional similarity and the IL-4Rα receptor with IL-4 [105]; however, unlike IL-4, it does not induce

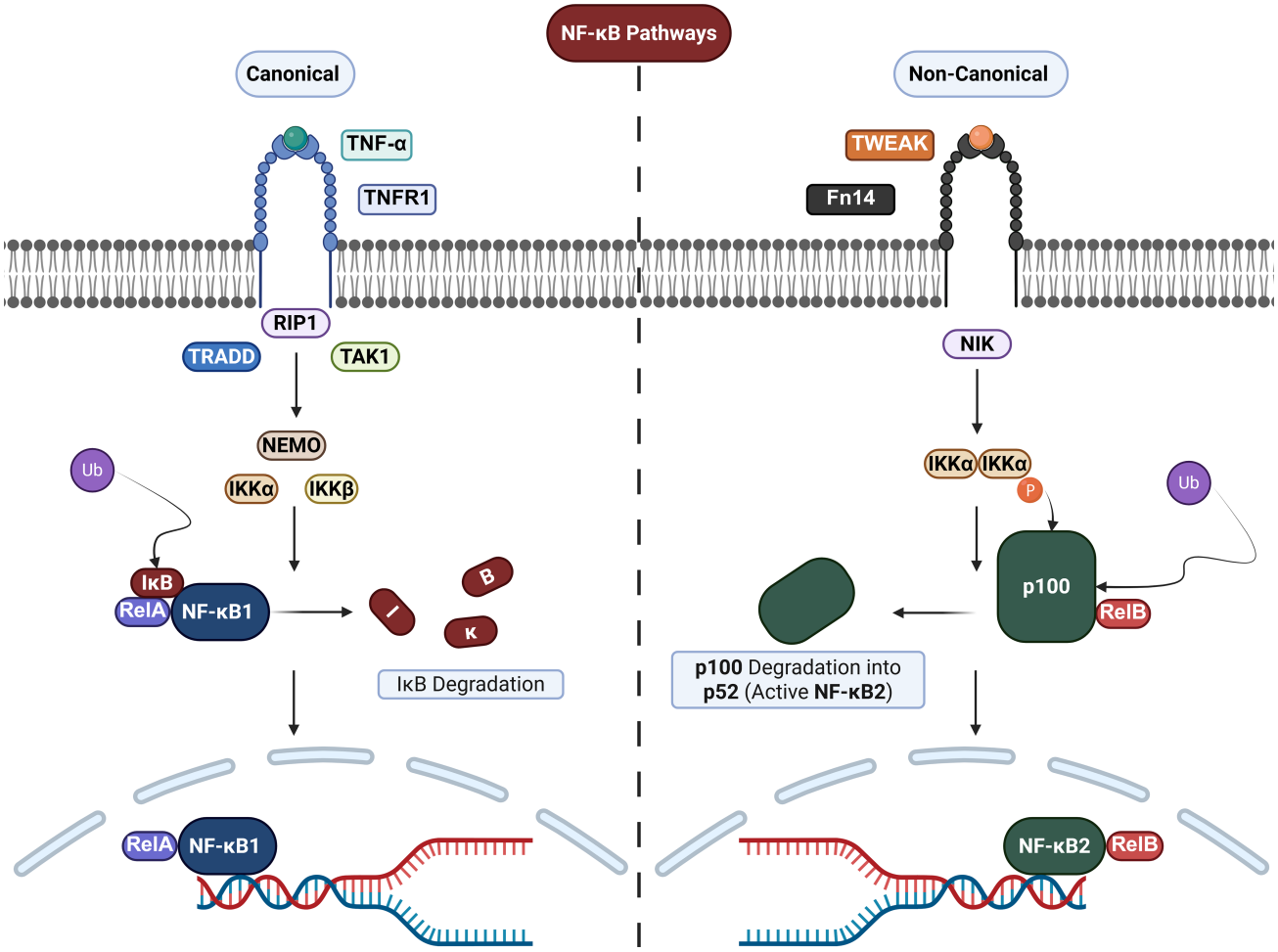

Fig. 6. NF-κB activation pathways. Canonical pathway activating the RelA/NF-κB1 transcription factor (left). Non-Canonical pathway activating the RelB/NF-κB2 transcription factor (right). Created in BioRender. https://BioRender.com/iblstyx.

T cell proliferation or drive Th2 differentiation [106]. Both IL-4 and IL-13 have been implicated in the pathogenesis of chronic inflammatory conditions such as bronchial asthma [107].

Interleukin-4 exerts its effects through two distinct receptor complexes formed by the IL-4 receptor alpha chain (IL-4Rα). In the first pathway, IL-4 pairs with the common gamma chain to create the type I receptor, which is predominantly expressed on blood cells [108]. This receptor is critical for driving Th2 cell differentiation and the activation of AAMΦs [104]. In the second pathway, IL-4 can associate with IL-13 receptor alpha 1 (IL-13Rα1), generating the type II receptor complex expressed mainly on non-blood cells [109]. The type II receptor mediates responses to both IL-4 and IL-13, including mucus hypersecretion and airway hyperresponsiveness [104].

Therapeutic targeting of IL-4 and IL-13–mediated signals can be achieved with *Dupilumab*, an FDA-approved monoclonal antibody used to treat moderate-to-severe asthma, atopic dermatitis, and chronic rhinosinusitis with nasal polyps, among other conditions (Fig. 5C) [110]. *Dupilumab* is a fully human IgG4 monoclonal antibody that targets the IL-4Rα, a subunit common to both the type I (IL-4-specific) and type II (IL-4/IL-13 shared) receptors, thereby inhibiting signaling from both cytokines and alleviating type 2 inflammation [110].

Similarly, *Pitrakinra* is an investigational biologic that also blocks IL-4 and IL-13 signaling by competitively inhibiting IL-4Rα. However, unlike *Dupilumab*, *Pitrakinra* remains in early-phase clinical trials and has not yet been approved for clinical use [111].

Gap Knowledge and Future Directions

Key challenges remain in validating the proposed immunophenotypes across larger, multi-center cohorts and in standardizing cytokine evaluation assays for clinical utility. Furthermore, the mechanistic basis of these phenotypes warrants further investigation. Moreover, future studies should prioritize biomarker-driven clinical trial designs to assess the therapeutic significance and clinical efficacy of phenotype-guided treatment strategies.

Conclusions

Meniere Disease represents a spectrum of disorders including 3 distinct immunophenotypes, each defined by specific cytokine profiles and levels of systemic inflammation. A combination of clinical audiovestibular assessments and cytokine profiling is essential to further refine MD phenotypic classification and deepen the understanding of the complex pathophysiology of the disease. Targeted treatments using immunomodulators for IL-1β, NF-κB, IL-6 and Th2 pathways hold promises for providing more effective therapeutic options for these patients.

Availability of Data and Materials

Not applicable.

Author Contributions

JALE – Conceptualization, funding acquisition, writing – original draft, writing – review & editing. PCG – Data curation, formal analysis, visualization, figure design, writing – original draft, writing – review & editing. Both authors contributed to critical revision of the manuscript for important intellectual content. Both authors read and approved the final manuscript. Both authors agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

Jose A. Lopez-Escamez is serving as one of the Editorial Board members of this journal. We declare that Jose A. Lopez-Escamez had no involvement in the peer review of this article and has no access to information regarding its peer review.

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