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New Directions in the Treatment of Progressive Forms of Multiple Sclerosis

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Annotation: Progressive forms of multiple sclerosis (MS), including primary progressive MS (PPMS) and secondary progressive MS (SPMS), present significant treatment challenges due to their complex pathophysiology and limited responsiveness to conventional disease-modifying therapies (DMTs). This article explores the most recent advancements in the treatment of progressive MS, including emerging pharmacologic therapies, regenerative medicine, and personalized approaches. The development and application of monoclonal antibodies, autologous hematopoietic stem cell transplantation (AHSCT), remyelination-promoting agents, and precision medicine strategies are discussed in depth. Special emphasis is placed on ongoing clinical trials, the role of biomarkers in treatment selection, and the impact of new therapies on patient quality of life and long-term disease progression. The article also critically evaluates the limitations of existing therapeutic modalities and explores promising directions for future research. By synthesizing the latest clinical and translational findings, this review provides a comprehensive foundation for optimizing treatment strategies in patients with progressive MS.

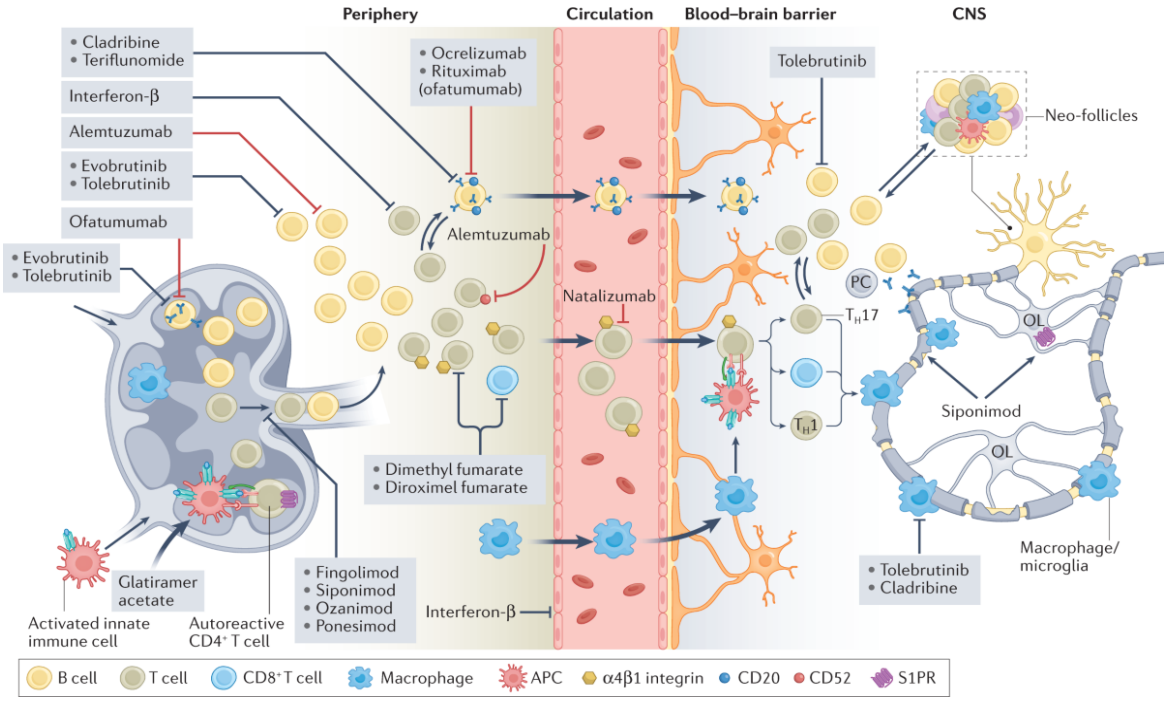
Keywords: Multiple sclerosis, progressive MS, neurodegeneration, remyelination, stem cell therapy, monoclonal

antibodies, precision medicine.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disorder of the central nervous system (CNS) that leads to significant neurological disability. While relapsing-remitting MS (RRMS) is the most common form at initial diagnosis, many patients eventually transition to progressive forms of the disease, namely secondary progressive MS (SPMS) or primary progressive MS (PPMS). These forms are characterized by a steady progression of neurological dysfunction with or without superimposed relapses, reflecting underlying neurodegeneration, chronic inflammation, and axonal loss.

The treatment landscape for progressive MS has historically lagged behind that of RRMS due to the more insidious disease course and reduced inflammatory activity. However, recent advances in the understanding of MS pathophysiology have spurred the development of novel therapeutic strategies aimed at halting progression and promoting neuroprotection and remyelination. The present article provides a comprehensive overview of these new directions, with a focus on pharmacologic innovations, regenerative interventions, and individualized care approaches.



Pathophysiology and Challenges in Progressive MS

Progressive MS is distinguished from RRMS by the predominance of neurodegenerative mechanisms, such as chronic microglial activation, mitochondrial dysfunction, and oxidative stress. Demyelination and failure of remyelination lead to irreversible axonal damage and neuroaxonal loss. The blood-brain barrier remains intact in many progressive MS lesions, limiting the effectiveness of traditional anti-inflammatory agents.

Key pathophysiological features of progressive MS include:

a. Diffuse cortical demyelination

b. Chronic active lesions with iron-laden microglia

c. Mitochondrial failure in neurons and oligodendrocytes

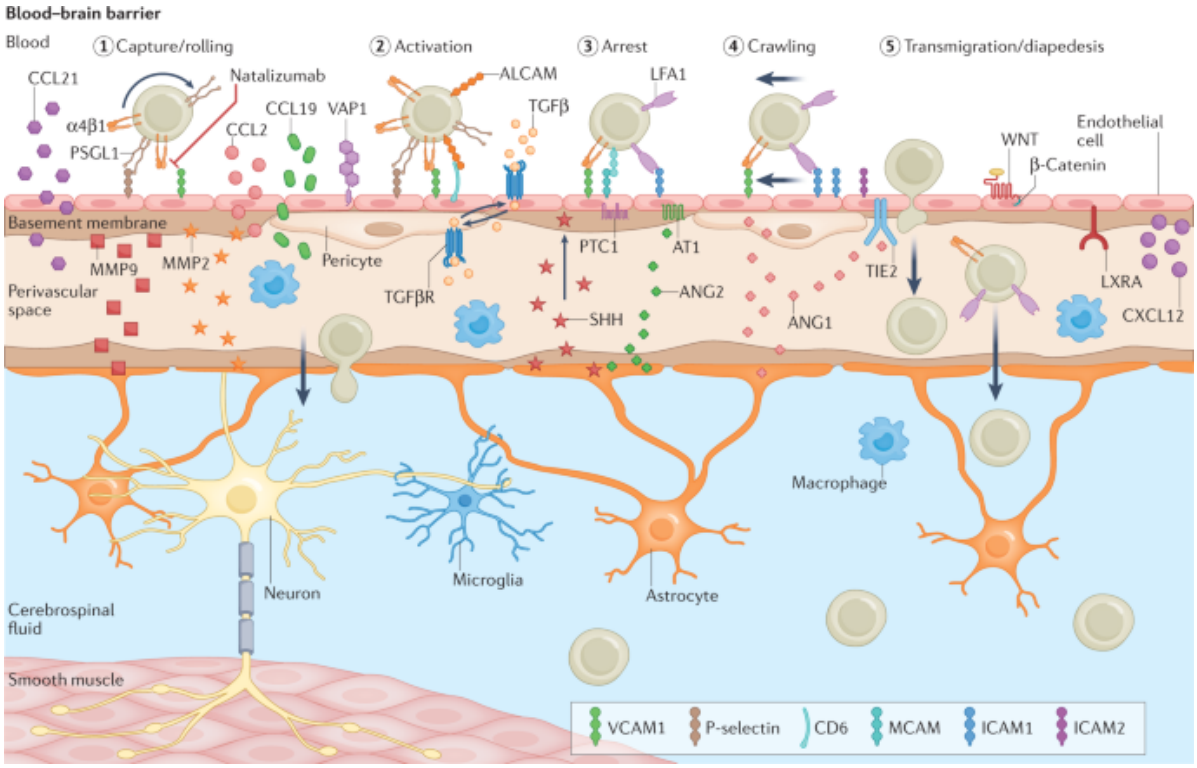
d. Reduced oligodendrocyte precursor cell (OPC) recruitment and differentiation

The multifactorial and compartmentalized nature of progressive MS pathology underscores the

need for therapies targeting multiple disease mechanisms, including immune modulation, neuroprotection, and repair.

Limitations of Existing Therapies

Historically, the mainstay of MS treatment has been immunomodulatory therapies, which have shown robust efficacy in RRMS. However, these agents have limited efficacy in progressive MS. For example:



Interferon beta-1a and glatiramer acetate: Show modest or no effect on progression in SPMS and PPMS.

Mitoxantrone: Approved for SPMS, but limited by cardiotoxicity and leukemia risk.

Ocrelizumab: First DMT approved for PPMS, showing modest benefit in delaying progression.

The limited efficacy of these therapies is attributed to the relative absence of inflammatory activity and the predominance of neurodegenerative mechanisms in progressive MS. There is a critical need for treatments that can modulate chronic inflammation, support axonal integrity, and promote remyelination.

Emerging Pharmacologic Therapies

Monoclonal Antibodies

a. Monoclonal antibodies (mAbs) targeting B cells and other immune components have emerged as promising options for progressive MS:

b. Ocrelizumab: A humanized anti-CD20 mAb, shown to reduce disability progression in PPMS (ORATORIO trial).

c. Ofatumumab: Subcutaneous anti-CD20 mAb, currently approved for RRMS, under evaluation for progressive MS.

d. Ublituximab: A novel glycoengineered anti-CD20 mAb with enhanced antibody-dependent cytotoxicity.

Bruton's Tyrosine Kinase (BTK) Inhibitors

BTK inhibitors target B-cell and myeloid cell signaling pathways involved in chronic CNS inflammation. Examples:

Evobrutinib, Tolebrutinib, Fenebrutinib: Currently in phase 2/3 trials for progressive MS.

Neuroprotective Agents

These include agents aimed at preserving neuronal integrity:

Biotin (MD1003): A high-dose formulation showed some benefit in progressive MS.

Ibudilast: A phosphodiesterase inhibitor with anti-inflammatory and neuroprotective effects.

Regenerative Medicine and Remyelination Strategies

Autologous Hematopoietic Stem Cell Transplantation (AHSCT)

AHSCT aims to reboot the immune system by eliminating autoreactive immune cells. While mostly used in aggressive RRMS, evidence suggests benefit in early SPMS.

Mesenchymal Stem Cell Therapy

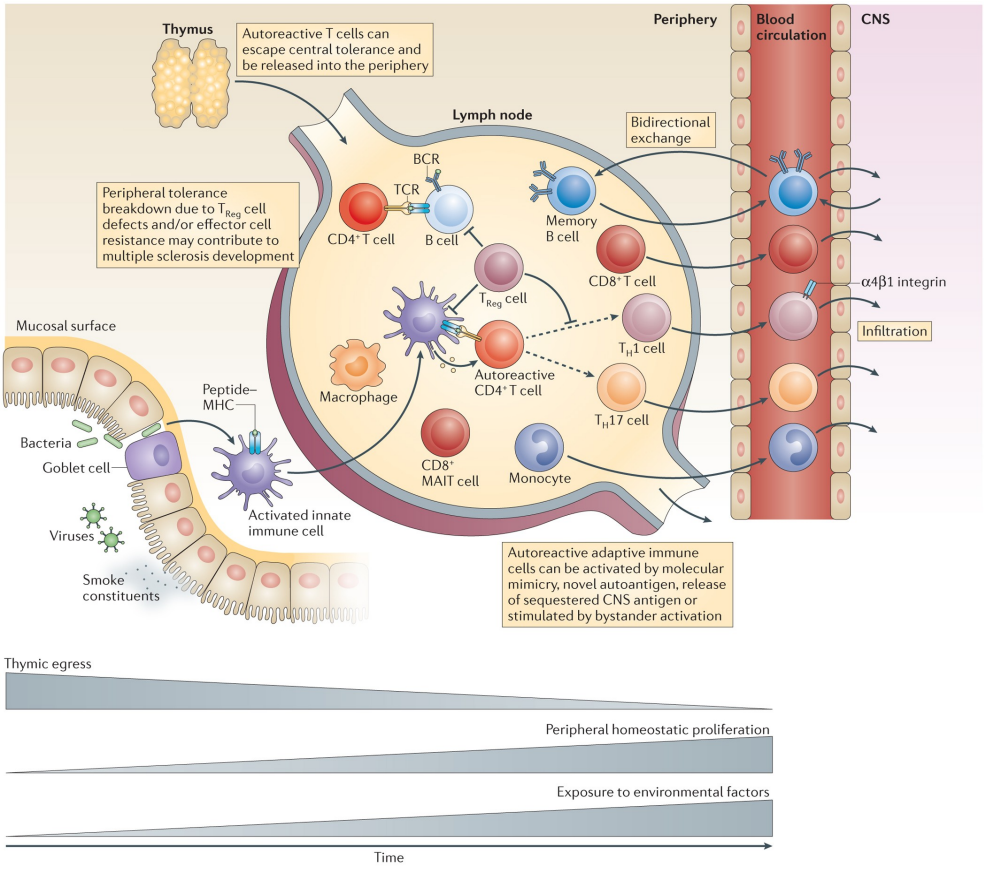
These cells have immunomodulatory and trophic properties and may support remyelination. Phase 2 trials have demonstrated safety and feasibility.

Remyelinating Agents

Several compounds aim to enhance endogenous remyelination:

Clemastine fumarate: An antihistamine promoting OPC differentiation (ReBUILD trial).

Opicinumab (anti-LINGO-1): Failed to meet endpoints in trials but spurred further research into remyelination targets.



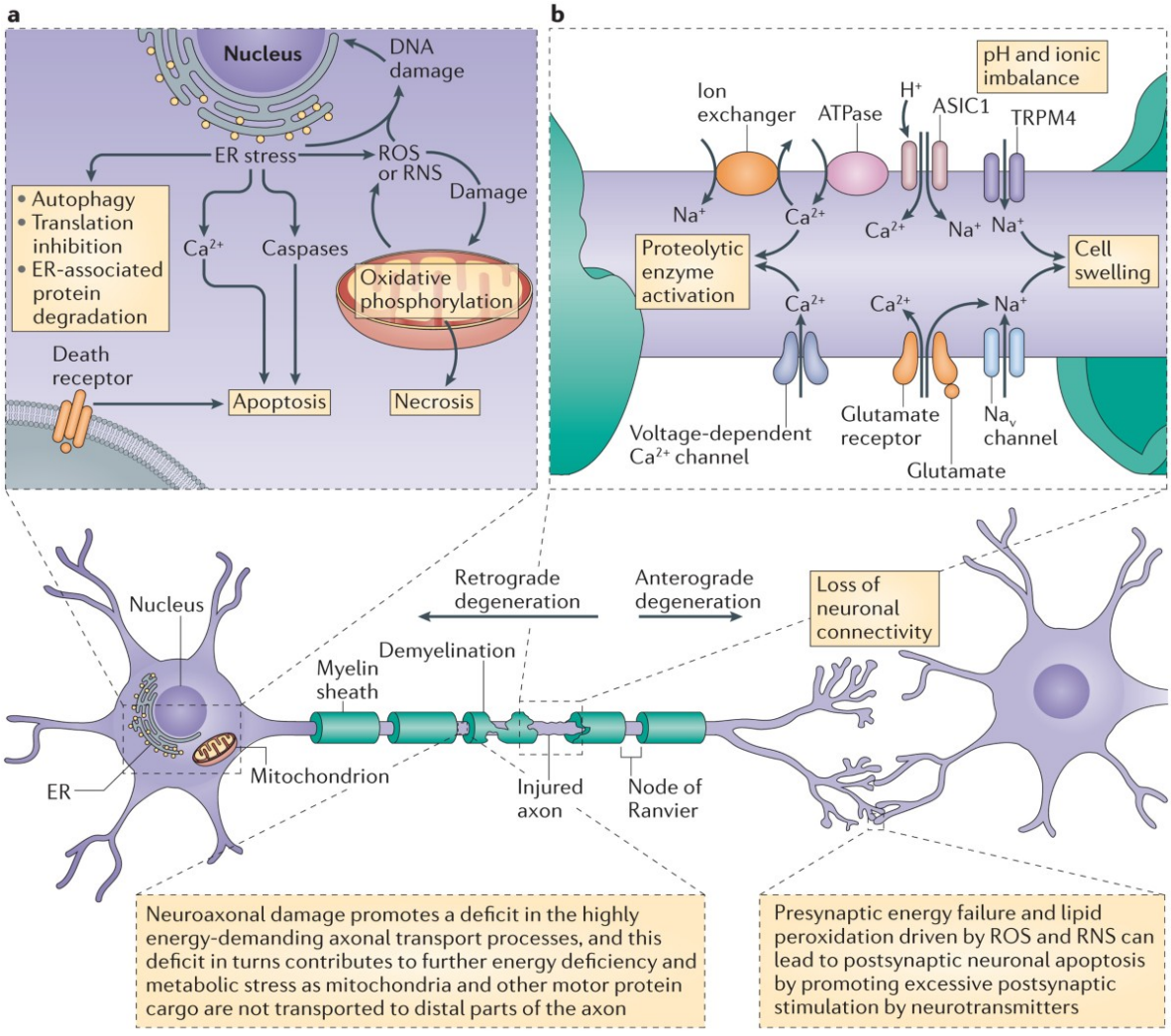
Personalized and Precision Medicine Approaches

Genetic, epigenetic, and molecular profiling may guide individualized treatment decisions. Emerging tools include:

Biomarkers (e.g., neurofilament light chain, CHI3L1)

Imaging techniques (e.g., magnetization transfer ratio, PET imaging)

Machine learning models for predicting progression and treatment response



Clinical Trials and Future Perspectives

a. Numerous trials are ongoing or recently completed:

b. ORATORIO: Ocrelizumab in PPMS

c. SPI2: MD1003 in progressive MS

d. SPRINT-MS: Ibudilast neuroprotection study

Future research directions include:

a. Combination therapies targeting inflammation, degeneration, and repair

b. Improved patient stratification using biomarkers

c. Integration of digital health and remote monitoring tools

Discussion

The current therapeutic landscape for progressive MS is rapidly evolving. Although challenges remain, especially in achieving sustained functional improvement, a paradigm shift is underway. The integration of immunomodulatory agents with regenerative and precision-based approaches holds promise for modifying the course of progressive MS. It is imperative to conduct longer and larger trials with diverse populations to validate these interventions.

Conclusion

Progressive MS represents a formidable therapeutic challenge. However, recent advances have broadened the scope of potential interventions. Monoclonal antibodies, BTK inhibitors, stem cell therapies, and remyelination-promoting agents offer hope for improved outcomes. Personalized approaches and biomarker-guided therapies are expected to further optimize treatment efficacy. A multidisciplinary and translational strategy is crucial to advance care for individuals living with progressive MS.

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