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Neuroimmune Interactions in Multiple Sclerosis: Mechanisms of Inflammation and Prospects for Therapy

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A B S T R A C T

Neuroinflammation is a central feature in the development and progression of multiple sclerosis (MS), a chronic autoimmune disorder of the central nervous system. This review provides a comprehensive overview of the molecular and cellular mechanisms underlying neuroinflammation in MS, focusing on the involvement of immune cells, pro-inflammatory cytokines, and the disruption of the blood-brain barrier. Furthermore, it summarizes current therapeutic strategies and highlights emerging approaches aimed at mitigating neuroinflammatory responses. By consolidating recent findings, this article seeks to enhance our understanding of the complex interplay between neuroinflammatory processes and MS pathogenesis, offering insights into potential therapeutic advancements.

Keywords: Neuroinflammation, Multiple Sclerosis, Immune Cells, Cytokines, Blood-Brain Barrier, Pathogenesis, Immunotherapy.

1. INTRODUCTION

Multiple sclerosis (MS) is a chronic and complex autoimmune disorder of the central nervous system (CNS), characterized by inflammation, demyelination, and neurodegeneration. Neuroinflammation is a central pathological feature of MS and plays a crucial role in disease progression and the development of neurological disability.[1] It results from a dysregulated immune response involving peripheral immune cell infiltration, glial cell activation, and disruption of the blood-brain barrier (BBB).[2] This review provides a comprehensive analysis of the mechanisms driving neuroinflammation in MS, with particular focus on the roles of immune cells (such as T cells, B cells, and macrophages), resident CNS cells (microglia and astrocytes), and BBB dysfunction. It also examines how these factors contribute to the pathogenesis of MS, including immune dysregulation, myelin damage, and axonal loss. [3,4] Finally, the review discusses current and emerging therapeutic strategies targeting neuroinflammatory pathways. These include immunomodulatory and anti-inflammatory agents, therapies aimed at promoting remyelination, and neuroprotective interventions designed to preserve neuronal integrity and function. [5,6] Through this detailed exploration, the review aims to enhance the understanding of neuroinflammation in MS and its potential as a target for innovative treatment approaches.

Figure 1. Neuroinflammation in multiple sclerosis.

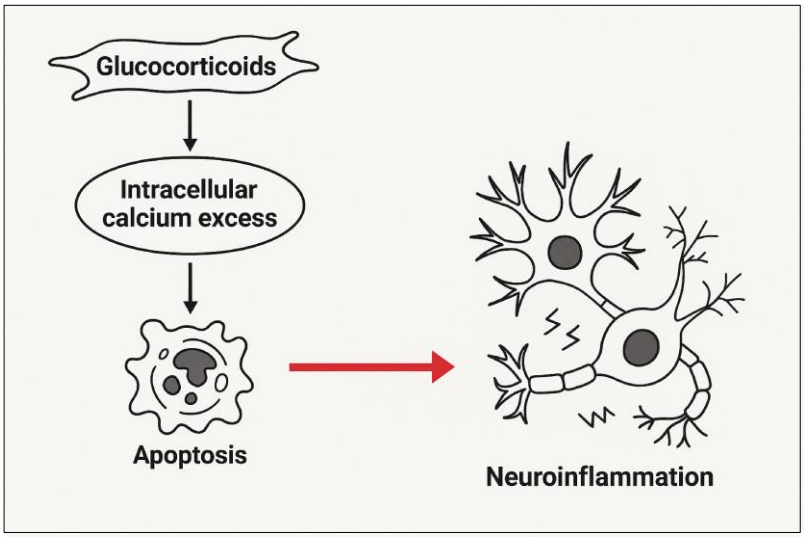

Figure 2. Neuroinflammation in multiple sclerosis when Glucocorticoids contribute apoptosis by Intracellular calcium excess.

1. Multiple Sclerosis□Causes, Risk Factors, and Types

1.1. Causes

Multiple sclerosis (MS) is a chronic, immune-mediated disorder of the central nervous system (CNS), the precise etiology of which remains elusive. However, accumulating evidence suggests that a multifactorial interplay between genetic predisposition and environmental exposures contributes significantly to disease development [7 – 9]. Several key mechanisms and hypotheses have been proposed:

1. Immune System Dysfunction

MS is widely recognized as an autoimmune disease in which the immune system erroneously targets self-antigens, particularly the myelin sheath that insulates neuronal axons in the CNS. This immune-mediated demyelination leads to neuroinflammation, axonal damage, and progressive neurological decline [10,11].

2. Genetic Susceptibility

Although MS is not a directly inherited condition, genetic predisposition plays an important role. Individuals with a family history of MS, particularly first-degree relatives, exhibit a higher risk of developing the disease. Specific genes associated with immune regulation—particularly those in the human leukocyte antigen (HLA) region—have been implicated in increasing susceptibility [12,13].

3. Environmental Triggers

Environmental factors may act as external triggers in genetically predisposed individuals.

- **Viral Infections:** Epstein– Barr virus (EBV), in particular, has been strongly associated with increased MS risk. A history of infectious mononucleosis, caused by EBV, is more common in MS patients [14].
- **Vitamin D Deficiency:** Low serum vitamin D levels have been linked to higher MS risk, suggesting a potential role in immune regulation.
- **Smoking:** Cigarette smoking has been correlated with both an elevated risk of developing MS and an accelerated disease course.
- **Geography and Sunlight Exposure:** Higher MS prevalence is observed in populations residing at higher latitudes, potentially due to reduced sunlight exposure and corresponding vitamin D synthesis.
- **Other Factors:** Childhood infections and certain dietary habits are also under investigation as potential contributors.

4. Gender and Age

MS predominantly affects women, with a female-to-male ratio of approximately 3:1. The disease most commonly manifests between the ages of 20 and 40, suggesting a potential hormonal influence on disease onset and progression.

5. Other Hypotheses

Additional areas of investigation include abnormalities in the blood– brain barrier (BBB), which regulates the exchange between peripheral blood and the CNS, as well as dysregulation of immune checkpoints and cytokine signalling pathways [15,16].

1.1. Risk Factors

Multiple sclerosis is associated with a number of risk factors that may increase an individual's likelihood of developing the condition. These include:

1. Gender

Women are disproportionately affected by MS, and the higher incidence among females points to potential hormonal or sex-linked immunological differences [18].

2. Age

MS most often presents in young adults, typically between 20 and 40 years of age, though it can also occur in pediatric and older populations [19,20].

3. Genetics

A familial history of MS, especially in first-degree relatives such as parents or siblings, is a well-documented risk factor. While MS is not directly inherited, familial clustering suggests shared genetic and environmental influences [21].

4. Ethnicity and Geography

Individuals of Northern European descent are at higher risk compared to those of African, Asian, or Native American ancestry. Moreover, MS prevalence increases with distance from the equator, reinforcing the role of environmental factors such as sunlight and vitamin D.

5. Viral Infections

Previous infection with EBV, particularly when it results in symptomatic mononucleosis, has been strongly correlated with the later development of MS.

6. Smoking

Tobacco use is associated with increased susceptibility to MS and more rapid disease progression, including earlier onset of secondary progressive MS (SPMS) [22,23].

7. Vitamin D Deficiency

Numerous studies support the hypothesis that vitamin D plays a protective role in MS, with low levels correlating with increased disease risk.

8. Other Autoimmune Disorders

Individuals with other autoimmune diseases such as type 1 diabetes or autoimmune thyroid disorders may have a slightly increased risk of developing MS, indicating shared immunogenetic mechanisms.

9. Obesity

Obesity, particularly during adolescence, has emerged as a modifiable risk factor for MS. It may influence immune system development and pro-inflammatory states linked to MS onset [11,24].

It is important to note that while these risk factors may increase the probability of developing MS, they are neither necessary nor sufficient for disease development. Many individuals with MS lack identifiable risk factors, highlighting the complexity of its pathogenesis.

1.2. Types of Multiple Sclerosis

MS manifests in various clinical forms, each with distinct patterns of progression and symptomatology. These subtypes can evolve and influence therapeutic decisions. The major classifications include:

1. **Relapsing-Remitting Multiple Sclerosis (RRMS)**
- **Description:** RRMS is the most common form, characterized by clearly defined relapses (exacerbations) followed by periods of partial or complete recovery (remissions).
- **Progression:** There may be no or minimal progression between relapses.
- **Treatment:** Disease-modifying therapies (DMTs) are often effective in reducing relapse frequency and disease activity [24,25].

2. **Secondary Progressive Multiple Sclerosis (SPMS)**
- **Description:** Many individuals with RRMS transition into SPMS, where there is a gradual worsening of neurological function over time, which may still include relapses and remissions.
- **Progression:** Disability accumulates more steadily, and inflammatory activity may decline.
- **Treatment:** While some DMTs used in RRMS may be beneficial, the focus often shifts to symptom management and maintaining quality of life [26,32].

3. **Primary Progressive Multiple Sclerosis (PPMS)**
- **Description:** PPMS is marked by a gradual accumulation of disability from the onset, without distinct relapses or remissions.
- **Progression:** The disease course is steadily progressive, typically resulting in increasing physical disability.
- **Treatment:** Fewer treatment options are approved for PPMS; care often emphasizes rehabilitation and symptom control [24,27].

4. **Progressive-Relapsing Multiple Sclerosis (PRMS)**
- **Description:** PRMS is a rare form characterized by a progressive neurological decline from disease onset, with superimposed acute relapses.
- **Symptoms:** Unlike RRMS, relapses in PRMS occur without periods of full remission.
- **Treatment:** Management involves therapies that address both inflammatory and progressive aspects of the disease [30].

5. **Clinically Isolated Syndrome (CIS)**
- **Description:** CIS refers to a first, isolated episode of neurological symptoms resulting from demyelination in the CNS. It may represent an early manifestation of MS.
- **Progression:** Not all individuals with CIS will go on to develop MS. Risk stratification is crucial.
- **Diagnosis and Treatment:** MRI findings and biomarkers help determine the likelihood of progression to MS. Early treatment with DMTs may delay or prevent disease onset in high-risk individuals [24,31,32].

4.3. Role of Regulatory Adaptive Immune Cells in Multiple Sclerosis (MS)

4.3.1. Regulatory T Cells (Tregs)

Regulatory T cells (Tregs) are a specialized subset of $CD4^+$ T cells that maintain immune homeostasis and tolerance by suppressing autoreactive T cell responses. In the context of multiple sclerosis (MS), Tregs play a crucial role in modulating central nervous system (CNS) inflammation and autoimmunity. Xie et al. provided groundbreaking evidence of Tregs residing in the mouse brain, emphasizing their involvement in CNS immune surveillance and regulation of inflammatory responses. Their study demonstrated that Tregs mitigate lipopolysaccharide (LPS)-induced neuroinflammation—originating from microglia and macrophages—by secreting the anti-inflammatory cytokine IL-10, and by limiting $CD4^+$ T cell recruitment in experimental autoimmune encephalomyelitis (EAE), a murine model of MS [61]. Furthermore, recent reviews have explored the potential role of Tregs in oligodendrocyte biology. Dombrowski and colleagues reported that Treg-deficient mice exhibited significantly reduced oligodendrocyte progenitor cell (OPC) activation and differentiation, along with impaired remyelination, compared to wild-type or Treg-depleted mice. These findings suggest that Tregs may directly support remyelination by promoting oligodendrocyte maturation through the

secretion of connective tissue growth factor CCN3. Thus, Tregs may not only act as immunoregulators but also facilitate CNS repair mechanisms.

4.3.2. Regulatory B Cells (Bregs)

While T cells have traditionally been the focus of MS immunopathology, regulatory B cells (Bregs) have emerged as important modulators of immune responses. These cells exert their immunosuppressive functions primarily through the secretion of anti-inflammatory cytokines, including IL-10 and IL-35. Among the various subsets, IL-10-producing Bregs (often termed B10 cells) are the most well-studied for their role in controlling aberrant immune activation in MS and EAE models [48,49,73]. Due to the lack of unique surface markers, Breg subsets are typically identified based on their cytokine secretion profiles. Shen et al. demonstrated that reduced production of IL-10 and IL-35 by Bregs in EAE may lead to enhanced T cell activation and plasma cell differentiation, thereby exacerbating disease activity [64]. Further supporting this, Wang et al. observed that blockade of IL-35—either pharmacologically or genetically—resulted in reduced Breg populations and increased severity of autoimmune uveitis in mice [63]. These findings underscore the potential of targeting Bregs and their cytokines as a therapeutic strategy in MS.

5. Mechanisms of Neuroinflammation in Multiple Sclerosis

Neuroinflammation is a hallmark of MS pathology, driven by a complex interplay of immune cells, glial responses, and neurodegenerative processes. Key mechanisms include:

1. **Immune Cell Activation:** Infiltration of activated T cells, B cells, and antigen-presenting cells into the CNS results in the release of pro-inflammatory cytokines and chemokines. Th1 and Th17 cells are particularly implicated, with cytokines such as interferon-gamma (IFN-γ) and interleukin-17 (IL-17) contributing to demyelination and axonal injury.
2. **Microglial Activation:** Resident CNS immune cells—microglia—become reactive in response to injury or inflammation. Activated microglia secrete inflammatory mediators, including TNF-α and reactive oxygen species (ROS), which amplify neuroinflammation and promote myelin damage through phagocytosis of myelin debris.
3. **Astrocyte Dysfunction:** While astrocytes support neuronal function and repair, their reactive phenotypes in MS contribute to pathology. Reactive astrocytes release pro-inflammatory cytokines, such as IL-1β and TNF-α, exacerbating inflammation and disrupting the blood-brain barrier (BBB).
4. **Blood-Brain Barrier Disruption:** Breakdown of the BBB allows peripheral immune cells and inflammatory molecules to infiltrate the CNS, intensifying tissue injury. Increased BBB permeability is often an early feature of MS and correlates with disease relapses and progression.
5. **Oligodendrocyte Damage and Demyelination:** MS targets oligodendrocytes—the myelinating cells of the CNS—leading to demyelination, axonal dysfunction, and impaired neural conduction. Chronic demyelination further impairs neural communication and repair.
6. **Neurodegeneration:** Progressive neuronal and axonal loss, synaptic dysfunction, and cellular apoptosis contribute to irreversible disability in MS. Neurodegeneration is especially prominent in progressive forms of the disease and is closely tied to sustained inflammation and mitochondrial dysfunction.

6. Therapeutic Implications

Current and emerging therapies for MS aim to mitigate immune dysregulation, reduce inflammation, and promote neurorepair. These include:

1. **Immunomodulatory Therapies:** First-line disease-modifying treatments (DMTs) such as interferon-β and glatiramer acetate modulate the immune response to reduce relapse rates and delay disease progression.
2. **Targeted Anti-Inflammatory Agents:** Monoclonal antibodies such as natalizumab (anti-VLA-4) and fingolimod (a sphingosine-1-phosphate receptor modulator) specifically inhibit immune cell trafficking and activation, offering potent disease control in relapsing forms of MS.
3. **Remyelination-Promoting Agents:** Therapies like clemastine fumarate and anti-LINGO-1 antibodies are under investigation for their potential to enhance remyelination and oligodendrocyte regeneration in demyelinated CNS regions.
4. **Neuroprotective Strategies:** Neuroprotective interventions targeting oxidative stress, excitotoxicity, and mitochondrial dysfunction—using agents such as antioxidants and neurotrophic factors—may help preserve neuronal integrity and reduce disability accumulation in progressive MS.

4. Pathogenesis and Pathophysiology

Multiple sclerosis (MS) is characterized by a multifactorial pathophysiology involving disrupted blood-brain barrier (BBB) permeability, genetic predisposition, immune dysregulation, demyelination, axonal injury, and gliosis. These processes contribute to chronic inflammation and neurodegeneration within the central nervous system (CNS) [9,13].

4.1. MS Pathogenesis

1. Autoimmune Response and Inflammation

The hallmark of MS is an autoimmune response in which the immune system erroneously targets CNS components, particularly the myelin sheath that insulates nerve fibers. Activated T cells infiltrate the CNS and orchestrate an inflammatory cascade:

- **Antigen Presentation:** Myelin antigens are presented to autoreactive T cells by antigen-presenting cells (APCs), including dendritic cells and macrophages. This interaction leads to T cell activation, promoting immune-mediated myelin destruction and neuroinflammation.
- **Th1 and Th17 Cells:** MS patients exhibit elevated levels of pro-inflammatory T helper cells, particularly Th1 and Th17 subsets. These cells secrete cytokines such as interferon-gamma (IFN-γ) and interleukin-17 (IL-17), which further recruit inflammatory cells into the CNS and exacerbate tissue damage.
- **B Cells and Autoantibodies:** B cells contribute to disease pathology through the production of autoantibodies targeting myelin antigens, thereby amplifying inflammation and demyelination [10].

2. Genetic Susceptibility

- **HLA Genes:** The strongest genetic association in MS is with HLA-DRB1*15:01. HLA molecules are crucial for antigen presentation and modulating immune responses, significantly influencing MS risk.
- **Non-HLA Genes:** Several non-HLA loci are also implicated, many of which regulate immune signaling, cytokine production, and myelin integrity. These genetic variations collectively increase the likelihood of autoimmunity and CNS vulnerability [13,14].

3. Environmental Triggers

- **Epstein-Barr Virus (EBV):** EBV infection is a well-established environmental risk factor. It infects B cells and is hypothesized to induce molecular mimicry or aberrant immune responses in genetically predisposed individuals.
- **Vitamin D Deficiency:** Low serum vitamin D levels, often due to limited sun exposure, are associated with increased MS risk. Vitamin D modulates immune function and may reduce autoreactive T-cell responses [35,36].

4. Demyelination and Axonal Injury

- **Demyelination:** The primary pathological feature of MS is the immune-mediated destruction of the myelin sheath, impairing saltatory conduction and leading to neurological deficits.
- **Axonal Injury:** In addition to demyelination, axons themselves suffer damage from chronic inflammation, mitochondrial dysfunction, and loss of trophic support, contributing to irreversible neurodegeneration and disability progression [36,38,39].

5. Blood-brain barrier (BBB) Dysfunction

- **Increased Permeability:** The BBB, which normally restricts immune cell entry into the CNS, becomes compromised in MS. This breakdown permits infiltration of T cells, B cells, cytokines, and antibodies, perpetuating inflammation and CNS damage.

6. Gliosis and Scar Formation

- **Astrocyte and Microglial Activation:** In response to injury, glial cells become reactive, leading to gliosis. This process involves the proliferation of astrocytes and microglia, resulting in glial scar formation (sclerosis) that disrupts neural repair and contributes to disease progression.

7. Lesion Formation and Clinical Manifestations

- **MS Lesions:** MRI imaging typically reveals multifocal lesions composed of demyelination, inflammation, and gliosis. These lesions vary in activity and distribution over time.
- **Clinical Presentation:** Symptoms are highly heterogeneous, depending on lesion location and CNS involvement. Common manifestations include sensory disturbances, motor weakness, spasticity, vision problems, fatigue, cognitive dysfunction, and mood disorders [41,43].

8. Oligodendrocyte Dysfunction and Myelin Repair

Oligodendrocytes are the myelin-producing cells of the central nervous system (CNS), responsible for insulating axons and ensuring efficient neural signal transmission. In multiple sclerosis (MS), oligodendrocyte damage leads to inadequate myelin production and impaired remyelination. Although the CNS possesses intrinsic capacity for remyelination, this process is often incomplete or ineffective in MS, contributing to progressive neurological dysfunction. The mechanisms influencing remyelination include the recruitment and differentiation of oligodendrocyte

progenitor cells (OPCs), the integrity of the inflammatory environment, and the presence of growth factors and signaling molecules. Enhancing remyelination has become a promising therapeutic target aimed at promoting functional recovery and halting disease progression [15,33,44].

9. Neurodegeneration and Brain Atrophy

- Neurodegenerative processes, alongside chronic inflammation and demyelination, significantly contribute to axonal degeneration in MS. Axonal loss is a key driver of irreversible neurological disability.
- Progressive brain atrophy—marked by a reduction in both gray and white matter volumes—is commonly observed in MS patients. It correlates strongly with disease duration, cognitive decline, and physical disability. Mechanistically, neurodegeneration in MS is multifactorial, involving mitochondrial dysfunction, glutamate excitotoxicity, oxidative stress, and diminished neurotrophic support [37,40].

10. Microglial Activation and Neuroinflammation

- Microglia are the resident immune cells of the CNS and play a pivotal role in immune surveillance and homeostasis. In MS, microglia become persistently activated, contributing to chronic neuroinflammation through the release of pro-inflammatory cytokines, antigen presentation, and phagocytosis of myelin debris.
- Sustained activation of microglia not only amplifies demyelination and axonal damage but also impedes repair mechanisms. Therefore, targeting microglial-mediated inflammation is a central goal in the development of neuroprotective therapies for MS [50,51].

11. Heterogeneity and Disease Course

- MS is a clinically heterogeneous disease, with significant inter-individual variability in symptoms, progression rate, and treatment response. This heterogeneity arises from a combination of genetic predispositions, environmental exposures, and diverse immune mechanisms.
- The disease can evolve through various clinical phenotypes, including relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and clinically isolated syndrome (CIS). Understanding the dynamic nature of MS is essential for the development of personalized therapeutic strategies [53,54].

12. Emerging Therapeutic Approaches

- Current disease-modifying therapies (DMTs) aim to modulate the immune response, reduce CNS inflammation, and potentially support remyelination and neuroprotection. Emerging strategies include selective depletion of B cells, inhibition of immune cell trafficking across the BBB, and enhancement of oligodendrocyte regeneration.
- In addition to immunomodulatory treatments, symptomatic and supportive care is vital for managing fatigue, spasticity, and cognitive dysfunction, and improving overall quality of life in MS patients [55,56].

4.2. The Experimental Autoimmune Encephalomyelitis (EAE) Model of MS

- Although no single animal model can fully replicate the human pathology of MS, experimental autoimmune encephalomyelitis (EAE) remains the most widely used and well-characterized model. EAE has provided critical insights into the immunopathogenesis of MS and is instrumental in the preclinical evaluation of novel therapeutic agents.
- The model exhibits a biphasic immune response, with distinct cellular recruitment patterns during the acute and chronic phases. Elevations in IL-1β levels during disease progression are associated with the recruitment of different immune cells, supporting the relevance of EAE in modeling the inflammatory milieu of MS [42,57].

Table 1. Immune Cell Involvement and Cytokine Profiles in Different Phases of EAE.

S. No.	Cell Type	MS Phase / Released Cytokine	Reference
1	Neutrophils	Acute Phase / IL-1β	[58]
2	Monocytes and Monocyte-Derived Macrophages (MDMs)	Acute Phase / IL-1β	[58]
3	T Helper Cells (Th17)	Chronic Phase / IL-1β	[59]
4	Microglia	Chronic Phase / IL-1β	[44]
5	Astrocytes	Chronic Phase / IL-1β	[60]
6	B Cells	Acute–Chronic and Secondary Progressive Phases	[49]
7	T Regulatory Cells (Tregs)	Chronic Phase – Remission / IL-10	[61,62]
8	B Regulatory Cells (Bregs)	Chronic Phase – Remission / IL-10 and IL-35	[48,63,64]

Nevertheless, there is some evidence that IL-1β plays a role in remyelination in addition to its pro-inflammatory effect. Researchers are beginning to believe that these advantageous functions may be attributed to the stimulatory

activity of IL-1β on the production and local release of trophic factors, such as insulin-like growth factor (IGF), by cells that participate in the demyelination process in the first place. The cytokine appears to be crucial for the aggregation, proliferation, and activation of oligodendrocyte progenitors around the areas of demyelination [65]. The temporal pattern of cytokine release and the cell types involved appear to be determinants of the apparent bipartite roles of IL-1β in immune cell recruitment and remyelination. It seems that during the acute phases of CNS inflammation, the first release of IL-1β encourages T and B cell recruitment; in the second stage, IL-1β appears to promote CNS repair [65,66]. (Please see Table 2 for more information on the major interleukins' roles in the pathophysiology of MS.).

Table 2. Interleukin Functions, Sources, and Activities in CNS Disorders (e.g., MS).

Interleukin (IL) Type	Primary Source(s)	Function	Cell Recruitment / Activity	References
IL-17	Th17 cells, $CD8^+$ T cells, Glial cells, Mucosal-associated invariant T cells, NK cells	Proinflammatory; promote acute inflammation	Recruitment of $CD4^+$ and $CD8^+$ T cells; neutrophil infiltration and CNS migration	[38,43, 65]
IL-1α	Microglial cells, Antigen-presenting cells (APCs)	Proinflammatory; inflammation from trauma	Recruitment of $CD4^+$ T cells	[41, 43]
IL-1β	Microglial cells, APCs	Proinflammatory; autoinflammatory and infection-related	Recruitment of $CD4^+$ T cells	[41, 43]
IL-23, IL-12, IL-2	APCs, Microglial cells, Monocyte-derived macrophages (MDMs)	Proinflammatory	Polarization of Th1/Th17 cells; CNS homing by autoreactive effector cells	[38-40, 66,67]
IL-10	Microglia/macrophages, Tr1 cells	Anti-inflammatory	Reduces $CD4^+$ T cell recruitment; promotes Treg cell expansion	[60, 68]
IL-2	Astrocytes	Anti-inflammatory	Regulation and recruitment of Treg cells	[60]
IL-1	Th1 $CD4^+$ T cells	Pro-remyelination	Differentiation and recruitment of oligodendrocyte progenitor cells (OPCs)	[61, 64, 70]
IL-2	Treg cells	Pro-remyelination	Differentiation and recruitment of OPCs	[60]

Role of Regulatory Adaptive Immune Cells in Multiple Sclerosis (MS)

1. Regulatory T Cells (Tregs)

Regulatory T cells (Tregs) are a specialized subset of $CD4^+$ T cells that maintain immune homeostasis and tolerance by suppressing autoreactive T cell responses. In the context of multiple sclerosis (MS), Tregs play a crucial role in modulating central nervous system (CNS) inflammation and autoimmunity. Xie et al. provided groundbreaking evidence of Tregs residing in the mouse brain, emphasizing their involvement in CNS immune surveillance and regulation of inflammatory responses. Their study demonstrated that Tregs mitigate lipopolysaccharide (LPS)-induced neuroinflammation—originating from microglia and macrophages—by secreting the anti-inflammatory cytokine IL-10, and by limiting $CD4^+$ T cell recruitment in experimental autoimmune encephalomyelitis (EAE), a murine model of MS [61]. Furthermore, recent reviews have explored the potential role of Tregs in oligodendrocyte biology. Dombrowski and colleagues reported that Treg-deficient mice exhibited significantly reduced oligodendrocyte progenitor cell (OPC) activation and differentiation, along with impaired remyelination, compared to wild-type or Treg-depleted mice. These findings suggest that Tregs may directly support remyelination by promoting oligodendrocyte maturation through the secretion of connective tissue growth factor CCN3. Thus, Tregs may not only act as immunoregulators but also facilitate CNS repair mechanisms.

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4. **Neuroprotective Strategies:** Neuroprotective interventions targeting oxidative stress, excitotoxicity, and mitochondrial dysfunction—using agents such as antioxidants and neurotrophic factors—may help preserve neuronal integrity and reduce disability accumulation in progressive MS.

DISCUSSION

This review aimed to synthesize recent findings on the role of neuroinflammation in the onset and progression of multiple sclerosis (MS), with a particular focus on the involvement of immune cells and cytokines across different disease stages. Our meta-analysis highlights that current research is heavily centered on elucidating the specific contributions of various immune cell populations and their secreted factors in the pathogenic cascades that sustain and exacerbate MS. While most studies have traditionally emphasized the roles of T helper cell subsets, emerging evidence has shifted attention toward cytotoxic CD8+ T cells. These cells appear to play a critical role, especially in the secondary progressive phase of MS, where their elevated presence around demyelinated lesions correlates with poorer clinical outcomes [74– 76]. Regarding B cells, their precise involvement remains somewhat ambiguous. Nonetheless, they are increasingly recognized as key contributors, primarily acting as professional antigen-presenting cells that facilitate the activation of cytotoxic T cells. Clinically, B cells hold diagnostic importance, as oligoclonal immunoglobulin bands detected in cerebrospinal fluid (CSF) remain the gold standard for MS diagnosis. Elevated levels of these bands during early disease stages are also associated with a more severe prognosis [49,72]. Current MS therapies predominantly aim to modulate the immune system to suppress neuroinflammation and minimize tissue damage. While these treatments effectively reduce relapse frequency, their efficacy in halting long-term disability progression remains limited. This underscores an urgent need for more targeted therapeutic approaches. Recent advances have focused on selectively targeting autoreactive immune cells and their mediators, showing promising improvements in efficacy and safety by avoiding broad immunosuppression. Strategies such as vaccine development and cytokine- or antigen-specific antibodies

are being actively explored as novel immunopharmacological interventions for MS [77]. However, further research is essential to fully understand the complex intercellular immune communications underlying MS pathology and neuroinflammation, which may ultimately lead to more precise and effective treatments.

CONCLUSION

Multiple sclerosis is fundamentally characterized by inflammatory demyelination of the central nervous system. Advances in our understanding of the intricate interplay between immune cells and cytokines during various disease stages— including acute inflammation, endogenous immune modulation, demyelination and remyelination, and recovery—necessitate a reappraisal of current anti-inflammatory therapies. Whereas T cells and cytokines were once viewed solely as drivers of pathology, they are now recognized as critical mediators of tissue repair and regeneration. These insights suggest that anti-inflammatory drugs and T cell inhibitors, while beneficial in controlling inflammation, may inadvertently hinder myelin repair processes. Consequently, therapeutic strategies should consider the disease stage to optimize outcomes: initial treatment should focus on suppressing peak inflammation, followed by interventions that promote regulatory T and B cell (Treg/Breg) activity to support remyelination and recovery during remission. Adopting such a stage-specific approach could pave the way for more effective management of MS, balancing inflammation control with regenerative support.

REFERENCES

1. Sospedra M., Martin R. Immunology of multiple sclerosis. *Annu. Rev. Immunol.* 2005; 23: 683–747. https://doi.org/10.1146/annurev.immunol.23.021704.115707
2. Dendrou C. A., Fugger L., Friese M. A. Immunopathology of multiple sclerosis. *Nat. Rev. Immunol.* 2015 Sep; 15(9):545–558. https://doi.org/10.1038/nri3871
3. Ransohoff R. M., Perry V. H. Microglial physiology: unique stimuli, specialized responses. *Annu. Rev. Immunol.* 2009; 27:119–145. https://doi.org/10.1146/annurev.immunol.021908.132528
4. Lassmann H., Bradl M. Multiple sclerosis: experimental models and reality. *Acta Neuropathol.* 2017 Feb; 133(2):223–244. https://doi.org/10.1007/s00401-016-1631-4
5. Sofroniew M. V., Vinters H. V. Astrocytes: biology and pathology. *Acta Neuropathol.* 2010 Jan; 119(1):7–35. https://doi.org/10.1007/s00401-009-0619-8
6. Verkhratsky A., Nedergaard M. Astroglial cradle in the life of the synapse. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 2014 May 5; 369(1654):20130595. https://doi.org/10.1098/rstb.2013.0595
7. Alvarez J. I., Cayrol R., Prat A. Disruption of central nervous system barriers in multiple sclerosis. *Biochim. Biophys. Acta.* 2011 Feb; 1812(2):252–264. https://doi.org/10.1016/j.bbadis.2010.06.017
8. Lemus N. H., Warrington A. E., Rodriguez M. Multiple sclerosis: mechanisms of disease and strategies for myelin and axonal repair. *Neurol. Clin.* 2018 Feb; 36(1):1–11. https://doi.org/10.1016/j.ncl.2017.08.002
9. Franklin R. J. M., Ffrench-Constant C. Remyelination in the CNS: from biology to therapy. *Nat. Rev. Neurosci.* 2008 Nov; 9(11):839–855. https://doi.org/10.1038/nrn2480
10. Haider L., Zrzavy T., Hametner S., et al. The topography of demyelination and neurodegeneration in the multiple sclerosis brain. *Brain.* 2016 Mar; 139(Pt 3):807–815. https://doi.org/10.1093/brain/awv398
11. Pilli D., Zou A., Tea F., Dale R. C., Brilot F. Expanding role of T cells in human autoimmune diseases of the central nervous system. *Front. Immunol.* 2017; 8:652. https://doi.org/10.3389/fimmu.2017.00652
12. Dendrou C. A., McVean G., Fugger L. Multiple sclerosis genetics. *Lancet Neurol.* 2017 Oct; 16(10):844–854. https://doi.org/10.1016/S1474-4422(17)30258-1
13. Green A. J., Gelfand J. M., Cree B. A., et al. Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomized, controlled, double-blind, crossover trial. *Lancet.* 2017 Dec 16; 390(10111):2481–2489. https://doi.org/10.1016/S0140-6736(17)32346-2
14. Hauser S., Goodwin D. Multiple sclerosis and other demyelinating diseases. In: Fauci A. S., Braunwald E., Kasper D. L., eds. *Harrison's Principles of Internal Medicine*. 17th ed. New York, NY: McGraw-Hill Medical; 2008:2611–2621.
15. Kuhlmann T., Goldschmidt T., Antel J., Wegner C., König F., Metz I., Brück W. Gender differences in the histopathology of MS? *J. Neurol. Sci.* 2009 Dec 15; 286(1–2):86–91. https://doi.org/10.1016/j.jns.2009.07.026
16. Huseby E. S., Kamimura D., Arima Y., Parello C. S., Sasaki K., Murakami M. Role of T cell–glial cell interactions in creating and amplifying central nervous system inflammation and multiple sclerosis disease symptoms. *Front. Cell. Neurosci.* 2015; 9:295. https://doi.org/10.3389/fncel.2015.00295.
17. Zuvich R. L., McCauley J. L., Oksenberg J. R., Sawcer S. J., de Jager P. L., Aubin C., Cross A. H., Piccio L., Aggarwal N. T., Evans D., et al. Genetic variation in the IL7RA/IL7 pathway increases multiple sclerosis susceptibility. *Hum. Genet.* 2010 Apr; 127(5):525–535. https://doi.org/10.1007/s00439-010-0785-4
18. Hafler D. A., Compston A., Sawcer S., Lander E. S., Daly M. J., de Jager P. L., de Bakker P. I., Gabriel S. B., Mirel D. B., Ivinson A. J. Risk alleles for multiple sclerosis identified by a genomewide study. *N. Engl. J. Med.* 2007 Aug 30; 357(9):851–862. https://doi.org/10.1056/NEJMoa073493

19. Field J., Shahijanian F., Schibeci S., Johnson L., Gresle M., Laverick L., Parnell G., Stewart G., McKay F., Kilpatrick T., et al. The MS risk allele of CD40 is associated with reduced cell-membrane bound expression in antigen presenting cells: Implications for gene function. *PLoS ONE.* 2015; 11:e0127080. https://doi.org/10.1371/journal.pone.0127080
20. Olsson T., Barcellos L. F., Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nat. Rev. Neurol.* 2016 Jan; 13(1):25–36. https://doi.org/10.1038/nrneurol.2016.187
21. van der Mei I., Lucas R., Taylor B., Valery P., Dwyer T., Kilpatrick T., Pender M., Williams D., Chapman C., Otahal P., et al. Population attributable fractions and joint effects of key risk factors for multiple sclerosis. *Mult. Scler. J.* 2016 Apr; 22(4):461–469. https://doi.org/10.1177/1352458515594042
22. Sundström P. Managing Epstein–Barr virus and other risk factors in MS—Future perspectives. *Acta Neurol. Scand.* 2017 Jan; 136(S200):31–33. https://doi.org/10.1111/ane.12793
23. Ontaneda D., Hyland M., Cohen J. A. Multiple sclerosis: New insights in pathogenesis and novel therapeutics. *Annu. Rev. Med.* 2012; 63:389–404. https://doi.org/10.1146/annurev-med-062610-095210
24. Stewart N., Simpson S., van der Mei I., Ponsonby A.-L., Blizzard L., Dwyer T., Pittas F., Eyles D., Ko P., Taylor B. V. Interferon-β and serum 25-hydroxyvitamin D interact to modulate relapse risk in MS. *Neurology.* 2012 Jul 17; 79(3):254–260. https://doi.org/10.1212/WNL.0b013e31825fdf01
25. Runia T. F., Hop W. C., de Rijke Y. B., Buljevac D., Hintzen R. Q. Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis. *Neurology.* 2012 Jul 17; 79(3):261–266. https://doi.org/10.1212/WNL.0b013e31825fdf24
26. Simpson S., van der Mei I., Stewart G., Ponsonby A.-L., Dwyer T., Taylor B. Increasing levels of serum vitamin D are associated with lower rates of relapse in multiple sclerosis. *J. Clin. Neurosci.* 2009 Dec; 16(12):1520–1526. https://doi.org/10.1016/j.jocn.2008.12.003
27. Correale J., Farez M. F., Gaitán M. I. Environmental factors influencing multiple sclerosis in Latin America. *Mult. Scler. J. Exp. Transl. Clin.* 2017; 3:2055217317715049. https://doi.org/10.1177/2055217317715049
28. Libbey E. J., Fujinami R. S. Potential triggers of MS. In: *Molecular Basis of Multiple Sclerosis. Results Probl. Cell Differ.* 2009; 51:21–42. https://doi.org/10.1007/400_2009_16
29. McCoy L., Tsunoda I., Fujinami R. S. Multiple sclerosis and virus-induced immune responses: Autoimmunity can be primed by molecular mimicry and augmented by bystander activation. *Autoimmunity.* 2006 Feb; 39(1):9–19. https://doi.org/10.1080/08916930500484784
30. Goldenberg M. M. Multiple sclerosis review. *Pharm. Ther.* 2012 Mar; 37(3):175–184. [PMCID: PMC3351877]
31. Crawford M. P., Yan S. X., Ortega S. B., Mehta R. S., Hewitt R. E., Price D. A., Stastny P., Douek D. C., Koup R. A., Racke M. K., et al. High prevalence of autoreactive, neuroantigen-specific CD8+ T cells in multiple sclerosis revealed by novel flow cytometric assay. *Blood.* 2004 Jun 1; 103(10):4222–4231. https://doi.org/10.1182/blood-2003-09-3078
32. Pette M., Fujita K., Wilkinson D., Altmann D. M., Trowsdale J., Giegerich G., Hinkkanen A., Epplen J. T., Kappos L., Wekerle H. Myelin autoreactivity in multiple sclerosis: Recognition of myelin basic protein in the context of HLA-DR2 products by T lymphocytes of multiple-sclerosis patients and healthy donors. *Proc. Natl. Acad. Sci. USA.* 1990 Oct; 87(19):7968–7972. https://doi.org/10.1073/pnas.87.20.7968
33. Cua D. J., Sherlock J., Chen Y., Murphy C. A., Joyce B., Seymour B., Lucian L., To W., Kwan S., Churakova T., et al. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature.* 2003 Jan 30; 421(6924):744–748. https://doi.org/10.1038/nature01355
34. Langrish C. L., Chen Y., Blumenschein W. M., Mattson J., Basham B., Sedgwick J. D., McClanahan T., Kastelein R. A., Cua D. J. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J. Exp. Med.* 2005 Jan 17; 201(2):233–240. https://doi.org/10.1084/jem.20041257
35. Mangan P. R., Harrington L. E., O'Quinn D. B., Helms W. S., Bullard D. C., Elson C. O., Hatton R. D., Wahl S. M., Schoeb T. R., Weaver C. T. Transforming growth factor-β induces development of the TH17 lineage. *Nature.* 2006 May 11; 441(7090):231–234. https://doi.org/10.1038/nature04754
36. Bielekova B., Sung M.-H., Kadom N., Simon R., McFarland H., Martin R. Expansion and functional relevance of high-avidity myelin-specific CD4$^+$ T cells in multiple sclerosis. *J. Immunol.* 2004 Mar 15; 172(6):3893–3904. https://doi.org/10.4049/jimmunol.172.6.3893
37. Zhang J., Markovic-Plese S., Lacet B., Raus J., Weiner H. L., Hafler D. A. Increased frequency of interleukin 2-responsive T cells specific for myelin basic protein and proteolipid protein in peripheral blood and cerebrospinal fluid of patients with multiple sclerosis. *J. Exp. Med.* 1994 Mar 1; 179(3):973–984. https://doi.org/10.1084/jem.179.3.973
38. Tzartos J.S., Friese M.A., Craner M.J., Palace J., Newcombe J., Esiri M.M., Fugger L. Interleukin-17 production in central nervous system-infiltrating T cells and glial cells is associated with active disease in multiple sclerosis. *Am. J. Pathol.* 2008 Feb; 172(1):146– 155. https://doi.org/10.2353/ajpath.2008.070494
39. Kebir H., Kreymborg K., Ifergan I., Dodelet-Devillers A., Cayrol R., Bernard M., Giuliani F., Arbour N., Becher B., Prat A. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nat. Med.* 2007 Sep; 13(9):1173–1175. https://doi.org/10.1038/nm1656

40. Pare A., Mailhot B., Levesque S.A., Lacroix S. Involvement of the IL-1 system in experimental autoimmune encephalomyelitis and multiple sclerosis: Breaking the vicious cycle between IL-1β and GM-CSF. *Brain Behav. Immun.* 2017 Aug; 62:1–8. https://doi.org/10.1016/j.bbi.2017.01.003
41. Dinarello C.A. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood* 2011 Sep; 117(14):3720–3732. https://doi.org/10.1182/blood-2010-07-273417
42. Lévesque S.A., Paré A., Mailhot B., Bellver-Landete V., Kébir H., Lécuyer M.-A., Alvarez J.I., Prat A., Vaccari J.P.d.R., Keane R.W., et al. Myeloid cell transmigration across the CNS vasculature triggers IL-1β–driven neuroinflammation during autoimmune encephalomyelitis in mice. *J. Exp. Med.* 2016 Apr; 213(5):929–949. https://doi.org/10.1084/jem.20151437
43. Waldner H., Collins M., Kuchroo V.K. Activation of antigen-presenting cells by microbial products breaks self tolerance and induces autoimmune disease. *J. Clin. Investig.* 2004 Jul; 113(7): 990– 997. https://doi.org/10.1172/JCI20500
44. Junker A., Malotka J., Eiglmeier I., Lassmann H., Wekerle H., Meinl E., Hohlfeld R., Dornmair K. Multiple sclerosis: T-cell receptor expression in distinct brain regions. *Brain* 2007 Nov; 130(Pt 11):2789– 2799. https://doi.org/10.1093/brain/awm187
45. Babbe H., Roers A., Waisman A., Lassmann H., Goebels N., Hohlfeld R., Friese M., Schröder R., Deckert M., Schmidt S., Ravid R., et al. Clonal expansions of CD8+ T cells dominate the T cell infiltrate in active multiple sclerosis lesions as shown by micromanipulation and single cell polymerase chain reaction. *J. Exp. Med.* 2000 Aug; 192(3):393– 404. https://doi.org/10.1084/jem.192.3.393
46. Egwuagu E.C., Yu C.R. Interleukin 35-producing B Cells (i35-Breg): A new mediator of regulatory B-cell functions in CNS autoimmune diseases. *Crit. Rev. Immunol.* 2015; 35(1):49– 57. https://doi.org/10.1615/CritRevImmunol.2015012820
47. Staun-Ram E., Miller A. Effector and regulatory B cells in multiple sclerosis. *Clin. Immunol.* 2017 Dec; 184:11– 25. https://doi.org/10.1016/j.clim.2017.07.015
48. Constantinescu C.S., Aram J., Tanasescu R., Morandi E., Frakich N., Spendlove I., Gran B. Expression and regulation of GMCSF in immune cell subsets in MS (P1.391). *Neurology* 2017 Apr; 88 (Suppl. 16): P1.391. https://doi.org/10.1212/WNL.0000000000004063
49. Li R., Rezk A., Miyazaki Y., Hilgenberg E., Touil H., Shen P., Moore C.S., Michel L., Althekair F., Rajasekharan S., et al. Proinflammatory GM-CSF– producing B cells in multiple sclerosis and B cell depletion therapy. *Sci. Transl. Med.* 2015 Nov; 7(310):310ra166. https://doi.org/10.1126/scitranslmed.aab4176
50. Steinman L., Martin R., Bernard C., Conlon P., Oksenberg J.R. Multiple sclerosis: Deeper understanding of its pathogenesis reveals new targets for therapy. *Annu. Rev. Neurosci.* 2002; 25:491– 505. https://doi.org/10.1146/annurev.neuro.25.112701.142802
51. Pröbstel A.-K., Sanderson N., Derfuss T. B cells and autoantibodies in multiple sclerosis. Int. J. Mol. Sci. 2015 Dec; 16(8):16576– 16592. https://doi.org/10.3390/ijms160816576
52. Barr T.A., Shen P., Brown S., Lampropoulou V., Roch T., Lawrie S., Fan B., O' Connor R.A., Anderton S.M., Bar-Or A., et al. B cell depletion therapy ameliorates autoimmune disease through ablation of IL-6-producing B cells. *J. Exp. Med.* 2012 May; 209(5):1001– 1010. https://doi.org/10.1084/jem.20111675
53. Duddy M., Niino M., Adatia F., Hebert S., Freedman M., Atkins H., Kim H.J., Bar-Or A. Distinct effector cytokine profiles of memory and naive human B cell subsets and implication in multiple sclerosis. *J. Immunol.* 2007 Jul; 178(10):6092– 6099. https://doi.org/10.4049/jimmunol.178.10.6092
54. Guerrier T., Labalette M., Launay D., Lee-Chang C., Outteryck O., Lefevre G., Vermersch P., Dubucquoi S., Zephir H. Proinflammatory B-cell profile in the early phases of MS predicts an active disease. *Neurol. Neuroimmunol. Neuroinflamm.* 2018 Sep; 5(5): e431. https://doi.org/10.1212/NXI.0000000000000431
55. Robinson A.P., Harp C.T., Noronha A., Miller S.D. The experimental autoimmune encephalomyelitis (EAE) model of MS: Utility for understanding disease pathophysiology and treatment. *Handb. Clin. Neurol.* 2014; 122: 173– 189. https://doi.org/10.1016/B978-0-444-52001-2.00009-7
56. Aubé B., Lévesque S.A., Paré A., Chamma É., Kébir H., Gorina R., Lécuyer M.-A., Alvarez J.I., de Koninck Y., Engelhardt B., et al. Neutrophils mediate blood– spinal cord barrier disruption in demyelinating neuroinflammatory diseases. *J. Immunol.* 2014 Mar 1; 193(5): 2438– 2454. https://doi.org/10.4049/jimmunol.1400205
57. Martin B.N., Wang C., Zhang C.-J., Kang Z., Gulen M.F., Zepp J.A., Zhao J., Bian G., Do J.-S., Min B., et al. T cell– intrinsic ASC critically promotes TH17-mediated experimental autoimmune encephalomyelitis. *Nat. Immunol.* 2016 Jun; 17(6): 583– 592. https://doi.org/10.1038/ni.3429
58. Mayo L., Trauger S.A., Blain M., Nadeau M., Patel B., Alvarez J.I., Mascanfroni I.D., Yeste A., Kivisäkk P., Kallas K., et al. Regulation of astrocyte activation by glycolipids drives chronic CNS inflammation. *Nat. Med.* 2014 Oct; 20(10): 1147– 1155. https://doi.org/10.1038/nm.3707
59. Xie L., Choudhury G.R., Winters A., Yang S.-H., Jin K. Cerebral regulatory T cells restrain microglia/macrophage-mediated inflammatory responses via IL-10. *Eur. J. Immunol.* 2015 Jan; 45(1):180– 191. https://doi.org/10.1002/eji.201444651

60. Dombrowski Y., OHagan T., Dittmer M., Penalva R., Mayoral S.R., Bankhead P., Fleville S., Eleftheriadis G., Zhao C., Naughton M., et al. Regulatory T cells promote myelin regeneration in the central nervous system. *Nat. Neurosci.* 2017 Jun; 20(6): 674– 680. https://doi.org/10.1038/nn.4547
61. Wang R.X., Yu C.R., Dambuza I.M., Mahdi R.M., Dolinska M.B., Sergeev Y.V., Wingfield P.T., Kim S.H., Egwuagu C.E. Interleukin-35 induces regulatory B cells that suppress autoimmune disease. *Nat. Med.* 2014 May; 20(5): 633– 641. https://doi.org/10.1038/nm.3554
62. Shen P., Li R., Jouneau L., Boudinot P., Wilantri S., Sakwa I., Miyazaki Y., Leech M.D., McPherson R.C., Wirtz S., et al. IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. *Nature* 2014 Mar 13; 507(7492): 366– 370. https://doi.org/10.1038/nature12979
63. Mason J.L., Suzuki K., Chaplin D.D., Matsushima G.K. Interleukin-1β promotes repair of the CNS. *J. Neurosci.* 2001 Aug 1; 21(15): 7046–7052. https://doi.org/10.1523/JNEUROSCI.21-15-07046.2001
64. Mendiola S.A., Cardona A.E. The IL-1beta phenomena in neuroinflammatory diseases. *J. Neural Transm.* (Vienna) 2017 Sep; 124(9): 1179– 1191. https://doi.org/10.1007/s00702-017-1733-0
65. Ellwardt E., Walsh J.T., Kipnis J., Zipp F. Understanding the role of T cells in CNS homeostasis. *Trends Immunol.* 2016 Mar; 37(3): 154– 165. https://doi.org/10.1016/j.it.2015.12.006
66. Gyulveszi G., Haak S., Becher B. IL-23-driven encephalo-tropism and Th17 polarization during CNS-inflammation *in vivo*. *Eur. J. Immunol.* 2009 Jul; 39(7): 1864– 1869. https://doi.org/10.1002/eji.200839140
67. Segal B.M. Getting to the crux of the matter: IL-23 and Th17 cell accumulation in the CNS. *Eur. J. Immunol.* 2009 Jul;39(7):1713– 1715. https://doi.org/10.1002/eji.200939614
68. Ma A., Xiong Z., Hu Y., Qi S., Song L., Dun H., Zhang L., Lou D., Yang P., Zhao Z., et al. Dysfunction of IL-10-producing type 1 regulatory T cells and CD4(+)CD25(+) regulatory T cells in a mimic model of human multiple sclerosis in Cynomolgus monkeys. *Int. Immunopharmacol.* 2009 Apr; 9(4): 599– 608. https://doi.org/10.1016/j.intimp.2009.01.009
69. Vela J.M., Molina-Holgado E., Arévalo-Martín Á., Almazán G., Guaza C. Interleukin-1 regulates proliferation and differentiation of oligodendrocyte progenitor cells. *Mol. Cell. Neurosci.* 2002 Jun; 20(3):489– 502. https://doi.org/10.1006/mcne.2002.1163
70. Miron V.E. Beyond immunomodulation: The regenerative role for regulatory T cells in central nervous system remyelination. *J. Cell Commun. Signal.* 2017 Mar;11(2):191– 192. https://doi.org/10.1007/s12079-017-0399-x
71. Okada Y., Ochi H., Fujii C., Hashi Y., Hamatani M., Ashida S., Kawamura K., Kusaka H., Matsumoto S., Nakagawa M., et al. Signaling via toll-like receptor 4 and CD40 in B cells plays a regulatory role in the pathogenesis of multiple sclerosis through interleukin-10 production. *J. Autoimmun.* 2017 Dec; 84: 16– 24. https://doi.org/10.1016/j.jaut.2017.09.004
72. Moore C.S., Cui Q.L., Warsi N.M., Durafourt B.A., Zorko N., Owen D.R., Antel J.P., Bar-Or A. Direct and indirect effects of immune and central nervous system-resident cells on human oligodendrocyte progenitor cell differentiation. *J. Immunol.* 2015 Jan 15; 194(2):761– 772. https://doi.org/10.4049/jimmunol.1401105
73. Sinha S., Itani F.R., Karandikar N.J. Immune regulation of multiple sclerosis by CD8+ T cells. *Immunol. Res.* 2014 Oct; 59(1-3):254– 265. https://doi.org/10.1007/s12026-014-8547-7
74. Kashi P.V., Ortega S.B., Karandikar N.J. Neuroantigen-specific autoregulatory CD8+ T cells inhibit autoimmune demyelination through modulation of dendritic cell function. *PLoS ONE*. 2014 Sep 30; 9(9): e105763. https://doi.org/10.1371/journal.pone.0105763
75. El Behi M., Sanson C., Bachelin C., Guillot-Noel L., Fransson J., Stankoff B., Maillart E., Sarrazin N., Guillemot V., Abdi H., et al. Adaptive human immunity drives remyelination in a mouse model of demyelination. *Brain.* 2017 Apr 1; 140(4): 967– 980. https://doi.org/10.1093/brain/awx010
76. Farjam M., Zhang G.X., Ciric B., Rostami A. Emerging immunopharmacological targets in multiple sclerosis. *J. Neurol. Sci.* 2015 Sep 15; 358(1-2): 22– 30. https://doi.org/10.1016/j.jns.2015.07.036
77. Lee D.-H., Lee J.-Y., Hong D.-Y., Lee E.-C., Park S.-W., Lee Y.-K., Oh J.-S. Pharmacological treatment for neuroinflammation in stress-related disorder. *Biomedicines.* 2022 Oct 17; 10(10):2518. https://doi.org/10.3390/biomedicines10102518