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Astrocyte Heterogeneity in Multiple Sclerosis From Reactive Glia to Therapeutic Targets

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Multiple sclerosis (MS) has long been viewed through a lymphocyte-centered lens, with astrocytes considered merely as passive responders to immune-mediated injury. That perspective is no longer tenable, since advances in single-cell transcriptomics, spatial mapping, and epigenetic profiling over the past decade have revealed astrocytes to act as dynamic regulators of neuroinflammation, being able to both increase and repair tissue injuries. In this issue of the *Journal of Clinical Neurology*, Hong et al.[1] provide a comprehensive and timely review of astrocyte functional heterogeneity in MS, synthesizing recent advances in single-cell transcriptomics, spatial profiling, and epigenetic regulation to redefine our understanding of glial biology in this disease. Their review provides an excellent basis for considering how these basic science discoveries can be translated into meaningful clinical tools and therapeutic strategies.

A central challenge highlighted by that review is the translational gap between experimental autoimmune encephalomyelitis (EAE) models and human MS. While EAE models have been instrumental in defining astrocyte subtypes and intercellular signaling pathways, the degree to which these findings rationalize the complexity of human disease remains uncertain. This gap is particularly relevant when considering late-onset and progressive forms of MS in which there is a critical interplay between aging and neuroinflammation. Indeed, Soares-Dos-Reis et al.[2] recently demonstrated that patients with late-onset MS (onset after 50 years of age) reach significant disability milestones faster than patients of the same age with adult-onset MS, with a higher proportion presenting as primary progressive MS. These clinical observations suggest that age-dependent changes in astrocyte biology—including senescence, impaired homeostatic functions, and altered inflammatory memory—fundamentally influence disease trajectories in ways not fully captured by conventional EAE models using young animals.

The review by Hong et al.[1] also raises an important question related to clinical translation: how can astrocyte heterogeneity be monitored in patients? Although neurofilament light chain (NfL) is now an established marker of neuroaxonal injury, it does not capture astrocyte-specific biology. In contrast, glial fibrillary acidic protein (GFAP) has emerged as a candidate marker of astrocyte reactivity, and there is recent evidence of GFAP elevation in the cerebrospinal fluid (CSF) being associated with progressive, nonrelapsing MS biology and worse long-term disability.[3] However, the currently available assays do not distinguish neurotoxic from neuroprotective astrocyte states. As this field advances, subtype-specific astrocyte biomarkers will be essential for the precision monitoring of progressive MS.

The distinction between MS and neuromyelitis optica spectrum disorder (NMOSD) offers useful information about astrocyte pathology. Aquaporin-4 (AQP4)-positive astrocytes are the primary targets of autoimmune attack in NMOSD, whereas astrocyte dysfunction emerges within a broader inflammatory and demyelinating milieu in MS. Hong et al.[4] have shown that more subclinical lesions accumulate during remission in MS than in AQP4-posi-

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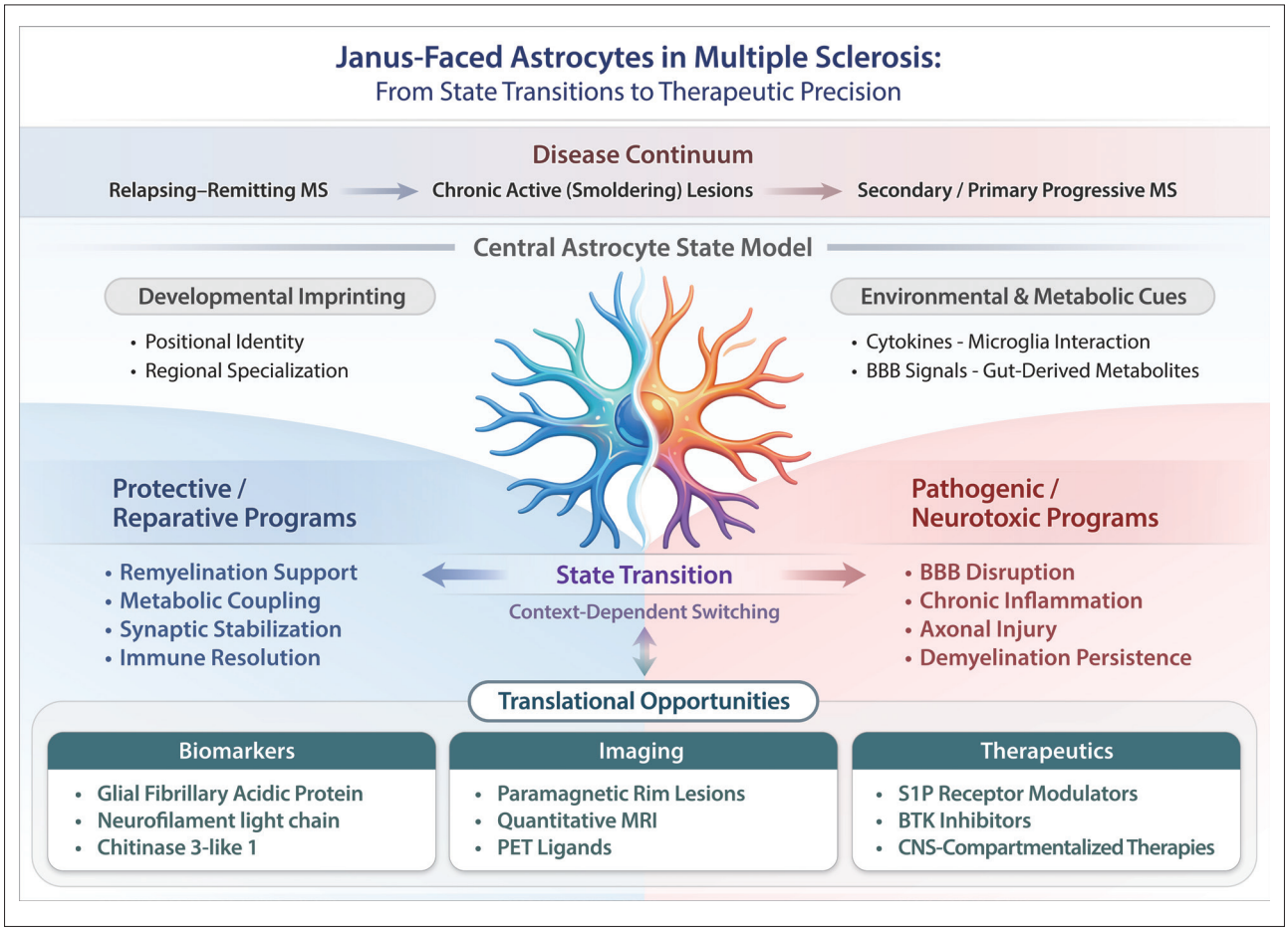

Fig. 1. Astrocyte-state programs determine the progression of MS. Astrocytes in MS are state-dependent regulators that influence disease evolution, rather than simply acting as passive responders. Across relapsing, chronic active, and progressive stages, astrocytes integrate developmental imprinting, local inflammatory and metabolic cues, and epigenetic memory to generate context-specific programs. These programs lie along a dynamic spectrum, with some stabilizing compartmentalized inflammation and axonal vulnerability, and others enabling remyelination and the restoration of neural homeostasis. Lesion persistence may therefore reflect the continuation of maladaptive astrocyte states, while recovery depends on their reprogramming. MS progression may be driven less by the magnitude of immune-system responses than by the durability—and reversibility—of astrocyte-state programs. BBB, blood–brain barrier; BTK, Bruton's tyrosine kinase; CNS, central nervous system; MS, multiple sclerosis; PET, positron emission tomography; S1P, sphingosine-1-phosphate.

tive NMOSD, supporting the concept that chronic compartmentalized inflammation in MS is biologically distinct from the primary astrocytopathy of NMOSD. This contrast supports the view that astrocyte heterogeneity in MS is not merely a byproduct of injury severity, but rather a state-dependent response influenced by the local inflammatory environment. The differences reported between NMOSD populations[5] further suggest that race-specific disease heterogeneity deserves greater attention in future studies of clinical translation.

From a therapeutic perspective, the review by Hong et al.[1] highlights several astrocyte-relevant strategies that are now entering clinical development. Among these, those involving sphingosine-1-phosphate receptor modulators are notable because they influence both peripheral immune trafficking and astrocyte function. By modulating astrocytic inflammatory signaling and metabolic support, this class of drug illustrates how glial biology can inform treatment design beyond purely lymphocyte-based approaches. Similarly, brain-penetrating Bruton's tyrosine kinase inhibitors represent a shift toward targeting central nervous system (CNS)-compartmentalized inflammation, with potential relevance to both microglial and astrocytic networks.[6]

Several important gaps remain. The review would have benefited from consideration of sex differences in astrocyte biology, given the marked female predominance of MS. Population-specific considerations—particularly the differing phenotypes seen in Asian and Western cohorts, where the distinction from NMOSD remains clinically important—also deserve greater attention. In addition, multimodal CSF biomarker panels combining GFAP, NfL, and chitinase 3-like 1

may further strengthen the clinical-translation framework proposed by Hong et al.[1]

The review by Hong et al.[1] marks a conceptual turning point in MS research, with astrocytes no longer seen as passive reactive cells, but rather as dynamic, state-dependent regulators of inflammation and repair. The challenge now is not merely to catalog their diversity, but to define the different astrocyte states that drive progression and resilience, and also how these states can be selectively modulated (Fig. 1). Precision neurology in MS will depend not only on suppressing peripheral immunity, but also on characterizing and influencing CNS-compartmentalized inflammation. The future of MS research might ultimately be defined not by how aggressively inflammation is suppressed, but by how precisely we can regulate the microglial and astrocytic networks that sustain it.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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