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REVIEW

The IL-12 family cytokines in neurodegenerative diseases: dual roles in neurotoxicity and neuroprotection

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Abstract

Neurodegenerative diseases (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) are characterized by progressive neuronal loss and chronic neuroinflammation. Increasing evidence highlights the interleukin-12 (IL-12) cytokine family—including IL-12, IL-23, IL-27, and IL-35—as central regulators of immune responses in the central nervous system (CNS). IL-12 and IL-23 predominantly promote pro-inflammatory pathways by driving Th1/Th17 activity, microglial activation, and neurotoxicity, whereas IL-27 and IL-35 exert anti-inflammatory and neuroprotective effects through IL-10 induction and expansion of regulatory immune subsets. This review synthesizes disease-specific expression patterns and experimental findings, underscoring the dual pathogenic and protective roles of these cytokines. Therapeutic strategies targeting IL-12 family signaling have shown promise in preclinical and clinical contexts. In AD, blockade of IL-12/IL-23 reduced amyloid burden and improved cognition, while agents such as tadalafil and bergapten enhanced IL-27-mediated neuroprotection via PI3K/Akt, Wnt/β-catenin, and cGMP/PKG pathways. In MS, approaches including p40 blockade (ustekinumab, ABT-874), interferon-β therapy, hematopoietic stem cell transplantation, and B-cell depletion (ocrelizumab) variably suppressed IL-12/IL-23 and augmented IL-27/IL-35, influencing relapse rates and progression. Natural compounds such as curcumin, berberine, and vitamin D further highlight

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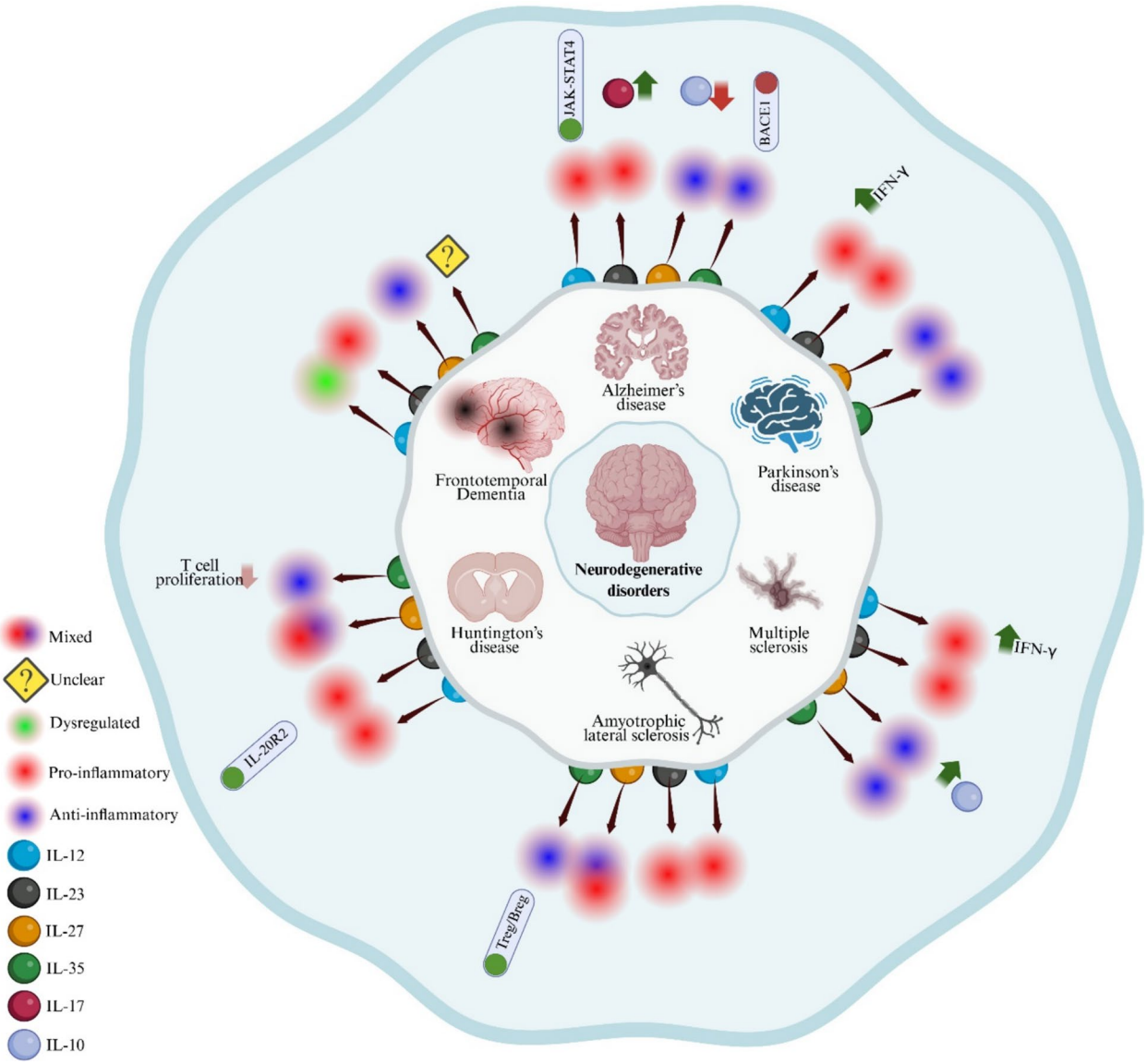
metabolic and dietary opportunities for cytokine modulation. In PD, combinatorial regimens combining herbal formulations with anti-inflammatory agents dampened IL-12-driven macrophage activation and supported dopaminergic neuron survival. Taken together, IL-12 family cytokines emerge as both biomarkers and therapeutic targets in NDs. However, context-dependent activity, blood–brain barrier constraints, and incomplete understanding—particularly of IL-35—pose translational challenges warranting further investigation.

Graphical abstract



Keywords IL-12 family cytokines · Neurodegenerative diseases · Neuroinflammation · Therapeutic targets · Cytokine signaling · Molecular mechanisms

Introduction

NDs, including AD, PD, and Huntington's disease (HD), are recognized as major medical challenges of the twenty-first century. This is largely due to their increased incidence, progressive and disabling symptoms, and the absence of effective cures (Rosser et al. 2022; Van Schependom and D'haeseleer 2023). While traditional research has focused on protein misfolding and aggregation, such as amyloid-β, tau, and α-synuclein, recent findings suggest that

neuroinflammation may play a central, rather than merely secondary, role in driving neuronal damage. Within this context, the interleukin-12 (IL-12) family cytokines (comprising the heterodimeric cytokines IL-12, IL-23, IL-27, and IL-35) has gained attention as a critical link between peripheral immune responses and CNS homeostasis (Vignali and Kuchroo 2012; Gałecka et al. 2021; Mortada et al. 2021). Although cytokines of the IL-12 family exploit a shared JAK–STAT signaling pathway, they produce a wide range of effects ranging from pro-inflammatory (IL-12 and IL-23) to immunoregulatory (IL-27 and IL-35) based on factors, such as receptor expression and cellular environment (Liu et al. 2020a, b, c; Mirlekar and Pylayeva-Gupta 2021; Ye et al. 2021). In the peripheral immune system, IL-12 facilitates the differentiation of Th1 cells and stimulates IFN-γ production, while IL-23 plays a key role in maintaining Th17 cell populations (Ullrich et al. 2020; Schinocca et al. 2021). Conversely, IL-27 and IL-35 are generally involved in dampening inflammatory responses. Recent evidence indicates that these cytokines also directly affect cellular function, including microglia, oligodendrocytes, and neuronal viability, thereby contributing to the progression or resolution of neuropathological conditions (Stumhofer and Hunter 2008; Ye et al. 2021; Kennedy and Silver 2022). IL-12 is significantly upregulated in the brains of individuals with AD, contributing to neurodegeneration by affecting both oligodendrocyte and neuronal signaling pathways. In murine models of AD, genetic deletion of IL-12 receptors led to the restoration of myelin structure, improved survival of interneurons, and enhanced microglial phagocytic activity (Ano et al. 2020; Schneeberger et al. 2025a, b; Shateri et al. 2025a, b). These findings are corroborated by elevated IL-12 levels in human AD brain tissue, highlighting the translational potential of targeting this cytokine. Collectively, these discoveries position IL-12 as a compelling therapeutic target, shifting the focus of the IL-12 family cytokines from its traditional role in peripheral immunity to a central role in neurodegenerative disease intervention (Yang et al. 2022; Schneeberger et al. 2025a, b).

Supporting these preclinical findings, recent biomarker analyses have detected increased levels of plasma IL-12p70 in individuals with AD and PD, often accompanied by heightened concentrations of other inflammatory markers, including IL-1α, IL-1β, and TNF-α. This systemic inflammatory profile reinforces the concept of peripheral-to-CNS communication in driving neurodegenerative processes, implying that circulating IL-12 is not simply a byproduct of disease but may play an active, pathogenic role in its progression (Winston and Rissman 2023; Shateri et al. 2025a, b). Within the AD brain, exposure to IL-12 and IL-23 drives microglia toward a dysfunctional, pro-inflammatory state that hampers the clearance of amyloid-β and intensifies neuronal damage. These pathogenic microglia exhibit increased production of inflammatory cytokines alongside reduced phagocytic capacity, a profile that mirrors broader findings linking neuroinflammation to key processes underlying demyelination and neurodegeneration (Chen et al. 2024; Bhardwaj et al. 2025). Experimental studies have demonstrated that IL-12, especially in combination with IL-18, initiates robust neuroinflammatory responses characterized by activated microglia, infiltration of peripheral immune cells, and neuronal injury. These inflammatory processes mirror human neurodegenerative disorders, such as synaptic degradation, loss of myelin, and cognitive or behavioral impairments, underscoring the value of IL-12-driven inflammation in replicating disease mechanisms within model systems (Gaviglio et al. 2022a, b; Nikolopoulos et al. 2023). In summary, the IL-12 cytokine family, particularly IL-12, emerges as a significant contributor to the pathology of neurodegenerative diseases. Their ability to exert both neuroprotective and neurotoxic effects underscores the complex and context-dependent nature of cytokine signaling (Luo et al. 2021; Nitsch et al. 2021; Schneeberger et al. 2025a, b). Targeted inhibition of IL-12, such as by blocking the p40 subunit it shares with IL-23, has demonstrated promising outcomes in preclinical studies, including reduced amyloid plaque accumulation, decreased neuroinflammation, and improved neural function (Eede et al. 2020; Nitsch et al. 2021). Nonetheless, translating these findings into effective clinical therapies remains challenging, with obstacles such as achieving efficient CNS drug delivery, maintaining essential immune functions, and minimizing unintended side effects. Therefore, the aim of this study is to explore the relationship between IL-12 family cytokines and neurodegenerative diseases, with the goal of identifying their potential as therapeutic targets (Nortey et al. 2022; Krueger et al. 2024; Schneeberger et al. 2025a, b; Stacchiotti et al. 2025).

The IL-12 family cytokines: structure, receptors, and function

The IL-12 family cytokines represent a distinct class of heterodimeric cytokines that are central to the regulation of both innate and adaptive immune responses. This group consists of IL-12, IL-23, IL-27, and IL-35, each formed by the combination of two subunits, which may be covalently or non-covalently associated. Despite sharing several structural components, including common subunits and receptor elements, these cytokines exert diverse immunological effects (Mirlekar and Pylayeva-Gupta 2021; Wang et al. 2023a, b). IL-12 is formed by the combination of two subunits: p35 (IL-12A) and p40 (IL-12B). The p40 subunit also partners with p19 (IL-23A) to create IL-23. In a similar fashion, IL-27 consists of p28 (IL-27A) paired with Epstein–Barr virus-induced gene 3 (EBI3), whereas IL-35 is composed of p35 and EBI3 (Cassatella et al. 2020; Ullrich et al. 2020).

Each cytokine in the IL-12 family exerts its effects through a receptor complex composed of two transmembrane chains, each linked to Janus kinases (JAKs). Upon ligand binding, these kinases trigger phosphorylation cascades that activate specific STAT (signal transducer and activator of transcription) proteins (Yadav et al. 2025). IL-12 signals via a receptor composed of IL-12Rβ1 and IL-12Rβ2, predominantly activating STAT4, a pathway critical for IFN-γ production and the differentiation of Th1 cells (Gao et al. 2023). In contrast, IL-23 utilizes IL-12Rβ1 paired with IL-23R, leading mainly to STAT3 activation, thereby supporting the persistence and pathogenic activity of Th17 cells (Schinocca et al. 2021). IL-27 engages a receptor consisting of WSX-1 (IL-27Rα) and gp130, activating both STAT1 and STAT3, which supports early Th1 differentiation while also inducing IL-10 production, thus exerting anti-inflammatory effects (Xiong et al. 2022; An et al. 2025). IL-35, a heterodimer composed of p35 and EBI3 subunits, exerts its immunosuppressive effects through receptor complexes that include gp130 and IL-12Rβ2, which may form either homodimeric or heterodimeric assemblies. These receptor interactions activate STAT1 and STAT3 signaling pathways, depending on the receptor combination and the responding cell type. In classical regulatory T cells (Tregs), which rely on the transcription factor Foxp3 to maintain their identity and suppressive function, IL-35 enhances their regulatory capacity. Notably, IL-35 also drives the development of a unique and recently described Treg subset known as iTr35 cells. Unlike conventional Tregs, iTr35 cells function independently of Foxp3 and gain their suppressive properties through IL-35-driven autocrine signaling. In parallel, IL-35-producing regulatory B cells (i35-Bregs), an emerging Breg subset, contribute to immune regulation by promoting the expansion of both $Foxp3^+$ Tregs and iTr35 cells, thereby inhibiting pro-inflammatory Th17 responses and reinforcing peripheral tolerance during autoimmune inflammation (Choi and Egwuagu 2021; Ye et al. 2021).

The IL-12 family cytokines play a pivotal role in shaping immune responses, particularly by influencing T cell differentiation and regulating the balance between inflammation and tolerance. IL-12, the first member identified, is renowned for its ability to drive Th1 polarization by promoting IFN-γ production from both T cells and natural killer (NK) cells (Mehrotra et al. 2020; Tuzlak et al. 2021). It is essential for host defense against intracellular pathogens, such as Mycobacterium tuberculosis and Toxoplasma gondii, and serves as a key "third signal" in T cell priming, effectively bridging innate and adaptive immunity (Mahmoudzadeh et al. 2021; Wang et al. 2025). However, IL-23 exerts distinct immunological effects. Rather than promoting Th1 responses, it supports the stabilization and expansion of Th17 cells, which secrete IL-17 and IL-22, cytokines crucial for neutrophil recruitment and maintaining epithelial barriers (Schinocca et al. 2021; Pavlidis et al. 2022). However, dysregulation of the IL-23/Th17 axis has been strongly implicated in the pathogenesis of several autoimmune diseases, including psoriasis, multiple sclerosis, and inflammatory bowel disease (Sewell and Kaser 2022; Sharma et al. 2022). IL-27 exhibits both pro- and anti-inflammatory effects, depending on the immune environment and target cells. Composed of the EBI3 and p28 subunits, it signals through a receptor complex made up of WSX-1 (IL-27Rα) and gp130, activating downstream JAK/STAT1 and STAT3 pathways. In autoimmune conditions such as spondyloarthritis, IL-27 acts predominantly as an anti-inflammatory mediator by suppressing Th17 cell differentiation, downregulating RORγt, and promoting IL-10-producing Tr1 regulatory T cells. However, under conditions like preterm labor, IL-27 enhances inflammation by upregulating IFN-γ, IL-6, TNF-α, and CXCL10 through the ERK signaling pathway, particularly in fetal membrane and uterine cells. This context-dependent function positions IL-27 as a key immunoregulatory cytokine capable of modulating both protective and pathological immune responses (Huang et al. 2021; Jouhault et al. 2023). IL-35, a heterodimeric cytokine from the IL-12 family, exerts powerful immunosuppressive effects by orchestrating both innate and adaptive immune responses. In sepsis, its serum levels rise significantly during the acute phase and show strong correlations with clinical severity, forming an interactive network with other key cytokines, such as IL-6, IL-10, IL-17A, TNF-α, and IFN-γ. Experimental models demonstrate that administering recombinant IL-35 suppresses pro-inflammatory cytokine production, reduces effector T cell activity, and enhances the expansion of Tregs) and iTr35, leading to reduced inflammation and improved outcomes. In the tumor microenvironment, IL-35 similarly establishes an immunosuppressive landscape by limiting cytotoxic T cell responses, driving T cell exhaustion, and inducing both regulatory T and B cell populations that sustain IL-35 expression through a positive feedback mechanism. Collectively, these immunomodulatory properties allow IL-35 to undermine effective immune surveillance, promote disease progression, and contribute to immune escape in both infectious and oncologic settings (Liu et al. 2021; Wu et al. 2022).

Together, the IL-12 family cytokines including IL-12, IL-23, IL-27, and IL-35 exhibit considerable promise as therapeutic targets across both cancer and cardiovascular diseases due to their roles in modulating immune responses. In the context of cancer, these cytokines can either enhance anti-tumor immunity or contribute to immune suppression and tumor progression, depending on the tumor microenvironment and cytokine context. IL-12 and IL-27 primarily stimulate cytotoxic and pro-inflammatory responses, while IL-23 and IL-35 are more often linked to immunosuppressive and tumor-promoting functions. Conversely, in

cardiovascular conditions, IL-12 and IL-23 are generally associated with pathogenic inflammation and disease exacerbation, whereas IL-35 exerts protective, anti-inflammatory effects. These dual and context-dependent roles underscore the need for tailored strategies when targeting IL-12 family members in immunotherapy (Ye et al. 2020; Mirlekar and Pylayeva-Gupta 2021) (Fig. 1).

Therapeutic targeting of IL-12 family cytokines

IL-12 is an effective cytokine with the potential to enhance antitumor immunity by stimulating cytotoxic T lymphocytes and NK cell activation and thus emerging as a promising candidate for anticancer immunotherapy (Mirlekar and Pylayeva-Gupta 2021; Xu et al. 2024a, b). Tumor-specific IL-12 therapies in clinical trials have shown preliminary antitumor effects and acceptable safety profiles in advanced solid cancers, including ovarian cancer and multiple myeloma, by local enhancement of immunity with minimal systemic toxicity (Dong et al. 2024; Nash et al. 2025). New delivery methods, e.g., IL-12 gene therapies targeted to tumors, also are augmenting therapeutic indices (Livingston et al. 2024). Furthermore, IL-12 family cytokines, such as IL-12, regulate inflammatory diseases like psoriasis, IBD, and autoimmune CNS disease, highlighting their oncology-cum-therapeutic significance (Bastian et al. 2019; Moschen et al. 2019). IL-23, comprising the unique p19 subunit and the shared p40 subunit with IL-12, is essential for Th17 cell differentiation and is a key driver of chronic inflammation and autoimmune disorders, including IBD, psoriasis, and arthritis (Moschen et al. 2019). Selective blockade of IL-23 signaling, particularly targeting the p19 subunit, has emerged as a relevant therapeutic approach, with several monoclonal antibodies such as guselkumab, risankizumab, brazikumab, and mirikizumab demonstrating efficacy and safety (McDonald, Dyer et al. 2022; Bourgonje et al. 2024). Compared to first-generation therapies like ustekinumab that block IL-12/23 p40, second-generation IL-23p19-specific inhibitors may offer improved efficacy with fewer off-target effects. Biomarker-driven approaches, including baseline serum IL-22 levels, may guide patient selection for IL-23-targeted treatments to optimize clinical outcomes

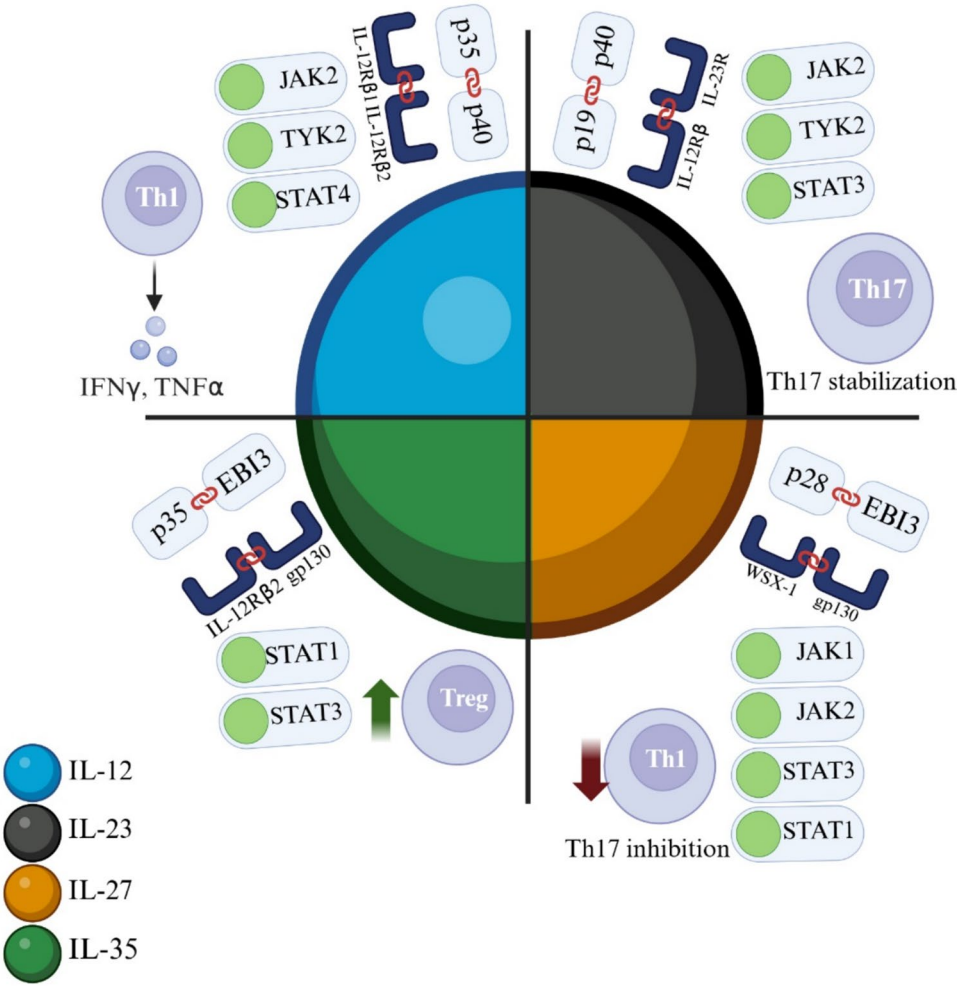


Fig. 1 Structure, receptor complexes, and downstream signaling pathways of the IL-12 family cytokines. All members of the IL-12 family of cytokines (IL-12, IL-23, IL-27, and IL-35) are heterodimers composed of two distinct subunits and signal through a heterodimeric receptor complex. IL-12 signals through IL-12Rβ1/β2 to activate STAT4 and drive Th1 differentiation. IL-23 signals through IL-12Rβ1/IL-23R to activate STAT3 and sustain Th17 cells. IL-27 signals through the WSX-1/gp130 receptor to activate STAT1/3 and generate IL-10. IL-35, made up of p35 and EBI3, is signaling via IL-12Rβ2 and gp130 combinations to activate STAT1/3 and broaden regulatory T cells (Tregs and iTr35). These diverse pathways highlight the family's dual roles in both pro-inflammatory and immune-suppressive response. Created with BioRender.com

(Bourgonje et al. 2024). IL-27 can induce Th1 differentiation but also suppress immune responses through IL-10 induction and Th17 suppression, thereby maintaining immune homeostasis. IL-27 is explored as a therapeutic target for autoimmune diseases, infections, and cancer due to its dual roles (Gong et al. 2013; Yoshida and Hunter 2015). Cancer immunotherapy, IL-27 exhibits potent antitumor activities by enhancing CD8 + T and NK cell function and anti-angiogenesis with no apparent side effects, but with protumorigenic activity by inducing immunosuppressive molecules such as PD-L1 and CD39 on Tregs (Yoshida and Hunter 2015; Yasmin-Karim et al. 2018). Therapeutic strategies include IL-27 gene therapy with adeno-associated virus (AAV) vectors to enhance antitumor immunity by eliminating Tregs and enhanced response to immune checkpoint inhibitors (Hu et al. 2020; Liu et al. 2020a, b, c). Neutralizing IL-27 in the tumor microenvironment can diminish immunosuppression and enhance immunotherapy effectiveness (Papargyris et al. 2024). IL-35 has also been implicated in regulating autoimmunity and cancer progression through TME regulation by modulating immunosuppressive activities that are supportive of tumor development and metastasis (Choi et al. 2015; Yi et al. 2024). IL-35-targeting therapies aim to block its production or activity as to enhance antitumor immunity and manage autoimmune reactions. Due to its immunosuppression activity, IL-35 is a promising candidate for cancer immunotherapy and has the potential to overcome resistance to existing immune checkpoint therapies (Liu et al. 2021) (Fig. 2)(Table 1).

Mechanisms of neuroinflammation in neurodegenerative diseases

Neuroinflammation is a core mechanism driving the onset and progression of neurodegenerative disorders. Rather than serving solely as a secondary response to neural injury,

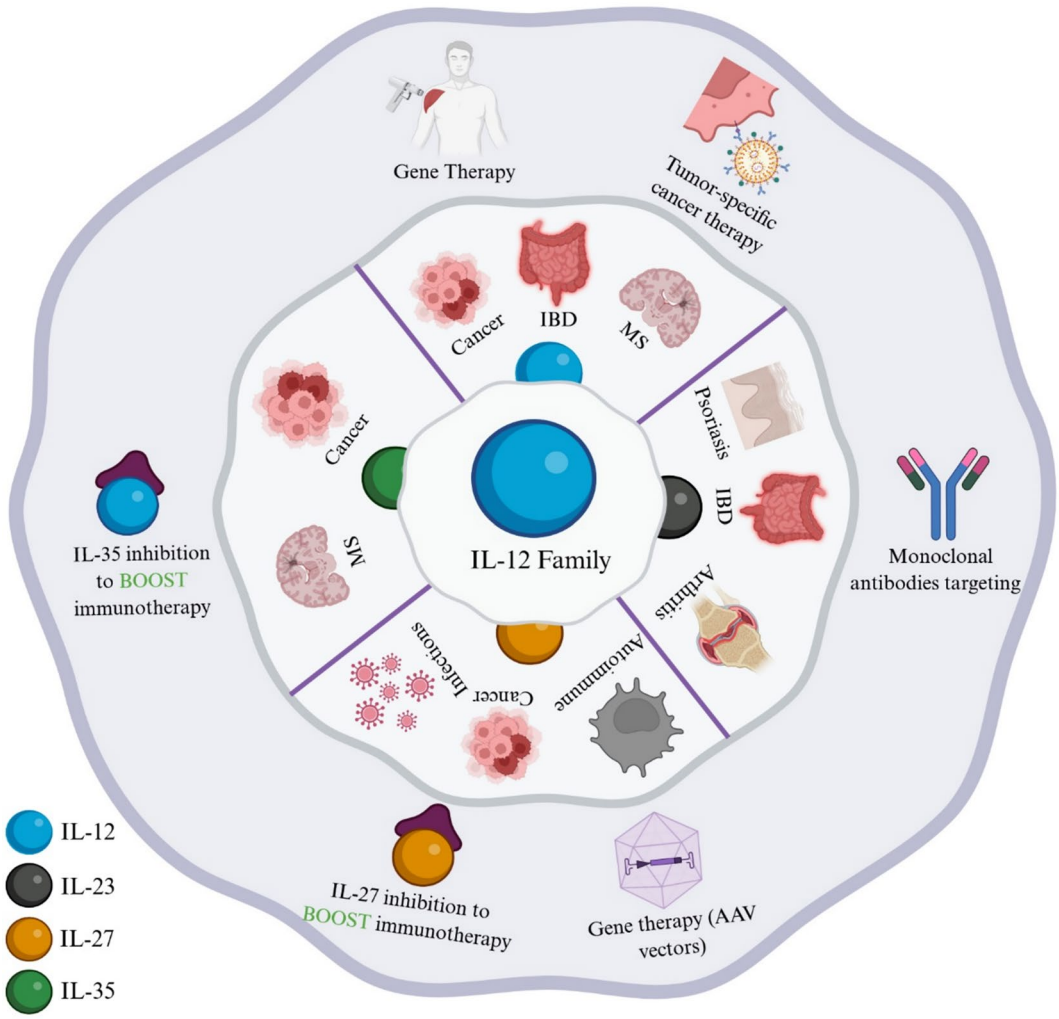


Fig. 2 Therapeutic targeting of IL-12 family cytokines. Created with BioRender.com

Table 1 Therapeutic potential and clinical targeting of IL-12 family cytokines

Cytokine	Immune role	Target diseases	Therapeutic strategies	Clinical status
IL-12	Immune activator, induces Th1 and IFN-γ	Cancers, inflammatory diseases like IBD, MS	IL-12 gene therapy, tumor-specific immunotherapy	Clinical trials demonstrate promising early efficacy
IL-23	Promotes Th17, chronic inflammation	Psoriasis, IBD, arthritis	Monoclonal antibodies targeting p19, such as Guselkumab and Risankizumab	Approved for some diseases; second-gen agents more selective than anti-p40
IL-27	Context-dependent role (pro- and anti-inflammatory), induces IL-10	Cancer, autoimmune diseases, infections	IL-27 gene therapy (AAV vectors), IL-27 inhibition in TME to enhance immunotherapy	Preclinical; promising in animal models
IL-35	Immunosuppressive, elevates Treg/Breg populations	Cancer, autoimmune diseases like MS	Inhibit IL-35 production/activity, increase immunotherapy	In development; preliminary data but promising potential

The information presented in this table is primarily synthesized from the narrative review outlined in the section Therapeutic targeting of IL-12 family cytokines, with full citations provided throughout the main text

inflammation within the CNS actively contributes to neuronal dysfunction and eventual cell death. Conditions such as AD, PD, multiple sclerosis (MS), and ALS are characterized by sustained inflammatory activity, largely mediated by activated glial cells most notably microglia and astrocytes (Kwon and Koh 2020; You et al. 2023). While acute inflammation may offer short-term protection, chronic inflammatory signaling has deleterious effects, leading to synaptic degradation, oxidative damage, and neurodegeneration (Leyane et al. 2022; Soliman and Barreda 2022).

Microglia, the resident immune sentinels of the CNS, are rapidly activated in response to pathological aggregates such as amyloid-β in AD and α-synuclein in PD (Gerrits et al. 2021; Wang et al. 2023a, b). Microglia act as the brain's primary immune sentinels and are rapidly activated in response to damage-associated or pathogen-derived signals through receptors such as TLR4. Once activated, they release inflammatory cytokines like IL-1β and TNF-α, which contribute to neuronal injury and drive astrocytes into a reactive A1 state. These A1 astrocytes then amplify the inflammatory cascade by producing complement factors, such as C1q and C3, matrix metalloproteinases, and additional cytokines, thereby exacerbating neuronal dysfunction and compromising the integrity of the blood–brain barrier (BBB). Astrocytes, due to their strategic anatomical positioning and abundance, can intensify this immune response. In toxin-induced models such as 1,2-dichloroethane exposure, astrocytes may become activated before microglia via ROS-dependent signaling pathways, including p38 MAPK, NF-κB, and AP-1. In turn, activated astrocytes release IL-1β, TNF-α, and nitric oxide, which in turn polarize microglia toward a pro-inflammatory M1 phenotype. However, if the pathological environment shifts, microglia and astrocytes can transition to anti-inflammatory M2 and A2 phenotypes, respectively, marked by the production of IL-10 and transforming growth factor-beta (TGF-β), supporting tissue repair and neuronal survival. This reciprocal, cytokine-driven communication between glial cells shapes the progression or resolution of neuroinflammation (Kwon and Koh 2020, Liu, Liu et al. 2020a, b, c, Wang et al. 2021).

Central to this neuroinflammatory process is the complex network of IL cytokines, which orchestrate both innate and adaptive immune responses in the CNS. Among the most prominent are IL-1β, IL-6, IL-17, and IL-18, all of which are elevated in the brain tissue and cerebrospinal fluid of patients with neurodegenerative diseases (Milovanovic et al. 2020; Gautam, Pulivarthi et al. 2023). IL-1β, predominantly secreted by activated microglia, acts as an early trigger of inflammatory cascades and is implicated in both tau hyperphosphorylation and amyloid accumulation in AD (Van Zeller et al. 2021). IL-6, produced by both microglia and astrocytes, promotes acute phase reactions and has been linked to impaired synaptic transmission and neurogenesis (Benarroch 2024). IL-17, derived from Th17 cells that infiltrate the CNS, is a key mediator in autoimmune neuroinflammation such as MS, and also plays a role in neurodegenerative damage in AD and PD (Fu et al. 2022).

Within this broader cytokine milieu, the IL-12 family stands out for its multifaceted regulatory influence on CNS immunity (Chen et al. 2024; Yadav et al. 2025). IL-12, a major promoter of Th1 immune responses, induces IFN-γ secretion, enhancing the cytotoxic functions of immune cells and contributing to inflammation-driven neurotoxicity. Although essential in fighting infections, dysregulated IL-12 signaling is associated with CNS autoimmunity and MS-related pathology (Dias de Sousa et al. 2022). IL-23 supports the expansion of Th17 cells and drives the production of IL-17 and IL-22, which are highly neurotoxic in demyelinating diseases. The IL-23/Th17 axis has been firmly established as a pathogenic mechanism in experimental models of MS and increasingly, in other neurodegenerative conditions (Jadidi-Niaragh and Mirshafiey 2011; Pourgholaminejad and Tahmasebinia 2025).

IL-27 plays a complex role in CNS inflammation by activating the JAK–STAT and p38 MAPK signaling pathways through its receptor on immune cells, contributing to both pro- and anti-inflammatory responses. Although originally recognized as a promoter of Th1-mediated immune responses, it is now recognized to exert anti-inflammatory effects by inducing IL-10 production and enhancing the function of regulatory T cell activity. Due to this dual function, IL-27 has attracted interest as a therapeutic target in neuroinflammatory and autoimmune CNS conditions, with emerging treatments showing promising results in experimental models (Shahi et al. 2020; Mei et al. 2022). Experimental evidence suggests that IL-27 expression in microglia can dampen harmful immune activity and protect against neurodegeneration in MS models (Kawanokuchi et al. 2013; Povroznik and Robinson 2020). IL-35, an immunosuppressive cytokine within the IL-12 family, contributes to CNS protection by inhibiting Th1 and Th17 inflammatory responses while promoting the expansion of regulatory cell types, such as iTr35 T cells and IL-10-producing Bregs. Its protective effects in the CNS are thought to stem from its ability to suppress proinflammatory cytokines, enhance regulatory immune pathways, and shift macrophage activity toward an anti-inflammatory M2 phenotype (Zhu and Shan 2020; Soltani et al. 2022).

In conclusion, members of the IL-12 family cytokines play diverse and context-specific roles in regulating CNS inflammation, facilitating tissue repair, and maintaining immune balance. Depending on the cellular and molecular context, these cytokines can either exacerbate neuroinflammatory damage or facilitate immune regulation and tissue repair (Kang et al. 2020; Schneeberger et al. 2025a, b). The wide-ranging functions of these cytokines highlight their promise not only as indicators of disease activity, but also as viable therapeutic targets for influencing the course of neurodegenerative disorders. Continued investigation into their signaling pathways is anticipated to provide essential knowledge for developing targeted strategies aimed at reducing harmful neuroinflammation and enhancing neural protection (Sun et al. 2015; Andreadou et al. 2023)(Fig. 3).

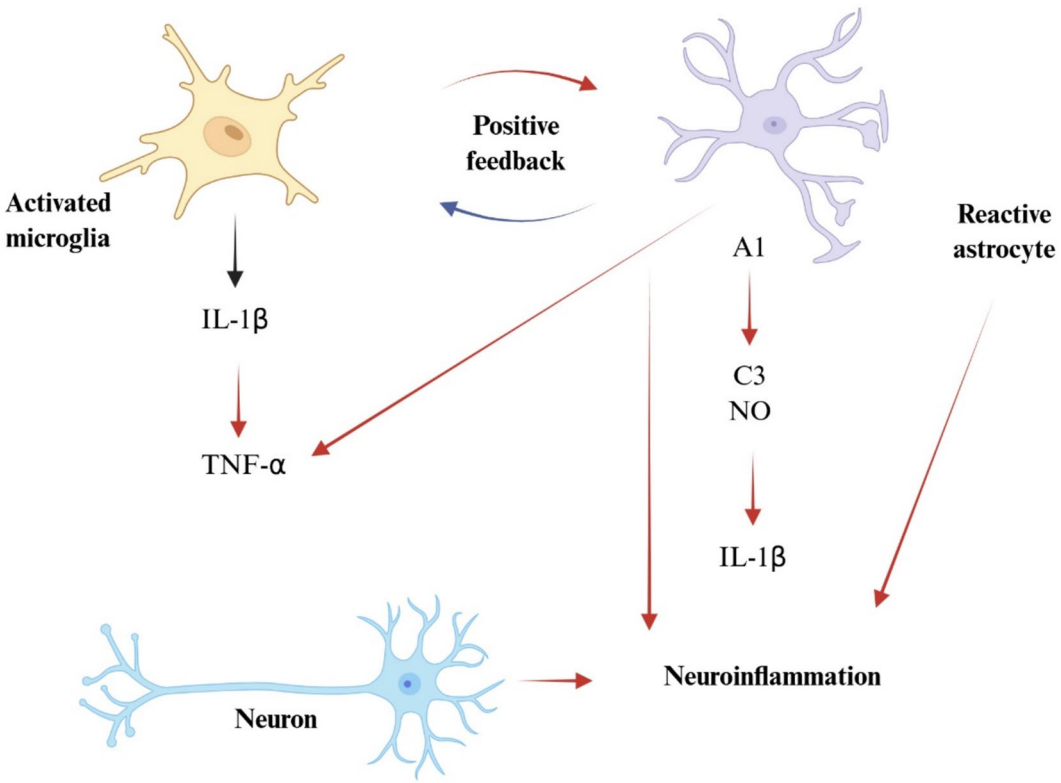


Fig. 3 Microglia–astrocyte crosstalk in CNS neuroinflammation. This illustration shows two-way inflammatory communication between activated microglia and A1 type reactive astrocytes within the central nervous system. Activated microglia, via pattern recognition receptors like TLR4, secrete pro-inflammatory cytokines IL-1β and TNF-α. These stimulate astrocytes to become A1 phenotype neurotoxic, which secrete complement factor C3, nitric oxide (NO), and additional IL-1β to exacerbate neuronal injury. The subsequent favorable assessment loop sustains recurrent neuroinflammation and induces neurodegenerative advancement. Created with BioRender.com

IL-12 family cytokines in specific neurodegenerative disorders

IL-12 family cytokines, including IL-12, IL-23, IL-27, and IL-35, play significant roles in the immune response regulation and are implicated in the pathogenesis and progression of neurodegenerative diseases, especially those involving the central nervous system, inflammation such as multiple sclerosis (Avarachan et al. 2021).

Alzheimer's disease

IL-12 signaling plays a central role in AD pathology primarily through the mechanism of neuroinflammation. Elevated IL-12 protein expression is found in human AD brains compared to controls, most strongly correlating with late Braak stages indicative of severe disease. In AD-like mouse models, IL-12 receptors are predominantly found on neurons and oligodendrocytes, not microglia, with IL-23 receptor expression being low. Conditional deletion of the IL-12 receptor in neuroectodermal cells reduces amyloid-β (Aβ) burden by about 50%, increases mature oligodendrocyte survival, restores myelin homeostasis, and rescues parvalbumin-positive interneurons that are responsible for cognition. IL-12 acts via JAK–STAT signaling, activating phosphorylated STAT4, which mediates cell death and neuronal and oligodendrocyte dysfunction. In vitro, IL-12 treatment of human oligodendrocyte-like cells stimulates pro-inflammatory cytokine secretion, validating their functional receptiveness. IL-12 signaling also disturbs gene expression by neurons that is linked to memory and synaptic plasticity, further disturbing neuronal homeostasis. Management of IL-12 signaling is a promising therapeutic technique for enhancing AD pathology, supported by reduced amyloid deposition and improved microglial phagocytic activity upon inhibition of IL-12 (Schneeberger et al. 2025a, b). IL-23 is also p40 shared with IL-12, but is not otherwise involved in AD pathology. IL-23 receptor mRNAs are barely traceable in neurons and oligodendrocytes in AD models and in human brains. Conditional deletion of IL-23 receptors in neuroectodermal cells has no effect on amyloid burden, myelin integrity, or cellular changes related to cognition in AD mouse models. However, IL-23 can induce peripheral immune responses that worsen AD, for example, by promoting Th17 cell differentiation and IL-17 production that disrupt Aβ clearance. However, in the CNS resident cells, IL-12, rather than IL-23, is the primary neuroinflammatory player (Obst 2017; Chen et al. 2024). IL-27 regulates neuroinflammation and neuronal survival, inducing mainly neuroprotective and anti-inflammatory effects. It is secreted largely by antigen-presenting cells and triggers the JAK–STAT pathway, inducing mainly STAT1 and STAT3 activation in microglia, macrophages, and astrocytes. IL-27 and the expression of its receptor are upregulated in CNS inflammatory disorders, such as multiple sclerosis and AD. IL-27 promotes production of the anti-inflammatory cytokine IL-10, suppresses pro-inflammatory cytokine production (TNF-α, IL-6, IL-12, and IL-23), inhibits inflammasome activation, and induces transcriptional regulators that maintain immune homeostasis. In neurons, IL-27 has been demonstrated to directly enhance survival pathways and inhibit apoptosis. Although some pro-inflammatory or pro-apoptotic activities have been reported in specific contexts, the overall effect of IL-27 is toward neuroprotection, making it a target for regulation of neuroimmune responses in AD. Direct studies on IL-27 in AD remain limited compared to other cytokines (Nortey et al. 2022). IL-35, comprising EBI3 and p35 subunits, is the sole IL-12 family cytokine possessing purely immunosuppressive activity. It is mainly secreted by Tregs and B cells and inhibits pro-inflammatory Th1 and Th17 cells while inducing anti-inflammatory responses. In AD, IL-35 levels and IL-35-producing cells are increased, suggesting a compensatory anti-inflammatory role. A recent experimental study demonstrated that IL-35 may reduce Aβ load and cognitive impairment in AD mouse models by inhibiting BACE1 transcription in neurons through the SOCS1/STAT1 pathway. The findings illustrate the therapeutic potential of IL-35 as a neuroprotective cytokine which can counteract the detrimental roles of IL-12 and IL-23 in AD (Chen et al. 2024) (Table 1).

Parkinson's disease

IL-12 is largely accountable for differentiating naive CD4 + T cells into IFN-γ-producing Th1 cells, while IL-23 is involved in the expansion and sustainability of IL-17-producing Th17 cells, which orchestrate inflammation. Although the search results did not address exactly the roles of IL-12 and IL-23 in PD, these cytokines are generally characterized as pro-inflammatory mediators that can exacerbate neuroinflammation in neurodegenerative disorders. High levels of IL-23 have been associated with pro-inflammatory profiles under disease conditions with immune activation. IL-12 and IL-23, therefore, can be involved in the chronic inflammatory milieu in PD, regulating progression through T-cell-mediated mechanisms (Dzamko 2023; Sun et al. 2024). IL-27 and its receptor are expressed on most immune cells, including macrophages, microglia, dendritic cells, and neurons and glia within the CNS. IL-27 signals through the JAK–STAT pathway, mainly STAT1 and STAT3, to regulate immune responses and promote neuronal survival. IL-27 has been shown to enhance neuronal survival through regulation of pro- and anti-inflammatory cytokines, reducing inflammasome activation, oxidative stress, and apoptosis. It promotes the generation of anti-inflammatory cytokine IL-10, additionally suppressing neuroinflammation.

Studies in animals indicate that IL-27 potentially reduces neuroinflammation and protects neurons from loss in CNS models of damage. IL-27 is overexpressed in inflammatory CNS cells in disease, suggesting a compensatory protective role (Nortey et al. 2022). Clinical research demonstrated PD patients to have lower levels of serum IL-27 compared to controls, with the levels correlating inversely with disease severity. This diminishment can impair the anti-inflammatory role, leading to enhanced neurodegeneration. Other studies, however, reported increased IL-27 correlating with cognitive impairment in PD, indicating multifaceted dynamics that may be dependent on disease stage or inflammatory context (Kouchaki et al. 2018; Nortey et al. 2022; Wan et al. 2024). No marked differences in plasma IL-35 levels have been found in PD patients compared with controls, suggesting a limited or complex role at early or untreated stages of disease. The reports indicate that there is a decrease in some regulatory immune populations in untreated PD patients like Tregs, Bregs, CD8 regulatory T cells, and tolerogenic dendritic cells, which may impair immune suppression. Although IL-35 is part of the regulatory cytokine milieu, direct evidence for its contribution to PD pathogenesis is inadequate owing to limited data (Álvarez-Luquín et al. 2019) (Table 1).

Multiple sclerosis

IL-23 is a major regulator of the pathogenic Th17 phenotype in experimental autoimmune encephalomyelitis (EAE), an animal model for MS, and MS lesions (Yang et al. 2011). IL-23 messenger RNA is increased in MS lesion tissues and cerebrospinal fluid and correlates with disease activity (Li et al. 2007; Wen et al. 2012; Ghaffari et al. 2017). IL-23 activates IL-23 receptor to signal activation of pathogenic Th17 and other type 17 immune cells, leading to local tissue inflammation by cytokines, including IL-17A, IL-17F, IL-22, and GM-CSF (Krueger et al. 2024). Yet, clinical efforts at treating MS through targeting IL-12/IL-23 have failed in the face of promising preclinical outcomes. Treatments with antibodies to the shared p40 subunit (inhibiting both IL-23 and IL-12) failed to show efficacy in chronic MS (Longbrake and Racke 2009). Such clinical failure to thrive could reflect the heterogeneity and stage-dependent roles of IL-23 and IL-12 in MS disease and limitations of antibody penetration and timing in therapy (Krueger et al. 2024). IL-12 also has a neuroprotective role. IL-12 induces Th1 differentiation, and IL-23 enhances Th17 responses, and both Th1 and Th17 cells contribute to MS lesion formation as well as to neuroinflammation (Clénet et al. 2021).

IL-27 is a member of the IL-12 family that suppresses Th17 differentiation and inflammation and plays an overall anti-inflammatory or regulatory role in MS (Sawant et al. 2015). IL-27 is a heterodimer of the EBI3 and IL-27p28 subunits and acts through the IL-27 receptor complex (Xu et al. 2024a, b). IL-27 expression is upregulated in MS patients, particularly in immune cells and astrocytes, whereby it modulates immune responses by downregulating pathogenic Th17 cytokines and promoting IL-10 production (Sénécal et al. 2016; Barac et al. 2023a, b). It modulates immune functions of various CNS cells, including astrocytes, and suppresses inflammation processes linked with demyelination. IL-27 activates regulatory T-cell function, inhibits Th17 cell proliferation, and regulates proinflammatory cytokine gene expression in monocytes, macrophages, dendritic cells, and T cells by STAT1/STAT3 and NF-κB pathways (Xu et al. 2024a, b). Regulatory effects of IL-27 may offer regulation of autoimmune neuroinflammation and protection of neurons, suggesting therapeutic potential in MS (Yazdanpanah et al. 2024). Its specific activity can nevertheless be microenvironment-dependent, showing pro- and anti-inflammatory activity based on the setting (Xu et al. 2024a, b). Studies show that IL-35 suppresses pathogenic Th1 and Th17 responses, increases the function of Treg cells, and mitigates autoimmune neuroinflammation in EAE, proposing a potential protective role in MS. Clinical investigations have shown decreased levels of serum IL-35 in patients with relapsing–remitting MS compared to healthy subjects, which reflects that production of regulatory cytokine is reduced during active disease. IL-35's action is regulating immune cell proliferation and cytokine generation, but its intracellular signaling pathways are not yet completely understood. The cytokine is a promising therapeutic target for reconstituting immune tolerance and inhibiting inflammation in MS (Moghadam et al. 2017; Duffy 2018)(Table 1).

Amyotrophic lateral sclerosis

The IL-12 family cytokines of IL-12 and IL-23 cytokines have also been implicated in ALS-induced neuroinflammation. IL-23 concentrations are significantly elevated within the CSF of ALS patients when compared to control subjects, indicating the existence of a pro-inflammatory environment causing motor neurodegeneration. IL-12, similarly, has been shown to exist at elevated concentrations within the patient group, indicating immune pathway activation potentially leading to sustained neuronal damage. These cytokines provide crosstalk between innate and adaptive immunity that promotes pathogenic T cell responses that cause neurodegeneration. IL-23 of the IL-12 family cytokines is reported to be involved in inflammatory processes in ALS. Higher IL-23 in CSF is associated with enhanced neuroinflammation and disease worsening. It is a facilitator in the expansion and proliferation of Th17 cells, which produce pro-inflammatory cytokines that enable motor neuron injury. The rising levels of IL-23 suggest it could be used as a biomarker of disease activity and as a therapeutic target (Jiang et al. 2022; Mimic

et al. 2023). IL-27 is a pleiotropic cytokine with anti-inflammatory and pro-inflammatory functions and acts via the JAK–STAT pathway. It is expressed by antigen-presenting cells and present in several CNS cells, including microglia, astrocytes, neurons, and macrophages. IL-27 could promote neuronal survival through the modulation of inflammation, oxidative stress, apoptosis, autophagy, and epigenetic modifications. It induces anti-inflammatory cytokines like IL-10 and suppresses pro-inflammatory cytokines like TNF-α and IL-6, potentially limiting neuronal injury. However, IL-27's function in ALS is complicated: under different situations, it activates inflammatory processes, and its levels in ALS have offered inconsistent correlations with disease intensity. Thus, IL-27 is both a potential biomarker and a potential therapeutic target for regulating neuroinflammation in ALS (Jiang et al. 2022; Nortey et al. 2022). IL-35 is a newly discovered immune regulatory cytokine with anti-inflammatory function. Though less characterized, IL-35 is also a member of the neuroinflammatory network in ALS and takes part in the regulation of immune responses. IL-35, along with other regulatory cytokines like IL-10 and TGF-β, has been implicated by recent research in limiting ALS-associated inflammation and motor neuron damage, but additional studies must be carried out to determine its precise role and therapeutic potential (Stacchiotti et al. 2025) (Table 1).

Huntington's disease

IL-12 is an inflammatory cytokine primarily secreted by antigen-presenting cells (APCs), such as macrophages, monocytes, and dendritic cells. IL-12 levels are increased in HD, showing an activated innate immune response and neuroinflammation. The activation of microglia and macrophages in HD produces IL-12 and other cytokines, which are components of the proinflammatory profile in both CNS and peripheral tissue. This cytokine induces Th1 cell differentiation and IFN-γ production, which may allow for neurodegenerative events to worsen in HD (Collison and Vignali 2008; Ellrichmann et al. 2013). There is no direct evidence of IL-23 involvement in HD in the literature; its role in autoimmune diseases and chronic inflammation suggests that it would be a likely candidate to be involved with HD's inflammatory aspects (García-Domínguez 2025; Goleij et al. 2025). IL-23 stimulates the production of IL-19, IL-20, and IL-24 via the IL-20R2 receptor, potentially indirectly influencing neurodegeneration (Chan et al. 2006). IL-27 is a pleiotropic cytokine that is primarily expressed by APCs with pro- and anti-inflammatory functions (Nortey et al. 2022). IL-27-induced inflammatory modulation is defined by the suppression of proliferation and apoptosis of monocytes, macrophages, dendritic cells, and B cells, whose modulation could regulate immune cell behavior in HD (Xu et al. 2024a, b). Although direct evidence for IL-27 in HD is limited, its immunoregulatory function predicts that it could modulate inflammatory processes in the disease (Collison and Vignali 2008). IL-35 is a relatively recently identified cytokine of the IL-12 family, differentiated mainly by its immunosuppressive activity, and most highly produced by regulatory Tregs. IL-35 suppresses T-cell proliferation and possibly regulates immune responses in autoimmune and inflammatory conditions (Collison and Vignali 2008). Direct studies on IL-35 in HD do not exist, but owing to the inflammatory environment in HD, IL-35 may play a part in regulating excessive proinflammatory cytokine activity (Jia et al. 2022; Rocha, Furr-Stimming et al. 2025) (Table 1).

Frontotemporal dementia

IL-12 levels are reduced in the cerebrospinal fluid of FTD and patients, suggesting that dysregulated IL-12-mediated immune responses, play a part in FTD (Rentzos et al. 2006; Lok et al. 2023). Peripheral inflammation in behavioral variant FTD patients showed elevations in the concentrations of IL-12p70, a biologically active species of IL-12, and IL-17A, another cytokine in the IL-23 downstream pathway, implicating the IL-12/IL-23 axis in bvFTD (Chu et al. 2023). IL-23 microglia expression and neuroinflammatory role have been extensively characterized in other dementias like AD, but direct evidence is scarce in FTD. Nevertheless, shared neuroinflammatory pathologies suggest the IL-23 family cytokines are implicated in FTD pathogenesis (Bright et al. 2019). IL-27 and IL-27p28 subunits, a member of the IL-12 family with pro- and anti-inflammatory potential depending on context. IL-27 has been shown to modulate neuroinflammation by the suppression of proinflammatory cytokines, such as TNF-α and inducible nitric oxide synthase (iNOS) in microglia, which may signify an anti-inflammatory neuroprotective mechanism in neurodegenerative disease (Rich et al. 2004). Though the direct investigation on IL-27 in FTD is restricted, its noted modulatory action on neuroinflammation and microglial activation puts IL-27 in the spotlight for further investigation on FTD immune dysregulation (Andres-Martin et al. 2024; Xu et al. 2024a, b; Erichsen et al. 2025). Research examining IL-35 polymorphisms reported that no evidence for significant association with cognitive impairment in coronary heart disease patients was detected over a 2-year period, indicating minimal direct evidence of an association between IL-35 gene polymorphisms and dementia-related cognitive impairment, but these results do not preclude a role for IL-35 in neuroinflammation (Shi et al. 2020) (Table 2).

Targeting IL-12 family in neurodegenerative diseases: current therapeutic approaches

The IL-12 cytokine family, encompassing IL-12, IL-23, IL-27, and IL-35, plays a pivotal role in the

Table 2 Roles of IL-12 family cytokines in specific neurodegenerative disorders

Disease	Cytokine	Role (pro/anti-inflammatory)	Key mechanism	Therapeutic implication
Alzheimer's disease	IL-12	Pro-inflammatory	Stimulates JAK–STAT4 in neurons/oligodendrocytes, enhances cell death, disrupts myelin homeostasis	Blocking IL-12 decreases amyloid deposition and restores microglial function
	IL-23	Pro-inflammatory (primarily peripheral)	Drives peripheral Th17 differentiation, elevates IL-17 production disrupting Aβ clearance	Restricted role in CNS, but may be targeted to moderate peripheral immune activation
	IL-27	Mainly anti-inflammatory	Promotes IL-10, inhibits TNF-α/IL-6/IL-12, supports neuronal survival	Promising neuroprotective target to balance CNS inflammation
	IL-35	Anti-inflammatory	Prevents BACE1 in neurons through SOCS1/STAT1, decreases Aβ load	Candidate therapeutic to counter neurodegeneration
Parkinson's disease	IL-12	Pro-inflammatory	Supports Th1 differentiation, promotes IFN-γ production	Could be targeted to reduce chronic neuroinflammation
	IL-23	Pro-inflammatory	Supports Th17 differentiation, enhances inflammatory milieu	Same, but clinical evidence scarce
	IL-27	Context-dependent (typically anti-inflammatory)	Modulates IL-10 production, decreases inflammasome activation	Reduced serum IL-27 linked to worse PD; supplementation could be explored
	IL-35	Anti-inflammatory	Supports Treg/Breg populations	Role unknown in PD, but may support immune regulation
Multiple sclerosis	IL-12	Pro-inflammatory	Enhances Th1 differentiation, increases IFN-γ	Prior p40-blockade failed clinically but still a target prospect
	IL-23	Pro-inflammatory	Drives pathogenic Th17 responses through IL-17/IL-22	Recognized MS pathogenic driver; p19-blockade of interest
	IL-27	Anti-inflammatory	Inhibits Th17, enhances IL-10	Neuroprotective, potential immunoregulatory therapeutic
	IL-35	Anti-inflammatory	Increases Treg function, decreases Th17 activity	Reduced serum levels linked to active MS; therapeutic promise high
ALS	IL-12	Pro-inflammatory	Drives pathogenic T cell responses, enhances neuroinflammation	Could be targeted for decreasing motor neuron damage
	IL-23	Pro-inflammatory	Enhances Th17-mediated inflammation, elevated in CSF	Biomarker and therapeutic target potential
	IL-27	Mixed (context-dependent)	Regulates IL-10 and decreases oxidative stress/apoptosis	Biomarker and possible neuroprotective therapy
	IL-35	Anti-inflammatory	Attenuates motor neuron damage through Treg/Breg pathways	Promising but scarcely studied so far
Huntington's disease	IL-12	Pro-inflammatory	Activates Th1 cells and IFN-γ production, supports neuroinflammation	Possible target to inhibit peripheral and CNS inflammation
	IL-23	Pro-inflammatory	Likely mediated effects through IL-20R2 pathways	Hypothetical target, data limited
	IL-27	Mixed	Moderates immune cell proliferation/apoptosis	Could regulate neuroinflammation but not explicitly studied
	IL-35	Anti-inflammatory	Inhibits T cell proliferation	Hypothetical protective function

Table 2 (continued)

Disease	Cytokine	Role (pro/anti-inflammatory)	Key mechanism	Therapeutic implication
Frontotemporal dementia	IL-12	Dysregulated	Reduced CSF IL-12 but higher peripheral IL-12p70 indicates complex immune dysfunction	Candidate biomarker
	IL-23	Pro-inflammatory	Scant direct evidence but implicated through shared pathways with AD	Could be prospective therapeutic target
	IL-27	Anti-inflammatory	Inhibits microglial pro-inflammatory activation	Promising neuroprotective target
	IL-35	/	Potentially supports regulatory pathways	Scarce data

The information here is derived from the narrative review outlined in IL-12 family cytokines in specific neurodegenerative disorders, with full citations detailed in the primary body of the text

immunopathology of neurodegenerative diseases. Therapeutic strategies aimed at modulating these cytokines have been extensively studied in preclinical models and clinical trials, revealing diverse mechanisms and variable efficacy across diseases, such as AD, multiple sclerosis (MS), PD, and ALS.

Alzheimer's disease

In AD, targeting IL-12 and IL-23 signaling pathways has shown promising results in reducing neuroinflammation and amyloid pathology. Using the APPPS1 transgenic mouse model, genetic deletion of IL-12 and IL-23 subunits (p35, p19, and the shared p40) or administration of anti-p40 antibodies (20 μg intracerebroventricular) effectively inhibited IL-12/IL-23 signaling. This blockade led to a reduction in microglial inflammatory responses and a significant decrease in cerebral amyloid load and soluble Aβ species, accompanied by improved cognitive performance (Berg et al. 2012).

Similarly, in a streptozotocin-induced AD mouse model, combined treatment with tadalafil (20 mg/kg) and bergapten (25 mg/kg), administered daily for 21 days, significantly reduced IL-27 and IL-23 serum levels. These treatments suppressed NF-κB expression by approximately 62% and 61%, respectively, while activating neuroprotective signaling cascades, including PI3K/Akt, Wnt/β-catenin, AMPK/mTOR, and cGMP/PKG pathways. This was further evidenced by upregulation of phosphorylated Akt and GSK-3β, beclin-1, methylated PP2A, cyclin D1, and brain-derived neurotrophic factor (BDNF), alongside decreased β-catenin and mTOR expression. Functionally, these molecular changes translated to attenuated hippocampal neurodegeneration, 79% and 89% reductions in Aβ deposition, 60% and 61% decreases in tau hyperphosphorylation, and improved memory and histological outcomes, underscoring the potential of IL-27-associated anti-inflammatory neuroprotection in AD (Salem et al. 2021) (Table 3).

Multiple sclerosis

MS is the most extensively studied neurodegenerative disease regarding IL-12 family-targeted therapies. Various strategies aim either to inhibit pro-inflammatory cytokines IL-12 and IL-23 or enhance anti-inflammatory cytokines IL-27 and IL-35.

Clinical studies in patients with relapsing–remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and progressive-relapsing MS (PRMS) have shown that conventional treatments such as interferon-β and methylprednisolone increase serum IL-35 levels by stimulating CD4 + FOXP3 + regulatory T cells, thus promoting immunosuppressive functions and modulating autoimmunity. These treated patients exhibited significantly elevated IL-35 compared to untreated patients and healthy controls.

Table 3 Clinical and preclinical studies on different therapeutic approaches targeting IL-12 cytokine family

Disease	Disease model	IL-12 cytokine family member targeted	Agent/intervention	Dosage	Molecular mechanism of action	Outcome
AD	APPPS1 Tg mouse model	IL-12, IL-23	Genetic deletion (p35, p19, p40); anti-p40 Ab (ICV and systemic)	Anti-p40 Ab: 20 μg ICV	Blocking p40 inhibits IL-12/IL-23 signaling, reducing microglial inflammatory responses and Aβ production	Cerebral amyloid load and soluble Aβ decrease; cognition improves
AD	Streptozotocin-induced mice	IL-27	Tadalafil, Bergapten	Tadalafil 20 mg/kg, Bergapten 25 mg/kg daily × 21 days	Reduces IL-27/IL-23; suppresses NF-κB; activates neuroprotective pathways; modulates proteins downstream	Neurodegeneration attenuates; memory improves; Aβ deposition and tau phosphorylation reduce substantially; histology and cognition improve
MS	Human RRMS, SPMS, PPMS, PRMS patients	IL-35	IFN-β, methylprednisolone, combined treatment	Not specified	Treatments increase IL-35 by CD4 + FOXP3 + Tregs, promoting immunosuppression and modulating autoimmunity	Treated patients show elevated serum IL-35; genetic polymorphism affects susceptibility
MS	Phase II trial in RRMS patients	IL-12, IL-23	Ustekinumab	SC injections: 27 mg or 90 mg q8w; weeks 0,1,2,3,7,11,15,19	Neutralizes IL-12/IL-23 by p40 binding, reducing pro-inflammatory signaling	No significant reduction in new Gd-enhancing T1 lesions; well-tolerated
MS	EAE in female C57BL/6 mice	IL-27, IL-35	Curcumin	Oral 100, 200 mg/kg daily from day 1 of EAE induction	Reduces pro-inflammatory cytokines; enhances IL-27, IL-35; promotes Th2 and Treg responses via anti-inflammatory mediators	Leukocyte infiltration, demyelination, severity decrease; clinical symptoms improve
MS	EAE in female C57BL/6 mice	IL-27, IL-35, IL-33	Berberine	IP 10, 30 mg/kg daily after EAE induction	Reduces pro-inflammatory cytokines; increases IL-27, IL-35, IL-33; promotes Th2 and Treg via anti-inflammatory mediators	CNS demyelination and infiltration reduce; severity scores lower
MS	PBMCs from MS patients	IL-23A	IFN-β	500 IU/mL on CD4 +, CD25 + T cells for 4–48 h	Downregulates IL23A; upregulates FOXP3 in CD4 + T cells; FOXP3 increases in CD25 + cells; IL-10 decreases; CD25 + cells resist IFN-β toxicity better	Immune response modulates toward regulatory function; cytokine expression indicates Treg immunoregulation
MS	Treatment-refractory MS patients	IL-12p70, IL-23	Autologous hematopoietic stem cell transplant	Not specified	Long-term suppression of IL-12p70, IL-23, IL-17, IFN-γ; induces immune tolerance	Proinflammatory cytokines reduce; long-term remission; relapse linked to IL-17 elevation

Table 3 (continued)

Disease	Disease model	IL-12 cytokine family member targeted	Agent/intervention	Dosage	Molecular mechanism of action	Outcome
MS	Monocyte-derived DCs from MS patients	IL-23 (p19, p40)	Antisense oligonucleotides	Ex vivo DC transfection	Suppresses IL-23 and IL-12 expression; decreases production; increases IL-10; decreases TNF-α; reduces DC all stimulation	Pro-inflammatory cytokines reduce; anti-inflammatory IL-10 increases; DC immune modulation observed
MS	Newly diagnosed, drug-naïve MS patients	IL-12	Vitamin D supplementation	Caltrate D BID; 50,000 IU/week for elevated iPTH; 12 month follow-up	Reduces pro-inflammatory cytokines; shifts balance toward anti-inflammatory profile	Pro-inflammatory cytokines decrease; improved cytokine ratios; potential relapse reduction
MS	RRMS patients	IL-23	IFN-β	30 mcg IM weekly × 2 months	Suppresses Th17-associated cytokines IL-17, IL-23; no effect on IL-4, IL-9, IL-10, TGF-β, IFN-γ	Early therapeutic effect through Th17 immunity modulation
MS	Phase I trial in relapsing MS patients	IL-12, IL-23	ABT-874 (IL-12/23 mAb)	SC single doses 0.3–3.0 mg/kg	Neutralizes IL-12, IL-23; suppresses Th1 and Th17 pathways	Well-tolerated; no dose-dependent adverse effects; no MRI lesion or relapse impact
MS	Phase II trials of RRMS and SPMS patients	IL-12, IL-23	ABT-874 (anti-IL-12/23 mAb)	200 mg every other week or weekly	Neutralizes IL-12 and IL-23; suppresses Th1 and Th17 responses	Gd-enhancing lesions and relapse rates reduce; no disability progression effect; safety acceptable
MS	RRMS patients	IL-12p40, IL-23	IFN-β	30 mcg IM weekly × 2 months	Reduces serum IL-12p40, IL-23; modulates Th1/Th17 and MMP-8, MMP-9 activity	Lesions reduce; clinical stabilization observed
MS	EAE in C57BL/6 mice	IL-23	Cucurbitacin B	0.5, 1 mg/kg IP every other day from day 0	Inhibits STAT3; suppresses IL-23/IL-17 axis; reduces microgliosis, neuroinflammation; increases MBP, Olig-2	Motor function improves; disease severity decreases
MS	RRMS, SPMS patients	IL-23, IL-27	IFNβ1A/B, Glatiramer acetate	Standard clinical doses	IL-23 elevated in RRMS R381Q GG genotype; IL-27 elevated in early onset RRMS	No significant correlation with disease duration or relapse except positive with treatment duration in SPMS
MS	RRMS, PPMS patients	IL-12p70	Ocrelizumab	600 mg IV every 6 months	Depletes B cells; modulates IL-12, IL-6, IFN-γ production	IL-12 suppressed after 6, 12 months; most patients achieve no evidence of disease activity at 12 months
MS	RRMS patients	IL-23	Vitamin D supplementation	High dose 2000 IU/day; low dose 15,960 IU/month × 6 months	Increases IL-4, IL-6, IL-17A, IL-22, IL-23, TNF-α; decreases IL-10	Dosage insufficient to modulate inflammation effectively

Table 3 (continued)

Disease	Disease model	IL-12 cytokine family member targeted	Agent/intervention	Dosage	Molecular mechanism of action	Outcome
PD	MPTP mouse model, RAW264.7 macrophages	IL-12 p70	Gagam–Sipjeondaebo–Tang + Ibuprofen	Oral gavage 5 days (mice); pretreatment in vitro	Reduces IL-12 p70 in LPS-stimulated macrophages; decreases activation and pro-inflammatory mediators	Neuroinflammation reduces; dopaminergic neuron survival and behavior improve; NO production decreases

The information here is derived from the narrative review outlined in Targeting IL-12 family in neurodegenerative diseases: current therapeutic approaches, with full citations detailed in the primary body of the text. *AD* Alzheimer's Disease; *MS* Multiple Sclerosis; *RRMS* Relapsing–Remitting MS; *SPMS* Secondary Progressive MS; *PPMS* Primary Progressive MS; *PRMS* Progressive Relapsing MS; *ALS* Amyotrophic Lateral Sclerosis; *PD* Parkinson's Disease; *APPPS1 Tg mouse model* APPPS1 Transgenic Mouse Model; *EAE* Experimental Autoimmune Encephalomyelitis; *PBMCs* Peripheral Blood Mononuclear Cells; *MPTP mouse model*: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine Mouse Model; *AHSCT* Autologous Hematopoietic Stem Cell Transplant; *DCs* Dendritic Cells; *IFN-β* Interferon-beta; *SC* Subcutaneous; *IP* Intraperitoneal; *IM* Intramuscular; *Ab* Antibody; *mAb* Monoclonal Antibody; *BID* Twice Daily; *IU* International Units; *Gd* Gadolinium; *MRI* Magnetic Resonance Imaging; *TNF-α* Tumor Necrosis Factor alpha; *NF-κB* Nuclear Factor kappa-light-chain-enhancer of activated B cells; *MMP* Matrix Metalloproteinase; *STAT3* Signal Transducer and Activator of Transcription 3; *MBP* Myelin Basic Protein; *NO* Nitric Oxide; *Tregs* Regulatory T cells; *Th1* T helper 1 cells; *Th2* T helper 2 cells; *Th17* T helper 17 cells; *FOXP3* Forkhead Box P3; *CNS* Central Nervous System; *Aβ* Amyloid Beta; *iPTH* Intact Parathyroid Hormone; *TGF-β* Transforming Growth Factor beta; *q8w* Every 8 weeks; *q* every; *EOW* Every Other Week; *EW* Every Week

In addition, FOXP3 gene polymorphisms were found to influence IL-35 serum levels and MS susceptibility, highlighting genetic factors in cytokine regulation (Jafarzadeh et al. 2015).

Monoclonal antibodies targeting the shared p40 subunit of IL-12 and IL-23, such as ustekinumab, have undergone clinical evaluation. In a Phase II trial involving RRMS patients, repeated subcutaneous injections of ustekinumab at doses of 27 mg, 90 mg every 8 weeks, or 90/180 mg administered at weeks 0, 1, 2, 3, 7, 11, 15, and 19 were well-tolerated. Ustekinumab neutralizes IL-12 and IL-23 by binding the p40 subunit, thereby reducing pro-inflammatory signaling. However, the study found no significant reduction in new gadolinium-enhancing T1 lesions compared to placebo (Segal et al. 2008). Similarly, ABT-874 (anti-IL-12/23 monoclonal antibody) showed good safety profiles at doses ranging from 0.3 to 3.0 mg/kg single subcutaneous doses and 200 mg administered every other week or every week in RRMS and SPMS patients. While the antibody reduced gadolinium-enhancing lesions and relapse rates, it did not significantly impact disability progression and was less effective compared to other MS therapies (Kasper et al. 2006; Vollmer et al. 2011).

Treatment-refractory MS patients undergoing autologous hematopoietic stem cell transplantation (AHSCT) exhibited long-term suppression of proinflammatory cytokines, including IL-12p70, IL-23, IL-17, and IFN-γ, along with induction of immunological tolerance. This is associated with sustained reductions in Th1 and Th17 cytokines and correlated with prolonged clinical remission. Notably, relapse is linked to elevations in IL-17 levels, underscoring the importance of IL-17 regulation post-AHSCT (Hendrawan et al. 2021).

Natural compounds such as curcumin and berberine have demonstrated immunomodulatory effects in EAE, a murine model of MS. Oral administration of curcumin at 100 and 200 mg/kg daily from the day of EAE induction decreased pro-inflammatory cytokines IFN-γ and TNF-α while enhancing IL-27 and IL-35 production. This treatment promoted Th2 and Treg responses through upregulation of IL-10, IL-4, TGF-β, IL-13, IL-33, and key transcription factors, such as Foxp3, CTLA4, GATA3, and STAT6, resulting in reduced leukocyte infiltration, demyelination, and clinical severity (Gaimari et al. 2022). Similarly, intraperitoneal administration of berberine at 10 and 30 mg/kg daily post-EAE induction reduced pro-inflammatory cytokines IFN-γ, TNF-α, and IL-17 while increasing anti-inflammatory IL-12 family cytokines IL-27, IL-35, and IL-33. This modulation of immune responses, mediated through IL-4, IL-10, and TGF-β, significantly lowered CNS demyelination, lymphocyte infiltration, and clinical severity scores (Tavaf et al. 2023).

Vitamin D supplementation has been explored as a modulator of IL-12 family cytokines in MS. In newly diagnosed,

drug-naïve MS patients, daily supplementation with Caltrate D and weekly high doses of 50,000 IU vitamin D for elevated iPTH patients over 12 months led to reductions in pro-inflammatory cytokines IL-12 and IFN-γ. This shifted the cytokine balance toward an anti-inflammatory profile, increasing IL-4, IL-5, and IL-10 levels, potentially reducing relapse rates (Al-Shammri et al. 2025). Contrastingly, in RRMS patients receiving lower doses (2000 IU/day or 15,960 IU/month for 6 months), vitamin D supplementation resulted in increased levels of pro-inflammatory cytokines IL-4, IL-6, IL-17A, IL-22, IL-23, and TNF-α, while IL-10 decreased, indicating the dose was insufficient to modulate inflammation effectively (Lis et al. 2024).

Additional immunomodulatory therapies include IFN-β treatment (30 mcg intramuscular weekly) in RRMS patients, which downregulated IL-23A and upregulated FOXP3 in CD4 + T cells, suggesting enhancement of regulatory T cell function and suppression of pro-inflammatory IL-23A. In CD25 + T cells, FOXP3 increased over time, while IL-10 expression decreased, indicating differential regulation among T cell subsets. These effects reflect early therapeutic modulation of Th17 immunity (Gezmis et al. 2021; Gaviglio et al. 2022a, b).

Antisense oligonucleotides targeting IL-23 subunits (p19 and p40) have been employed ex vivo to transfect monocyte-derived dendritic cells from MS patients. This approach suppressed IL-12 and IL-23 gene expression, reduced pro-inflammatory cytokine production (TNF-α), increased IL-10 secretion, and decreased dendritic cell allostimulatory capacity, highlighting potential for immune modulation in MS (Vaknin-Dembinsky et al. 2006).

Ocrelizumab, a B-cell depleting monoclonal antibody administered at 600 mg intravenously every 6 months, effectively suppressed IL-12p70 levels in RRMS and primary progressive MS (PPMS) patients. After 6 and 12 months, 100% of RRMS and 75% of PPMS patients achieved no evidence of disease activity, reflecting the drug's efficacy in modulating cytokine-mediated inflammation (Beckers et al. 2024).

In the EAE mouse model, cucurbitacin B administered intraperitoneally at 0.5 and 1 mg/kg every other day from day 0 of induction inhibited STAT3 activation and suppressed the IL-23/IL-17 axis. This intervention decreased microgliosis and neuroinflammation while increasing myelin basic protein and oligodendrocyte transcription factor Olig-2 expression, resulting in improved motor function and reduced disease severity (Reiszadeh-Jahromi et al. 2022) (Table 3).

Parkinson's disease

In PD models, combined treatment with Gagam–Sipjeondaebo–Tang and ibuprofen administered orally via gavage daily for 5 days reduced IL-12 p70 expression in LPS-stimulated RAW264.7 macrophages and decreased macrophage activation markers, including iNOS, COX-2, IL-1β, IL-6, and MCP-1. This synergistic effect led to reduced neuroinflammation, enhanced dopaminergic neuron survival, and improved behavioral outcomes in MPTP-induced mice (Won et al. 2021) (Table 3).

Conclusions and future perspectives

The IL-12 family cytokines, which include IL-12, IL-23, IL-27, and IL-35, exhibit complex and often contradictory roles in the context of neurodegenerative disorders. These cytokines can act either as inducers of inflammation or as modulators of immune suppression, depending on the specific cellular environment and disease stage. IL-12 and IL-23 typically aggravate neuroinflammatory responses by promoting Th1 and Th17 cell activity, which in turn contribute to neuronal damage and demyelination. Conversely, IL-27 and IL-35 are more frequently associated with neuroprotective effects via the inhibition of pro-inflammatory signaling and the support of regulatory immune networks.

Given their diverse immunomodulatory functions, IL-12 family members are increasingly recognized as viable therapeutic targets for conditions like AD, MS, and ALS. Approaches that inhibit pro-inflammatory cytokines (such as IL-12/IL-23 via p40 blockade) or boost the action of anti-inflammatory mediators (such as IL-27 or IL-35 mimetics) may afford considerable therapeutic potential. These strategies not only aim to attenuate disease progression but also strive to re-establish immune equilibrium within the central nervous system.

Therapeutic targeting of the IL-12 cytokine family has shown disease-specific promise in neurodegenerative disorders. In Alzheimer's disease, blockade of IL-12/IL-23 signaling (via genetic deletion or anti-p40 antibodies) reduced microglial activation, amyloid burden, tau pathology, and improved cognition, while agents such as tadalafil and bergapten further highlighted IL-27-associated neuroprotective pathways. Multiple sclerosis is the most extensively studied condition, where approaches including anti-IL-12/23 monoclonal antibodies (ustekinumab, ABT-874), vitamin D supplementation, IFN-β, ocrelizumab, and antisense oligonucleotides have variably modulated IL-12 family members, with natural compounds like curcumin and berberine enhancing IL-27/IL-35 while suppressing pro-inflammatory cytokines. Autologous hematopoietic stem cell transplantation has also demonstrated durable suppression of IL-12/23-driven inflammation. In Parkinson's disease models, combination therapies such as Gagam–Sipjeondaebo–Tang with ibuprofen reduced IL-12p70 and downstream inflammatory

mediators, preserving dopaminergic neurons and improving behavioral outcomes.

Nonetheless, key challenges remain. The biological functions of several cytokines, especially IL-35, have yet to be defined in PD and HD, underscoring the need for further mechanistic exploration and clinical studies. Moreover, obstacles such as limited drug delivery across the blood–brain barrier, individual variability in immune responses, and the multifaceted nature of cytokine signaling pose significant hurdles to therapeutic translation.

Although our understanding of IL-12 family cytokines in neurodegenerative disorders has advanced, numerous critical questions remain unresolved. Future investigations should focus on uncovering the context-specific roles of these cytokines, particularly the mechanisms by which individual members such as IL-27 and IL-35 exert opposing effects, ranging from neuroprotection to neurotoxicity, depending on the immune milieu or disease stage. Longitudinal studies in human subjects, especially those utilizing single-cell transcriptomic and spatial proteomic technologies, hold promise in delineating cell-specific responses and disease progression patterns. Nonetheless, the translation of preclinical findings into effective clinical interventions continues to face substantial hurdles, including limited penetration of the blood–brain barrier, unintended immunosuppressive effects, and inter-individual differences in cytokine expression profiles. Tailored immunotherapies, guided by cytokine-based biomarker panels, such as IL-12p70, IL-23, IL-27, and IL-35, may enable patient stratification and improve therapeutic precision. Furthermore, combining cytokine-targeted interventions with established neuroprotective or anti-amyloid treatments could produce enhanced synergistic outcomes. Ultimately, the IL-12 family cytokines hold considerable potential not only as a therapeutic focus but also as a biomarker platform for early detection and treatment monitoring in neurodegenerative disease.

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References

Al-Shammri S, Chattopadhyay A, Raghupathy R (2025) Vitamin D supplementation mediates a shift toward anti-inflammatory cytokine response in multiple sclerosis. Med Princ Pract. https://doi.org/10.1159/000544106

Álvarez-Luquín DD, Arce-Sillas A, Leyva-Hernández J, Sevilla-Reyes E, Boll MC, Montes-Moratilla E, Vivas-Almazán V, Pérez-Correa C, Rodríguez-Ortiz U, Espinoza-Cárdenas R (2019) Regulatory impairment in untreated Parkinson's disease is not restricted to Tregs: other regulatory populations are also involved. J Neuroinflammation 16:1–11

An J, Fu D, Chen X, Guan C, Li L, Bai J, Lv H (2025) Revisiting the role of IL-27 in obesity-related metabolic diseases: safeguard or perturbation? Front Immunol 15:1498288

Andreadou M, Ingelfinger F, De Feo D, Cramer TLM, Tuzlak S, Friebel E, Schreiner B, Eede P, Schneeberger S, Geesdorf M, Ridder F, Welsh CA, Power L, Kirschenbaum D, Tyagarajan SK, Greter M, Heppner FL, Mundt S, Becher B (2023) IL-12 sensing in neurons induces neuroprotective CNS tissue adaptation and attenuates neuroinflammation in mice. Nat Neurosci 26(10):1701–1712

Andres-Martin F, James C, Catalfamo M (2024) IL-27 expression regulation and its effects on adaptive immunity against viruses. Front Immunol 15:1395921

Ano Y, Ikado K, Uchida K, Nakayama H (2020) Amyloid β-induced mesenteric inflammation in an Alzheimer's disease transgenic mouse model. Curr Alzheimer Res 17(1):52–59

Avarachan J, Augustine A, Shinde PM, Gunasekaran V (2021) A mechanistic approach of peroxisome proliferator-activated receptors and its subtypes on clinical and preclinical model of neurodegenerative disorders. Res J Pharm Technol 14(7):3967–3975

Barac IS, Văcăraș V, Iancu M, Mureșanu DF, Procopciuc LM (2023a) Interleukins (IL-23 and IL-27) serum levels: relationships with gene polymorphisms and disease patterns in multiple sclerosis patients under treatment with interferon and glatiramer acetate. Heliyon. https://doi.org/10.1016/j.heliyon.2023.e17427

Barac IS, Văcăraș V, Iancu M, Mureșanu DF, Procopciuc LM (2023b) Interleukins (IL-23 and IL-27) serum levels: relationships with gene polymorphisms and disease patterns in multiple sclerosis patients under treatment with interferon and glatiramer acetate. Heliyon 9(6):e17427

Bastian D, Wu Y, Betts BC, Yu X-Z (2019) The IL-12 cytokine and receptor family in graft-vs.-host disease. Front Immunol 10:988

Beckers L, Baeten P, Popescu V, Swinnen D, Cardilli A, Hamad I, Van Wijmeersch B, Tavernier SJ, Kleinewietfeld M, Broux B, Fraussen J, Somers V (2024) Alterations in the innate and adaptive immune system in a real-world cohort of multiple sclerosis patients treated with ocrelizumab. Clin Immunol 259:109894

Benarroch E (2024) What is the role of cytokines in synaptic transmission? Neurology 103(8):e209928

Bhardwaj V, Kumari S, Dhapola R, Sharma P, Beura SK, Singh SK, Vellingiri B, HariKrishnaReddy D (2025) Shedding light on microglial dysregulation in Alzheimer's disease: exploring molecular mechanisms and therapeutic avenues. Inflammopharmacology 33(2):679–702

Bourgonje AR, Ungaro RC, Mehandru S, Colombel JF (2024) Targeting the IL-23 pathway in inflammatory bowel disease. Gastroenterology 168(1):29–52

Bright F, Werry EL, Dobson-Stone C, Piguet O, Ittner LM, Halliday GM, Hodges JR, Kiernan MC, Loy CT, Kassiou M (2019) Neuroinflammation in frontotemporal dementia. Nat Rev Neurol 15(9):540–555

Cassatella MA, Gardiman E, Arruda-Silva F, Bianchetto-Aguilera F, Gasperini S, Bugatti M, Vermi W, Larousserie F, Devergne O, Tamassia N (2020) Human neutrophils activated by

TLR8 agonists, with or without IFNγ, synthesize and release EBI3, but not IL-12, IL-27, IL-35, or IL-39. J Leukoc Biol 108(5):1515–1526
Chan JR, Blumenschein W, Murphy E, Diveu C, Wiekowski M, Abbondanzo S, Lucian L, Geissler R, Brodie S, Kimball AB (2006) IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2–dependent mechanisms with implications for psoriasis pathogenesis. J Exp Med 203(12):2577–2587
Chen Z, Balachandran YL, Chong WP, Chan KW (2024) Roles of cytokines in Alzheimer's disease. Int J Mol Sci 25(11):5803
Choi JK, Egwuagu CE (2021) Interleukin 35 regulatory B cells. J Mol Biol 433(1):166607
Choi J, Leung PS, Bowlus C, Gershwin ME (2015) IL-35 and autoimmunity: a comprehensive perspective. Clin Rev Allergy Immunol 49:327–332
Chu M, Wen L, Jiang D, Liu L, Nan H, Yue A, Wang Y, Wang Y, Qu M, Wang N (2023) Peripheral inflammation in behavioural variant frontotemporal dementia: associations with central degeneration and clinical measures. J Neuroinflammation 20(1):65
Clénet ML, Laurent C, Lemaitre F, Farzam-kia N, Tastet O, Devergne O, Lahav B, Girard M, Duquette P, Prat A (2021) The IL-27/IL-27R axis is altered in CD4+ and CD8+ T lymphocytes from multiple sclerosis patients. Clin Trans Immunol 10(3):e1262
Collison LW, Vignali DA (2008) Interleukin-35: odd one out or part of the family? Immunol Rev 226(1):248–262
Dias de Sousa MA, Desidério CS, da Silva Catarino J, Trevisan RO, Alves da Silva DA, Rocha VFR, Bovi WG, Timoteo RP, Bonatti RCF, da Silva AE (2022) Role of cytokines, chemokines and IFN-γ+ IL-17+ double-positive CD4+ T cells in patients with multiple sclerosis. Biomedicines 10(9):2062
Dong C, Tan D, Sun H, Li Z, Zhang L, Zheng Y, Liu S, Zhang Y, He Q (2024) Interleukin-12 delivery strategies and advances in tumor immunotherapy. Curr Issues Mol Biol 46(10):11548–11579
Duffy, S. (2018). The role of regulatory T cells and interleukin-35 in pain associated with an animal model of multiple sclerosis, UNSW Sydney
Dzamko N (2023) Cytokine activity in Parkinson's disease. Neuronal Signaling. https://doi.org/10.1042/NS20220063
Eede P, Obst J, Benke E, Yvon-Durocher G, Richard BC, Gimber N, Schmoranzer J, Böddrich A, Wanker EE, Prokop S (2020) Interleukin-12/23 deficiency differentially affects pathology in male and female Alzheimer's disease-like mice. EMBO Rep 21(3):e48530
Ellrichmann G, Reick C, Saft C, Linker RA (2013) The role of the immune system in Huntington's disease. J Immunol Res 2013(1):541259
Erichsen PA, Henriksen EE, Nielsen JE, Ejlerskov P, Simonsen AH, Toft A (2025) Immunological fluid biomarkers in frontotemporal dementia: a systematic review. Biomolecules 15(4):473
Fu J, Huang Y, Bao T, Liu C, Liu X, Chen X (2022) The role of Th17 cells/IL-17A in AD, PD, ALS and the strategic therapy targeting on IL-17A. J Neuroinflammation 19(1):98
Gaimari A, Fusaroli M, Raschi E, Baldin E, Vignatelli L, Nonino F, De Ponti F, Mandrioli J, Poluzzi E (2022) Amyotrophic lateral sclerosis as an adverse drug reaction: a disproportionality analysis of the food and drug administration adverse event reporting system. Drug Saf 45(6):663–673
Gałecka M, Bliźniewska-Kowalska K, Orzechowska A, Szemraj J, Maes M, Berk M, Su K-P, Gałecki P (2021) Inflammatory versus anti-inflammatory profiles in major depressive disorders—the role of IL-17, IL-21, IL-23, IL-35 and Foxp3. J Pers Med 11(2):66
Gao H, Li K, Ai K, Geng M, Cao Y, Wang D, Yang J, Wei X (2023) Interleukin-12 induces IFN-γ secretion and STAT signaling implying its potential regulation of Th1 cell response in Nile tilapia. Fish Shellfish Immunol 140:108974
García-Domínguez M (2025) The role of IL-23 in the development of inflammatory diseases. Biol 14(4):347
Gautam AS, Pulivarthi Cb, Singh RK (2023) Proinflammatory IL-17 levels in serum/cerebrospinal fluid of patients with neurodegenerative diseases: a meta-analysis study. Naunyn Schmiedebergs Arch Pharmacol 396(3):577–588
Gaviglio EA, Peralta Ramos JM, Arroyo DS, Bussi C, Iribarren P, Rodriguez-Galan MC (2022a) Systemic sterile induced-co-expression of IL-12 and IL-18 drive IFN-γ-dependent activation of microglia and recruitment of MHC-II-expressing inflammatory monocytes into the brain. Int Immunopharmacol 105:108546
Gaviglio EA, Ramos JMP, Arroyo DS, Bussi C, Iribarren P, Rodriguez-Galan MC (2022b) Systemic sterile induced-co-expression of IL-12 and IL-18 drive IFN-γ-dependent activation of microglia and recruitment of MHC-II-expressing inflammatory monocytes into the brain. Int Immunopharmacol 105:108546
Gerrits E, Brouwer N, Kooistra SM, Woodbury ME, Vermeiren Y, Lambourne M, Mulder J, Kummer M, Möller T, Biber K (2021) Distinct amyloid-β and tau-associated microglia profiles in Alzheimer's disease. Acta Neuropathol 141:681–696
Gezmis H, Doran T, MaydaDomac F, Yucel D, Karaci R, Kirac D (2021) CD4+ and CD25+ T-cell response to short-time interferon-beta therapy on IL10, IL23A and FOXP3 genes in multiple sclerosis patients. Int J Clin Pract 75(7):e14238
Ghaffari SA, Nemati M, Hajghani H, Ebrahimi H, Sheikhi A, Jafarzadeh A (2017) Circulating concentrations of interleukin (IL)-17 in patients with multiple sclerosis: evaluation of the effects of gender, treatment, disease patterns and IL-23 receptor gene polymorphisms. Iran J Neurol 16(1):15
Goleij P, Amini A, Tabari MAK, Hadipour M, Rezaee A, Daglia M, Aschner M, Sanaye PM, Kumar AP, Khan H (2025) Unraveling the role of the IL-20 cytokine family in neurodegenerative diseases: mechanisms and therapeutic insights. Int Immunopharmacol 152:114399
Gong F, Pan Y-H, Huang X, Chen J, Xiao J-H, Zhu H-Y (2013) Interleukin-27 as a potential therapeutic target for rheumatoid arthritis: has the time come? Clin Rheumatol 32:1425–1428
Hendrawan K, Khoo MLM, Visweswaran M, Massey JC, Withers B, Sutton I, Ma DDF, Moore JJ (2021) Long-term suppression of circulating proinflammatory cytokines in multiple sclerosis patients following autologous haematopoietic stem cell transplantation. Front Immunol 12:782935
Hu A, Ding M, Zhu J, Liu J-Q, Pan X, Ghoshal K, Bai X-F (2020) Intra-tumoral delivery of IL-27 using adeno-associated virus stimulates anti-tumor immunity and enhances the efficacy of immunotherapy. Front Cell Dev Biol 8:210
Huang D, Ran Y, Liu Z, He J, Yin N, Qi H (2021) IL-27 mediates pro-inflammatory effects via the ERK signaling pathway during preterm labor. Front Immunol 12:709229
Jadidi-Niaragh F, Mirshafiey A (2011) Th17 cell, the new player of neuroinflammatory process in multiple sclerosis. Scand J Immunol 74(1):1–13
Jafarzadeh A, Jamali M, Mahdavi R, Ebrahimi HA, Hajghani H, Khosravimashizi A, Nemati M, Najafipour H, Sheikhi A, Mohammadi MM (2015) Circulating levels of interleukin-35 in patients with multiple sclerosis: evaluation of the influences of FOXP3 gene polymorphism and treatment program. J Mol Neurosci 55(4):891–897
Jia Q, Li S, Li X-J, Yin P (2022) Neuroinflammation in Huntington's disease: from animal models to clinical therapeutics. Front Immunol 13:1088124
Jiang Z, Wang Z, Wei X, Yu X-F (2022) Inflammatory checkpoints in amyotrophic lateral sclerosis: from biomarkers to therapeutic targets. Front Immunol 13:1059994
Jouhault Q, Cherqaoui B, Jobart-Malfait A, Glatigny S, Lauraine M, Hulot A, Morelle G, Hagege B, Ermoza K, El Marjou A

(2023) Interleukin 27 is a novel cytokine with anti-inflammatory effects against spondyloarthritis through the suppression of Th17 responses. Front Immunol 13:1072420
Kang M, Choi JK, Jittayasothorn Y, Egwuagu CE (2020) Interleukin 35-producing exosomes suppress neuroinflammation and autoimmune uveitis. Front Immunol 11:1051
Kasper LH, Everitt D, Leist TP, Ryan KA, Mascelli MA, Johnson K, Raychaudhuri A, Vollmer T (2006) A phase I trial of an interleukin-12/23 monoclonal antibody in relapsing multiple sclerosis. Curr Med Res Opin 22(9):1671–1678
Kawanokuchi J, Takeuchi H, Sonobe Y, Mizuno T, Suzumura A (2013) Interleukin-27 promotes inflammatory and neuroprotective responses in microglia. Clin Exp Neuroimmunol 4(1):36–45
Kennedy, R. H. and R. Silver (2022). Neuroimmune signaling: cytokines and the central nervous system. Neuroscience in the 21st century: from basic to clinical, Springer**:** 883–922.
Kouchaki E, Kakhaki RD, Tamtaji OR, Dadgostar E, Behnam M, Nikoueinejad H, Akbari H (2018) Increased serum levels of TNF-α and decreased serum levels of IL-27 in patients with Parkinson disease and their correlation with disease severity. Clin Neurol Neurosurg 166:76–79
Krueger JG, Eyerich K, Kuchroo VK, Ritchlin CT, Abreu MT, Elloso MM, Fourie A, Fakharzadeh S, Sherlock JP, Yang Y-W (2024) IL-23 past, present, and future: a roadmap to advancing IL-23 science and therapy. Front Immunol 15:1331217
Kwon HS, Koh S-H (2020) Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. Transl Neurodegener 9(1):42
Leyane TS, Jere SW, Houreld NN (2022) Oxidative stress in ageing and chronic degenerative pathologies: molecular mechanisms involved in counteracting oxidative stress and chronic inflammation. Int J Mol Sci 23(13):7273
Li Y, Chu N, Hu A, Gran B, Rostami A, Zhang G-X (2007) Increased IL-23p19 expression in multiple sclerosis lesions and its induction in microglia. Brain 130(2):490–501
Lis M, Niedziela N, Adamczyk-Zostawa J, Wierzbicki K, Czuba Z, Zalejska-Fiolka J, Bartman W, Świętek A, Adamczyk-Sowa M (2024) Can vitamin D supplementation improve inflammation in relapsing-remitting multiple sclerosis patients? Biomedicines. https://doi.org/10.3390/biomedicines12071580
Liu J-Q, Zhu J, Hu A, Zhang A, Yang C, Yu J, Ghoshal K, Basu S, Bai X-F (2020a) Is AAV-delivered IL-27 a potential immunotherapeutic for cancer? Am J Cancer Res 10(11):3565
Liu L-R, Liu J-C, Bao J-S, Bai Q-Q, Wang G-Q (2020b) Interaction of microglia and astrocytes in the neurovascular unit. Front Immunol 11:1024
Liu T, Li S, Ying S, Tang S, Ding Y, Li Y, Qiao J, Fang H (2020c) The IL-23/IL-17 pathway in inflammatory skin diseases: from bench to bedside. Front Immunol 11:594735
Liu K, Huang A, Nie J, Tan J, Xing S, Qu Y, Jiang K (2021) IL-35 regulates the function of immune cells in tumor microenvironment. Front Immunol 12:683332
Livingston JA, Ragoonanan D, Tewari P, Gill JB, Banck S, Gao M, Lin HY, Li Y, Xia X, Hu J (2024) A first-in-human phase 1 trial of T cell membrane-anchored tumor targeted IL12 (ATTIL12)-T cell therapy in advanced/metastatic soft tissue and bone sarcoma. J Clin Oncol. https://doi.org/10.1200/JCO.2024.42.16_suppl.TPS11586
Lok HC, Katzeff JS, Hodges JR, Piguet O, Fu Y, Halliday GM, Kim WS (2023) Elevated GRO-α and IL-18 in serum and brain implicate the NLRP3 inflammasome in frontotemporal dementia. Sci Rep 13(1):8942
Longbrake EE, Racke MK (2009) Why did IL-12/IL-23 antibody therapy fail in multiple sclerosis? Expert Rev Neurother 9(3):319–321
Luo C, Li B, Chen L, Zhao L, Wei Y (2021) IL-27 protects the brain from ischemia-reperfusion injury via the gp130/STAT3 signaling pathway. J Mol Neurosci 71(9):1838–1848
Mahmoudzadeh S, Nozad Charoudeh H, Marques CS, Bahadory S, Ahmadpour E (2021) The role of IL-12 in stimulating NK cells against *Toxoplasma gondii* infection: a mini-review. Parasitol Res 120(7):2303–2309
McDonald BD, Dyer EC, Rubin DT (2022) IL-23 monoclonal antibodies for IBD: so many, so different? J Crohns Colitis 16(Supplement_2):ii42–ii53
Mehrotra A, D'Angelo JA, Romney-Vanterpool A, Chu T, Bertoletti A, Janssen HL, Gehring AJ (2020) IFN-α suppresses myeloid cytokine production, impairing IL-12 production and the ability to support T-cell proliferation. J Infect Dis 222(1):148–157
Mei Y, Ran Y, Liu Z, Zhou Y, He J, Yin N, Qi H (2022) The role of IL-27 in the systemic inflammatory response that accompanies preterm labour. Inflammation. https://doi.org/10.1007/s10753-021-01592-y
Milovanovic J, Arsenijevic A, Stojanovic B, Kanjevac T, Arsenijevic D, Radosavljevic G, Milovanovic M, Arsenijevic N (2020) Interleukin-17 in chronic inflammatory neurological diseases. Front Immunol 11:947
Mimic S, Aru B, Pehlivanoğlu C, Sleiman H, Andjus PR, Yanıkkaya Demirel G (2023) Immunology of amyotrophic lateral sclerosis–role of the innate and adaptive immunity. Front Neurosci 17:1277399
Mirlekar B, Pylayeva-Gupta Y (2021) IL-12 family cytokines in cancer and immunotherapy. Cancers 13(2):167
Moghadam S, Erfanmanesh M, Esmaeilzadeh A (2017) Interleukin 35 and hepatocyte growth factor; as a novel combined immune gene therapy for multiple sclerosis disease. Med Hypotheses 109:102–105
Mortada I, Farah R, Nabha S, Ojcius DM, Fares Y, Almawi WY, Sadier NS (2021) Immunotherapies for neurodegenerative diseases. Front Neurol 12:654739
Moschen AR, Tilg H, Raine T (2019) IL-12, IL-23 and IL-17 in IBD: immunobiology and therapeutic targeting. Nat Rev Gastroenterol Hepatol 16(3):185–196
Nash A, DeBonis J, Murungi D, Castillo B, Kim B, Hu F, Chambers C, Nguyen A, Hernandez A, Wang Z (2025) IL-12-producing cytokine factories induce precursor exhausted T cells and elimination of primary and metastatic tumors. J Immunother Cancer 13(4):e010685
Nikolopoulos D, Manolakou T, Polissidis A, Filia A, Bertsias G, Koutmani Y, Boumpas DT (2023) Microglia activation in the presence of intact blood–brain barrier and disruption of hippocampal neurogenesis via IL-6 and IL-18 mediate early diffuse neuropsychiatric lupus. Ann Rheum Dis 82(5):646–657
Nitsch L, Schneider L, Zimmermann J, Müller M (2021) Microglia-derived interleukin 23: a crucial cytokine in Alzheimer's disease? Front Neurol 12:639353
Nortey AN, Garces KN, Hackam AS (2022) Exploring the role of interleukin-27 as a regulator of neuronal survival in central nervous system diseases. Neural Regen Res 17(10):2149–2152
Obst, J. (2017). Influence of IL-12/IL-23 signaling on Alzheimer's disease β-amyloid pathology.
Papargyris, L., Q. Glaziou, L. Basset, S. d'Almeida, P. Pignon, N. Jabrane-Ferrat, C. Blanquart, Y. Delneste and J. Tabiasco (2024). IL-27 neutralization to modulate the tumor microenvironment and increase immune checkpoint immunotherapy efficacy. bioRxiv: 2024.2009. 2013.612803
Pavlidis P, Tsakmaki A, Pantazi E, Li K, Cozzetto D, Digby-Bell J, Yang F, Lo JW, Alberts E, Sa ACC (2022) Interleukin-22 regulates neutrophil recruitment in ulcerative colitis and is associated with resistance to ustekinumab therapy. Nat Commun 13(1):5820

Pourgholaminejad, A. and F. Tahmasebinia (2025). Th17-Mediated Immune Responses in Pathogenesis of Neuroinflammatory. Neuroimmune Diseases: From Cells to the Living Brain: 105

Povroznik JM, Robinson CM (2020) IL-27 regulation of innate immunity and control of microbial growth. Future Sci OA 6(7):FSO588

Reiszadeh-Jahromi S, Haddadi M, Mousavi P, Sanadgol N (2022) Prophylactic effects of cucurbitacin B in the EAE model of multiple sclerosis by adjustment of STAT3/IL-23/IL-17 axis and improvement of neuropsychological symptoms. Metab Brain Dis 37(8):2937–2953

Rentzos M, Paraskevas GP, Kapaki E, Nikolaou C, Zoga M, Rombos A, Tsoutsou A, Vassilopoulos D (2006) Interleukin-12 is reduced in cerebrospinal fluid of patients with Alzheimer's disease and frontotemporal dementia. J Neurol Sci 249(2):110–114

Rich T, Harris J, Abrams R, Erickson B, Doherty M, Paradelo J, Small W Jr., Safran H, Wanebo HJ (2004) Phase II study of external irradiation and weekly paclitaxel for nonmetastatic, unresectable pancreatic cancer: RTOG-98-12. Am J Clin Oncol 27(1):51–56

Rocha NP, Furr-Stimming E, Teixeira AL (2025) Cytokines as biomarkers of Huntington's disease progression. Expert Rev Mol Diagn. https://doi.org/10.1080/14737159.2025.2498539

Rosser AE, Busse ME, Gray WP, Badin RA, Perrier AL, Wheelock V, Cozzi E, Martin UP, Salado-Manzano C, Mills LJ (2022) Translating cell therapies for neurodegenerative diseases: Huntington's disease as a model disorder. Brain 145(5):1584–1597

Salem MA, Budzyńska B, Kowalczyk J, El Sayed NS, Mansour SM (2021) Tadalafil and bergapten mitigate streptozotocin-induced sporadic Alzheimer's disease in mice via modulating neuroinflammation, PI3K/Akt, Wnt/β-catenin, AMPK/mTOR signaling pathways. Toxicol Appl Pharmacol 429:115697

Sawant DV, Hamilton K, Vignali DA (2015) Interleukin-35: expanding its job profile. J Interferon Cytokine Res 35(7):499–512

Schinocca C, Rizzo C, Fasano S, Grasso G, La Barbera L, Ciccia F, Guggino G (2021) Role of the IL-23/IL-17 pathway in rheumatic diseases: an overview. Front Immunol 12:637829

Schneeberger S, Kim SJ, Geesdorf MN, Friebel E, Eede P, Jendrach M, Boltengagen A, Braeuning C, Ruhwedel T, Hülsmeier AJ (2025a) Interleukin-12 signaling drives Alzheimer's disease pathology through disrupting neuronal and oligodendrocyte homeostasis. Nat Aging. https://doi.org/10.1038/s43587-025-00816-2

Schneeberger S, Kim SJ, Geesdorf MN, Friebel E, Eede P, Jendrach M, Boltengagen A, Braeuning C, Ruhwedel T, Hülsmeier AJ, Gimber N, Foerster M, Obst J, Andreadou M, Mundt S, Schmoranzer J, Prokop S, Kessler W, Kuhlmann T, Möbius W, Nave K-A, Hornemann T, Becher B, Edgar JM, Karaiskos N, Kocks C, Rajewsky N, Heppner FL (2025b) Interleukin-12 signaling drives Alzheimer's disease pathology through disrupting neuronal and oligodendrocyte homeostasis. Nat Aging 5(4):622–641

Segal BM, Constantinescu CS, Raychaudhuri A, Kim L, Fidelus-Gort R, Kasper LH (2008) Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing-remitting multiple sclerosis: a phase II, double-blind, placebo-controlled, randomised, dose-ranging study. Lancet Neurol 7(9):796–804

Sénécal V, Deblois G, Beauseigle D, Schneider R, Brandenburg J, Newcombe J, Moore CS, Prat A, Antel J, Arbour N (2016) Production of IL-27 in multiple sclerosis lesions by astrocytes and myeloid cells: modulation of local immune responses. Glia 64(4):553–569

Sewell GW, Kaser A (2022) Interleukin-23 in the pathogenesis of inflammatory bowel disease and implications for therapeutic intervention. J Crohns Colitis 16(Supplement_2):ii3–ii19

Shahi A, Afzali S, Salehi S, Aslani S, Mahmoudi M, Jamshidi A, Amirzargar A (2020) IL-27 and autoimmune rheumatologic diseases: the good, the bad, and the ugly. Int Immunopharmacol 84:106538

Sharma A, Upadhyay DK, Gupta GD, Narang RK, Rai VK (2022) IL-23/Th17 axis: a potential therapeutic target of psoriasis. Curr Drug Res Rev Formerly 14(1):24–36

Shateri S, Hossein KS, Alireza HT, Shima R, Meisam M, Somayeh MB, Gholam-Ali S, Hossein HA, Vajiheh A, Babak G, Lily S, Alireza D, Farzaneh S, Abbas T, Aliasghar K, Reza SM, Karima S (2025a) Plasma cytokines profile in patients with Alzheimer's and Parkinson's disease: a comparative study in terms of inflammation. Int J Neurosci 135(2):158–167

Shateri S, Khatami SH, Haghbin Toutounchi A, Rajaei S, Mahdavi M, Mahmoodi Baram S, Shahidi G-A, Habibi AH, Aghamollaii V, Ghlichnia B (2025b) Plasma cytokines profile in patients with Alzheimer's and Parkinson's disease: a comparative study in terms of inflammation. Int J Neurosci 135(2):158–167

Shi Y, Zhang S, Xue Y, Yang Z, Lin Y, Liu L, Liu H (2020) IL-35 polymorphisms and cognitive decline did not show any association in patients with coronary heart disease over a 2-year period: a retrospective observational study (STROBE compliant). Medicine (Baltimore) 99(31):e21390

Soliman AM, Barreda DR (2022) Acute inflammation in tissue healing. Int J Mol Sci 24(1):641

Soltani, M., P. Beshkar, K. Mokhtarian, M. Anjomshoa, M. M. Rezaei, F. Azadegan-Dehkordi, Y. Mirzaei, J. Majidi and N. Bagheri (2022). A study of autoantibodies against some central nervous system antigens and the il-35 serum level in schizophrenia. Iranian Journal of Allergy, Asthma and Immunology.

Stacchiotti C, Mazzella di Regnella S, Cinotti M, Spalloni A, Volpe E (2025) Neuroinflammation and Amyotrophic Lateral Sclerosis: Recent Advances in Anti-Inflammatory Cytokines as Therapeutic Strategies. Int J Mol Sci 26(8):3854

Stumhofer J, Hunter C (2008) Advances in understanding the anti-inflammatory properties of IL-27. Immunol Lett 117(2):123–130

Sun L, He C, Nair L, Yeung J, Egwuagu CE (2015) Interleukin 12 (IL-12) family cytokines: role in immune pathogenesis and treatment of CNS autoimmune disease. Cytokine 75(2):249–255

Sun X, Gu R, Bai J (2024) Differentiation and regulation of CD4+ T cell subsets in Parkinson's disease. Cell Mol Life Sci 81(1):352

Tavaf MJ, Soltanmohammadi A, Zargarani S, Yazdanpanah E, Sadighi-moghaddam B, Yousefi B, Sameni HR, Haghmorad D (2023) Berberine promotes immunological outcomes and decreases neuroinflammation in the experimental model of multiple sclerosis through the expansion of Treg and Th2 cells. Immun Inflamm Dis 11(1):e766

Tuzlak S, Dejean AS, Iannacone M, Quintana FJ, Waisman A, Ginhoux F, Korn T, Becher B (2021) Repositioning TH cell polarization from single cytokines to complex help. Nat Immunol 22(10):1210–1217

Ullrich KA, Schulze LL, Paap E-M, Müller TM, Neurath MF, Zundler S (2020) Immunology of IL-12: an update on functional activities and implications for disease. EXCLI J 19:1563

Vaknin-Dembinsky A, Balashov K, Weiner HL (2006) *IL*-23 is increased in dendritic cells in multiple sclerosis and down-regulation of *IL*-23 by antisense oligos increases dendritic cell *IL*-10 production. J Immunol 176(12):7768–7774

Van Schependom J, D'haeseleer M (2023) Advances in neurodegenerative diseases. J Clin Med 12:1709

Van Zeller M, Dias D, Sebastião AM, Valente CA (2021) NLRP3 inflammasome: a starring role in amyloid-β-and tau-driven pathological events in Alzheimer's disease. J Alzheimers Dis 83(3):939–961

Vignali DA, Kuchroo VK (2012) IL-12 family cytokines: immunological playmakers. Nat Immunol 13(8):722–728

Vollmer TL, Wynn DR, Alam MS, Valdes J (2011) A phase 2, 24-week, randomized, placebo-controlled, double-blind study examining the efficacy and safety of an anti-interleukin-12 and -23

monoclonal antibody in patients with relapsing-remitting or secondary progressive multiple sclerosis. Mult Scler 17(2):181–191
vom Berg J, Prokop S, Miller KR, Obst J, Kälin RE, Lopategui-Cabezas I, Wegner A, Mair F, Schipke CG, Peters O, Winter Y, Becher B, Heppner FL (2012) Inhibition of IL-12/IL-23 signaling reduces Alzheimer's disease–like pathology and cognitive decline. Nat Med 18(12):1812–1819
Wan Y, Zhao Y, Pan M, Gan J, Wu N, Zhang Y, Liu Z, Song L (2024) Peripheral biomarkers of Parkinson's disease and its correlation with clinical symptoms: a case-control study. BMC Neurol 24(1):417
Wang T, Sun Q, Yang J, Wang G, Zhao F, Chen Y, Jin Y (2021) Reactive astrocytes induced by 2-chloroethanol modulate microglia polarization through IL-1β, TNF-α, and iNOS upregulation. Food Chem Toxicol 157:112550
Wang R, Ren H, Kaznacheyeva E, Lu X, Wang G (2023a) Association of glial activation and α-synuclein pathology in Parkinson's disease. Neurosci Bull 39(3):479–490
Wang X, Zhang A, Qiu X, Yang K, Zhou H (2023b) The IL-12 family cytokines in fish: molecular structure, expression profile and function. Dev Comp Immunol 141:104643
Wang H, Ruan G, Li Y, Liu X (2025) The role and potential application of IL-12 in the immune regulation of tuberculosis. Int J Mol Sci 26(7):3106
Wen S-R, Liu G-J, Feng R-N, Gong F-C, Zhong H, Duan S-R, Bi S (2012) Increased levels of IL-23 and osteopontin in serum and cerebrospinal fluid of multiple sclerosis patients. J Neuroimmunol 244(1–2):94–96
Winston CN, Rissman RA (2023) Exosomal IL-12p70 is increased in minority participants at risk for Alzheimer's disease. Alzheimers Dement 19:e073141
Won S, Ko JH, Jeon H, Park SS, Kim SN (2021) Co-administration of Gagam-Sipjeondaebo-Tang and ibuprofen alleviates the inflammatory response in MPTP-induced Parkinson's disease mouse model and RAW264.7 macrophages. Pathogens. https://doi.org/10.3390/pathogens10030268
Wu D, Wang L, Hong D, Zheng C, Zeng Y, Ma H, Lin J, Chen J, Zheng R (2022) Interleukin 35 contributes to immunosuppression by regulating inflammatory cytokines and T cell populations in the acute phase of sepsis. Clin Immunol 235:108915
Xiong P, Liu T, Huang H, Yuan Y, Zhang W, Fu L, Chen Y (2022) IL-27 overexpression alleviates inflammatory response in allergic asthma by inhibiting Th9 differentiation and regulating Th1/Th2 balance. Immunopharmacol Immunotoxicol 44(5):712–718
Xu W-D, Wang D-C, Zhao M, Huang A-F (2024a) An updated advancement of bifunctional IL-27 in inflammatory autoimmune diseases. Front Immunol 15:1366377
Xu Y, Sun X, Tong Y (2024b) Interleukin-12 in multimodal tumor therapies for induction of anti-tumor immunity. Discover Oncol 15(1):170
Yadav MK, Singh SP, Egwuagu CE (2025) IL-6/IL-12 superfamily of cytokines and regulatory lymphocytes play critical roles in the etiology and suppression of CNS autoimmune diseases. Front Immunol 16:1514080
Yang Y, Lovett-Racke AE, Racke MK (2011) Role of IL-12/IL-23 in the Pathogenesis of Multiple Sclerosis. Elsevier, Neuroinflammation, pp 107–136
Yang HS, Zhang C, Carlyle BC, Zhen SY, Trombetta BA, Schultz AP, Pruzin JJ, Fitzpatrick CD, Yau WYW, Kirn DR (2022) Plasma IL-12/IFN-γ axis predicts cognitive trajectories in cognitively unimpaired older adults. Alzheimers Dement 18(4):645–653
Yasmin-Karim S, Moreau M, Mueller R, Sinha N, Dabney R, Herman A, Ngwa W (2018) Enhancing the therapeutic efficacy of cancer treatment with cannabinoids. Front Oncol 8:114
Yazdanpanah E, Pazoki A, Dadfar S, Nemati MH, SajadSiadati SM, Tarahomi M, Orooji N, Haghmorad D, Oksenych V (2024) Interleukin-27 and autoimmune disorders: a compressive review of immunological functions. Biomolecules 14(12):1489
Ye J, Wang Y, Wang Z, Liu L, Yang Z, Wang M, Xu Y, Ye D, Zhang J, Lin Y (2020) Roles and mechanisms of interleukin-12 family members in cardiovascular diseases: opportunities and challenges. Front Pharmacol 11:129
Ye C, Yano H, Workman CJ, Vignali DA (2021) Interleukin-35: structure, function and its impact on immune-related diseases. J Interferon Cytokine Res 41(11):391–406
Yi P, Yu W, Xiong Y, Dong Y, Huang Q, Lin Y, Du Y, Hua F (2024) IL-35: new target for immunotherapy targeting the tumor microenvironment. Mol Cancer Ther 23(2):148–158
Yoshida H, Hunter CA (2015) The immunobiology of interleukin-27. Annu Rev Immunol 33(1):417–443
You J, Youssef MM, Santos JR, Lee J, Park J (2023) Microglia and astrocytes in amyotrophic lateral sclerosis: disease-associated states, pathological roles, and therapeutic potential. Biology 12(10):1307
Zhu J-J, Shan N-N (2020) Immunomodulatory cytokine interleukin-35 and immune thrombocytopaenia. J Int Med Res 48(12):0300060520976477