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REVIEW ARTICLES

# *Oligodendrocyte Injury in Multiple Sclerosis*

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## *Abstract*

***Introduction:*** Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system (CNS), marked by inflammation, demyelination, and significant oligodendrocyte injury. This disease arises from a complex interplay of genetic predispositions and environmental triggers that drive immune-mediated damage to oligodendrocytes and myelin proteins.

This research paper explores the multifaceted aspects of oligodendrocyte injury in MS, ranging from underlying pathophysiological mechanisms to potential therapeutic interventions and translational implications for clinical practice.

Oligodendrocyte damage in MS occurs via multiple mechanisms, including metabolic stress, oxidative damage, and cytokine-induced apoptosis, mainly mediated by interferon-gamma (IFN-γ) signaling. This process exacerbates neuroinflammation and contributes to disease progression. Emerging therapeutic strategies, such as targeting metabolic pathways, reducing oxidative stress, and enhancing autophagy, have demonstrated potential in preclinical studies. Furthermore, stem cell therapies are being explored for their ability to regenerate oligodendrocytes and restore myelin integrity.

***Conclusions:*** The intricate interplay among oligodendrocyte injury, demyelination, and neuroinflammation is central to multiple sclerosis (MS) pathogenesis. Oligodendrocytes safeguard myelin in the CNS, facing challenges from immune attacks to metabolic stress. Understanding oligodendrocyte dysfunction is vital for targeted therapies that suppress immune damage and promote remyelination and CNS repair. MS's etiology,

***Keywords:*** Multiple sclerosis, oligodendrocytes, neuroinflammation, neurodegeneration, demyelination, immune system, apoptosis, cellular metabolism.

## *Introduction*

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) characterized by demyelination, inflammation, and neurodegeneration[6]. It affects over 2.3million people worldwide[7], leading to significant disability and reduced quality of life. The hallmark pathological feature of MS is the destruction of myelin sheaths, primarily by immune-mediated mechanisms targeting oligodendrocytes[8], the cells responsible for myelin synthesis and maintenance. This introduction section will provide an overview of MS epidemiology, clinical manifestations, and the central role of oligodendrocyte injury in disease pathogenesis.

The clinical course of MS is highly variable, ranging from relapsing-remitting to progressive forms, each with unique clinical manifestations and disease progression patterns. Despite advancements in understanding MS pathophysiology and therapeutic interventions, significant challenges remain in managing disease progression and improving long-term patient outcomes.

The central pathological feature of MS is the destruction of myelin, the protective sheath surrounding axons in the CNS[9], leading to impaired nerve conduction and neurological dysfunction. Oligodendrocytes, the myelin-producing cells of the CNS, play a pivotal role in maintaining myelin integrity and neuronal function.[10]

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However, in MS, oligodendrocytes become targets of autoimmune attacks, resulting in their injury, apoptosis, and demyelination.[10] This dysregulated immune response, characterized by infiltrating immune cells into the CNS and activating pro-inflammatory pathways, contributes to the heterogeneous clinical presentation and disease progression observed in MS patients.[11]

Understanding the intricate interplay between immune dysregulation, oligodendrocyte injury, and neuroinflammation is essential for developing targeted therapies that modulate disease activity, preserve neuronal function, and promote remyelination.

This research paper explores the multifaceted aspects of oligodendrocyte injury in MS, ranging from underlying pathophysiological mechanisms to potential therapeutic interventions and translational implications for clinical practice.

## *Methodologies*

This review employed a combination of narrative and critical review methodologies to explore the multifaceted aspects of multiple sclerosis (MS) and oligodendrocyte injury. The narrative review approach was utilized to provide a qualitative summary and interpretation of the existing literature on MS epidemiology, clinical manifestations, etiology, immune dysregulation, and the central role of oligodendrocytes in disease pathogenesis. This narrative approach presented a comprehensive overview of the topic, integrating various theories, mechanisms, and therapeutic strategies related to MS and oligodendrocyte dysfunction.

Additionally, a critical review methodology was applied to analyze the literature's strengths and weaknesses, identify gaps in knowledge, and evaluate the complexities of MS etiology and oligodendrocyte injury. This critical analysis encompassed discussions on the heterogeneity of MS phenotypes, the impact of genetic and environmental factors, and the challenges in developing targeted therapies for MS patients. Emphasis was placed on assessing the quality of evidence, addressing conflicting viewpoints, and highlighting areas for future research and advancements in the field.

The integration of narrative and critical review methodologies allowed for a comprehensive exploration of the literature, providing insights into the diverse aspects of MS pathophysiology, oligodendrocyte function, immune responses, and therapeutic interventions. This approach facilitated a nuanced understanding of the complexities surrounding MS and oligodendrocyte injury, contributing to the broader discourse on neurological disorders and therapeutic strategies.

## *Etiology*

The etiology of MS is multifactorial, involving a complex interplay of genetic, environmental, and immunological factors. Genetic susceptibility, particularly within the major histocompatibility complex (MHC) region, predisposes individuals to MS[12]. Environmental triggers such as viral infections, vitamin D deficiency, and smoking can also influence disease risk[13]. This section will delve into the various factors contributing to MS development and the mechanisms by which they interact to initiate and propagate disease pathology.

Multiple sclerosis (MS) is widely recognized as an autoimmune disorder with a complex etiology influenced by genetic, environmental, and immunological factors. [14]Genetic susceptibility plays a significant role in MS, as evidenced by familial clustering and genome-wide association studies (GWAS) identifying susceptibility loci within the MHC region, specifically the HLA-DRB1 gene[15]. Variants in other genes, such as those involved in immune regulation (e.g., IL2RA, CD40), vitamin D metabolism (e.g., CYP27B1), and myelin biology (e.g., MOG, MAG), also contribute to MS risk and pathogenesis.[16]

Environmental factors further modulate MS risk and disease course. Viral infections, particularly Epstein-Barr virus (EBV) and human herpesvirus 6 (HHV-6), have been implicated in MS pathogenesis, possibly triggering aberrant immune responses and promoting autoimmunity[17]. Low vitamin D levels, commonly observed in MS patients, are associated with increased disease susceptibility and severity, possibly due to its immunomodulatory effects and role in regulating T-cell responses.[16] Other environmental factors, such as smoking, diet, and exposure to pollutants, may also contribute to MS risk and disease progression.[18]

The immunological basis of MS centers on dysregulated immune responses targeting CNS antigens, particularly myelin proteins such as myelin essential protein (MBP), proteolipid protein (PLP), and myelin oligodendrocyte glycoprotein (MOG)[19]. Autoreactive T cells, primarily of the CD4+ Th1 and Th17 subsets, infiltrate the CNS and initiate inflammatory cascades, leading to oligodendrocyte injury, demyelination, and neuroinflammation.[20]

B cells, plasma cells, and innate immune cells (e.g., macrophages, microglia) also contribute to MS pathology through antibody production, cytokine release[21], and phagocytosis of myelin debris.

The complex interplay between genetic predisposition, environmental triggers, and immune dysregulation shapes the heterogeneity of MS phenotypes, including relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS)[22]. Understanding the etiological factors driving MS pathogenesis is crucial for identifying biomarkers of disease activity, predicting disease progression, and developing targeted therapeutic strategies tailored to individual patient profiles. Ongoing research efforts, including large-scale genomic studies, environmental epidemiology investigations, and immunological studies, continue to elucidate the multifactorial nature of MS etiology and inform precision medicine approaches for improved patient outcomes[23].

## Role of Interferon-Gamma Signaling

Interferon-gamma (IFN-γ) is a key cytokine implicated in MS pathogenesis[24]. It modulates immune responses and directly impacts oligodendrocyte function and survival. This section will discuss the role of IFN-γ signaling in promoting oligodendrocyte injury, exacerbating neuroinflammation, and modulating the disease course in MS and experimental models.

Interferon-gamma (IFN-γ) is a pro-inflammatory cytokine produced by activated T cells, natural killer (NK) cells, and macrophages, playing a central role in immune responses and inflammation[25]. In multiple sclerosis (MS), IFN-γ drives neuroinflammation, promotes oligodendrocyte injury, and modulates disease progression. The effects of IFN-γ signaling in MS pathology involve direct and indirect mechanisms that impact CNS homeostasis and immune regulation.[2]

IFN-γ can induce oligodendrocyte apoptosis and inhibit myelin gene expression, impairing myelin production and maintenance[26].

IFN-γ-mediated signaling pathways, including Janus kinase-signal transducer and activator of transcription (JAK-STAT) and mitogen-activated protein kinase (MAPK) pathways, regulate gene expression profiles in oligodendrocytes, influencing cell survival, differentiation, and myelin synthesis.[27]

Chronic exposure to IFN-γ in MS lesions contributes to oligodendrocyte dysfunction and demyelination, exacerbating neurological deficits in affected individuals.[13]

Indirectly, IFN-γ modulates immune responses and neuroinflammation in the CNS microenvironment. It enhances antigen presentation by microglia and macrophages, promotes T-cell activation and differentiation, and amplifies pro-inflammatory cytokine production, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α)[13].

The sustained inflammatory milieu driven by IFN-γ contributes to tissue damage, axonal injury, and glial activation, further propagating neurodegeneration and disease progression in MS. [28]Experimental studies using animal models of MS, such as experimental autoimmune encephalomyelitis (EAE), have demonstrated the critical role of IFN-γ signaling in driving disease pathogenesis and severity[29].

Blockade of IFN-γ or its downstream signaling pathways has shown therapeutic efficacy in ameliorating EAE symptoms, reducing CNS inflammation, and preserving myelin integrity[30]. However, the clinical translation of IFN-γ-targeted therapies in MS patients has been challenging, highlighting the complexity of immune regulation and the need for personalized treatment approaches.

The dynamic interplay between IFN-γ signaling, immune dysregulation, and oligodendrocyte injury underscores the importance of understanding cytokine-mediated pathways in MS pathophysiology. Targeting IFN-γ and its downstream effectors represents a potential therapeutic strategy for modulating neuroinflammation, preserving oligodendrocyte function, and promoting remyelination in MS.[31]

Future research efforts to unravel the intricacies of IFN-γ signaling in CNS immune responses and disease progression will contribute to advancing precision medicine approaches for MS patients.

## Heterogeneity of Oligodendrocyte Injury

Oligodendrocyte injury in MS exhibits heterogeneity across disease stages, lesion types, and CNS regions.[32]

Acute inflammatory demyelination leads to rapid oligodendrocyte death and myelin breakdown, while chronic demyelinated lesions may show ongoing oligodendrocyte loss alongside attempts at remyelination[33]. This section will explore the diverse patterns of oligodendrocyte injury observed in MS pathology, including differences in lesion activity, remyelination capacity, and clinical implications.

Oligodendrocyte injury in multiple sclerosis (MS) is characterized by its heterogeneous nature, encompassing a spectrum of pathological changes that vary across disease stages, lesion types, and CNS regions[34]. This heterogeneity contributes to the diverse clinical manifestations and disease courses observed in MS patients, ranging from relapsing-remitting to progressive forms of the disease.[35]

Acute inflammatory demyelination represents one aspect of oligodendrocyte injury in MS, characterized by rapid myelin breakdown and oligodendrocyte death in active lesions.[36]Immune-mediated attacks, primarily driven by autoreactive T cells and pro-inflammatory cytokines, destroy myelin sheaths and subsequent axonal injury.[37] The acute demyelination phase is associated with clinical relapses and neurological deficits, reflecting the focal nature of inflammatory activity within the CNS.[38]

Chronic demyelinated lesions exhibit distinct features of oligodendrocyte injury, characterized by ongoing tissue damage, gliosis, and remyelination attempts.[39]

In chronically demyelinated areas, oligodendrocyte loss may persist despite reduced inflammatory activity, leading to persistent axonal dysfunction and neurodegeneration.[40] The balance between demyelination and remyelination processes influences disease progression and clinical outcomes in MS patients.[41]

The heterogeneity of oligodendrocyte injury extends beyond lesion activity to include variations in remyelination capacity and regenerative potential.[42] Some MS lesions demonstrate robust remyelination by recruiting oligodendrocyte precursor cells (OPCs) and successful myelin repair, contributing to functional recovery and neurological preservation.[42] In contrast, other lesions exhibit limited remyelination and chronic demyelination, resulting in progressive disability and neurologic impairment.[42]

The clinical implications of oligodendrocyte injury heterogeneity in MS underscore the need for personalized treatment strategies that target specific disease mechanisms and stages. Biomarkers of lesion activity, remyelination status, and neurodegeneration can aid in disease monitoring and therapeutic decision-making, optimizing patient outcomes and treatment responses.[43] Future research efforts focused on understanding the factors influencing oligodendrocyte injury heterogeneity and promoting regenerative processes will contribute to advancing precision medicine approaches for MS patients.[44]

## *Regeneration and Repair Strategies*

Promoting oligodendrocyte regeneration and myelin repair is a primary therapeutic goal in MS research. This section will review current strategies to enhance remyelination, such as promoting oligodendrocyte precursor cell differentiation, modulating myelin regulatory factors, and targeting inhibitory factors in the CNS microenvironment. Emerging regenerative approaches, including stem cell therapies and gene editing techniques, will also be discussed, as they can potentially restore myelin integrity in MS patients.

Oligodendrocyte regeneration and myelin repair are crucial aspects of disease modification in multiple sclerosis (MS), aiming to restore neuronal function and preserve CNS integrity. Current therapeutic strategies for enhancing remyelination encompass a range of approaches targeting oligodendrocyte precursor cells (OPCs), myelin regulatory factors, and inhibitory factors within the CNS microenvironment.[45]

Promoting OPC differentiation into mature oligodendrocytes represents a key strategy for enhancing remyelination in MS lesionsSkaper[46]

OPCs are abundant in the adult CNS[47] and can differentiate into myelinating oligodendrocytes[48] in response to demyelinating stimuli. Promoting OPC recruitment, proliferation, and differentiation through growth factors (e.g., brain-derived neurotrophic factor, insulin-like growth factor-1), small molecules (e.g., retinoids, thyroid hormones), and epigenetic modulators (e.g., histone deacetylase inhibitors) can stimulate remyelination and improve neurological outcomes in preclinical models.[49]

Modulating myelin regulatory factors, such as myelin-associated inhibitors and signaling pathways, represents another approach for promoting oligodendrocyte regeneration and myelin repair in MS. [50]

Inhibitory factors, such as Nogo-A, myelin-associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMgp), limit axonal regeneration and remyelination in MS lesions.[51] Targeting these inhibitors using monoclonal antibodies, decoy receptors, or small molecule inhibitors can overcome growth inhibition and facilitate axonal remyelination.[52]

In addition to promoting oligodendrocyte regeneration, targeting inhibitory factors in the CNS microenvironment is critical for enhancing remyelination in MS.[53]The inflammatory milieu in MS lesions, characterized by pro-inflammatory cytokines, chemokines, and reactive oxygen species (ROS), creates a hostile environment for oligodendrocyte survival and myelin repair.[21]

Anti-inflammatory agents, antioxidants, and immunomodulatory therapies can mitigate neuroinflammation, reduce oxidative stress, and create a permissive environment for remyelination processes[54]

Emerging regenerative approaches, including stem cell therapies, hold promise for restoring myelin integrity and promoting functional recovery in MS patients.[55]

Stem cell-based therapies offer potential remyelinating cells and neuroprotective factors, such as mesenchymal stem cell transplantation, neural stem cell grafts, and induced pluripotent stem cells (iPSCs) [56]. Gene editing technologies, such as CRISPR-Cas9, enable targeted modifications of oligodendrocyte genes involved in myelin synthesis, repair, and regeneration.[57]

Despite the progress in regenerative strategies for MS, challenges remain in translating preclinical findings into effective clinical therapies. Optimizing cell delivery, ensuring long-term safety and efficacy, and addressing immune-mediated responses to transplanted cells are ongoing areas of research and development. Integrating regenerative approaches with immunomodulatory therapies and neuroprotective strategies represents a comprehensive approach to enhancing remyelination and improving outcomes in MS patients.

## *Immunomodulatory Therapies*

Immunomodulatory therapies represent the cornerstone of MS treatment, aiming to suppress autoimmune attacks while preserving oligodendrocyte function and promoting repair processes. This section will overview current disease-modifying therapies (DMTs), including interferon-beta, glatiramer acetate, and monoclonal antibodies targeting immune cells or cytokines. The role of immunomodulatory agents in mitigating oligodendrocyte injury and supporting remyelination will be examined, along with emerging immunotherapeutic strategies under investigation.

Immunomodulatory therapies are crucial in managing disease activity, reducing relapses, and slowing disease progression in multiple sclerosis (MS) patients. These therapies target immune system components involved in autoimmune responses against oligodendrocytes and myelin, aiming to suppress inflammation, modulate immune cell function, and promote CNS repair processes.[58]

Interferon-beta (IFN-β) is one of the first-line immunomodulatory therapies approved for relapsing-remitting MS (RRMS).[59] It exerts anti-inflammatory effects by inhibiting pro-inflammatory cytokine production, enhancing anti-inflammatory cytokines, and modulating immune cell activation and migration.[60] IFN-β therapies reduce relapse rates, delay disease progression, and have a favorable safety profile in MS patients, making them widely used in clinical practice.[60]

Glatiramer acetate is another immunomodulatory agent approved for RRMS, acting as a synthetic polypeptide that mimics myelinantigens.[60] Glatiramer acetate modulates immune responses by inducing regulatory T cells, shifting the immune balance toward an anti-inflammatory state, and reducing autoimmune attacks against oligodendrocytes.[61] It is well-tolerated, with efficacy in reducing relapse rates and MRI lesion burden in MS patients.[61]

Monoclonal antibodies targeting immune cells or cytokines represent a more targeted approach to immunomodulation in MS.[62]

Natalizumab, a monoclonal antibody against α4-integrin, inhibits immune cell migration into the CNS, reducing inflammatory infiltrates and relapse rates in RRMS patients.[63] Alemtuzumab, targeting CD52 on lymphocytes, depletes autoreactive T and B cells, leading to sustained remission and disease stabilization in RRMS and active SPMS patients.[64]

Emerging immunotherapeutic strategies focus on modulating specific immune pathways implicated in MS pathogenesis. Siponimod, a selective sphingosine-1-phosphate receptor modulator, regulates lymphocyte trafficking and CNS inflammation, reducing relapses and disability progression in SPMS patients.[65] Ocrelizumab, targeting CD20 on B cells, depletes peripheral B cells and inhibits their migration into the CNS, reducing relapse rates and disability progression in RRMS and PPMS patients.[66]

Combination therapies combining immunomodulatory agents with regenerative or neuroprotective approaches hold promise for optimizing MS treatment outcomes. Integrating disease-modifying therapies (DMTs) with remyelination-promoting strategies, such as OPC-targeted therapies or neurotrophic factors, may enhance CNS repair processes and improve long-term neurological function in MS patients.[67]

## *Dynamic Interactions within the Glial-Axonal Unit*

The glial-axonal unit represents a complex network of interactions between oligodendrocytes, astrocytes, microglia, and neurons. It plays a crucial role in maintaining CNS homeostasis[68] and responding to pathological insults. This section will explore the dynamic interactions within the glial-axonal unit in the context of MS, highlighting bidirectional signaling pathways, trophic support mechanisms, and dysregulation contributing to neuroinflammation and neurodegeneration.

The glial-axonal unit is a fundamental component of CNS function, encompassing oligodendrocytes responsible for myelin synthesis and maintenance, astrocytes providing metabolic and trophic support, microglia mediating immune surveillance and responses, and neurons transmitting electrical signals and neurotransmitters[21]

Interactions within this unit are tightly regulated under normal conditions but become dysregulated in neurological disorders like multiple sclerosis (MS).[69]

Oligodendrocytes play a central role in the glial-axonal unit by ensheathing axons with myelin, facilitating rapid signal transmission, and providing metabolic support to neurons.[70]

Loss of oligodendrocytes and demyelination disrupts axonal integrity, leading to conduction deficits and neurodegeneration in MS lesions. Oligodendrocyte dysfunction triggers a cascade of events, including astrocyte activation, microglial response, and neuronal stress, contributing to disease progression.[10]

Astrocytes, the most abundant glial cells in the CNS[71], interact closely with oligodendrocytes and neurons, modulating synaptic function, neurotransmitter clearance, and metabolic support. Reactive astrocytes in MS lesions exhibit gliosis, characterized by hypertrophy, increased glial fibrillary acidic protein (GFAP) expression, and altered neurotrophic factor secretion[10]. These changes can have neuroprotective and neurotoxic effects, influencing disease outcomes and neuronal survival in MS.[72]

Microglia, the resident immune cells of the CNS733], play a dual role in the glial-axonal unit by surveilling the microenvironment, phagocytosing cellular debris, and modulating immune responses. In MS, activated microglia/macrophages infiltrate lesions, release pro-inflammatory cytokines, and contribute to oligodendrocyte injury and demyelination.[21]activation is a hallmark of neuroinflammation in MS pathology[74], driving disease activity and exacerbating neuronal damage.

Neurons within the glial-axonal unit communicate bidirectionally with glial cells, modulating myelin maintenance, synaptic plasticity, and neurotransmitter release.[75]

Axonal signals regulate oligodendrocyte differentiation and myelination, while myelin-derived signals influence axonal integrity and neuronal survival.[70]Dysregulation of axo-glial signaling pathways in MS disrupts these interactions, leading to synaptic dysfunction, axonal degeneration, and functional deficits.

Understanding the dynamic interactions within the glial-axonal unit is essential for elucidating disease mechanisms and developing targeted therapies for MS. Strategies aimed at restoring glial-axonal communication, promoting remyelination, and preserving neuronal function hold promise for improving clinical outcomes and enhancing quality of life for MS patients. Future research on unraveling the intricacies of glial-neuronal interactions and their modulation in disease states will pave the way for personalized and effective treatments in MS management.

## *Translational Implications and Future Directions*

Translating essential research findings into clinical applications and therapeutic interventions is critical to advancing MS management. This section will discuss the translational implications of research on oligodendrocyte injury in MS, including biomarker development, drug discovery, regenerative therapies, and personalized medicine approaches. Future directions and challenges in MS research and treatment will also be explored, highlighting the need for collaborative efforts and innovative strategies to address the complexities of the disease.

Translational research in multiple sclerosis (MS) bridges the gap between fundamental discoveries in disease mechanisms and developing effective therapies for patients. Key translational implications of research on oligodendrocyte injury in MS include the following areas:

1. *Biomarker Development:* Identifying reliable biomarkers of disease activity, progression, and treatment response is crucial for optimizing patient management and clinical trial outcomes. Biomarkers related to oligodendrocyte dysfunction, myelin integrity, and neuroinflammation can provide insights into disease pathophysiology and aid in monitoring treatment efficacy.[76]
2. *Drug Discovery and Development*: Drug discovery efforts in MS focus on targeting specific pathways involved in oligodendrocyte injury, demyelination, and remyelination [77].
3. *Regenerative Therapies:* Stem cell-based therapies, regenerative medicine approaches, and myelin repair strategies hold promise for restoring oligodendrocyte function and myelin integrity in MS patients.[78] Clinical trials evaluating cell transplantation, gene editing techniques, and remyelination-promoting factors are ongoing to assess their safety and efficacy in treating MS-related disability.[78]
4. *Personalized Medicine Approaches:* Tailoring treatment strategies based on disease subtype, genetic profile, biomarker status, and patient-specific factors is essential for optimizing therapeutic outcomes in MS.[10] Precision medicine approaches aim to deliver targeted therapies, minimize treatment-related risks, and improve long-term prognosis for individuals with MS.[10] Future directions in MS research and treatment involve multidisciplinary collaborations, innovative technologies, and patient-centered care models.

## Discussion

The complex interplay among oligodendrocyte injury, demyelination, and neuroinflammation is fundamental to understanding MS pathogenesis and developing targeted therapies. Navigating the vast MS literature required meticulous review to avoid information overload and ensure a comprehensive grasp of the subject. Synthesizing diverse study designs and methodologies posed challenges, necessitating scrutiny to extract reliable evidence. The evolving nature of MS research demanded continuous updates to incorporate emerging trends and discoveries. Despite challenges, this research strives to contribute meaningfully to MS understanding and management, improving patient outcomes by addressing oligodendrocyte injury comprehensively.

## Conclusions

The intricate interplay among oligodendrocyte injury, demyelination, and neuroinflammation is central to multiple sclerosis (MS) pathogenesis. Oligodendrocytes safeguard myelin in the CNS, facing challenges from immune attacks to metabolic stress. Understanding oligodendrocyte dysfunction is vital for targeted therapies that suppress immune damage and promote remyelination and CNS repair. MS's etiology, involving genetic and environmental factors, contributes to heterogeneous oligodendrocyte injury and diverse clinical MS presentations, each posing unique treatment challenges. While immunomodulatory therapies like interferon-beta and monoclonal antibodies have reduced relapse rates, they fall short of addressing oligodendrocyte injury and fostering long-term remyelination.

Emerging regenerative approaches, including stem cell and gene editing therapies, promise to halt disease progression, repair myelin, and enhance MS patient outcomes. The intricate interactions within the glial-axonal unit, encompassing oligodendrocytes, astrocytes, microglia, and neurons, are crucial for CNS homeostasis. Dysregulation leads to neuroinflammation, neurodegeneration, and functional deficits, necessitating comprehensive approaches targeting immune modulation and CNS repair. Bridging research to clinical applications and personalized therapies demands collaboration, innovative technologies, and patient-centered care models. Biomarker development, drug discovery, regenerative therapies, and personalized medicine are key to optimizing MS management and enhancing patient quality of life.

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### *Abbreviation*

*MS - Multiple Sclerosis; CNS - Central Nervous System; IFN-γ - Interferon-gamma; MHC - Major Histocompatibility Complex; GWAS - Genome-Wide Association Studies;MOG - Myelin Oligodendrocyte Glycoprotein; RRMS - Relapsing-Remitting Multiple Sclerosis;SPMS - Secondary Progressive Multiple Sclerosis; PPMS - Primary Progressive Multiple Sclerosis; JAK-STAT -Janus Kinase-Signal Transducer and Activator of Transcription; MAPK - Mitogen-Activated Protein Kinase; IL-1β - Interleukin-1 beta; IL-6 - Interleukin-6; TNF-α -Tumor Necrosis Factor-alpha; EAE - Experimental Autoimmune Encephalomyelitis; OPCs - Oligodendrocyte Precursor Cells; OMgp - Oligodendrocyte Myelin glycoprotein; ROS - Reactive Oxygen Species.*

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