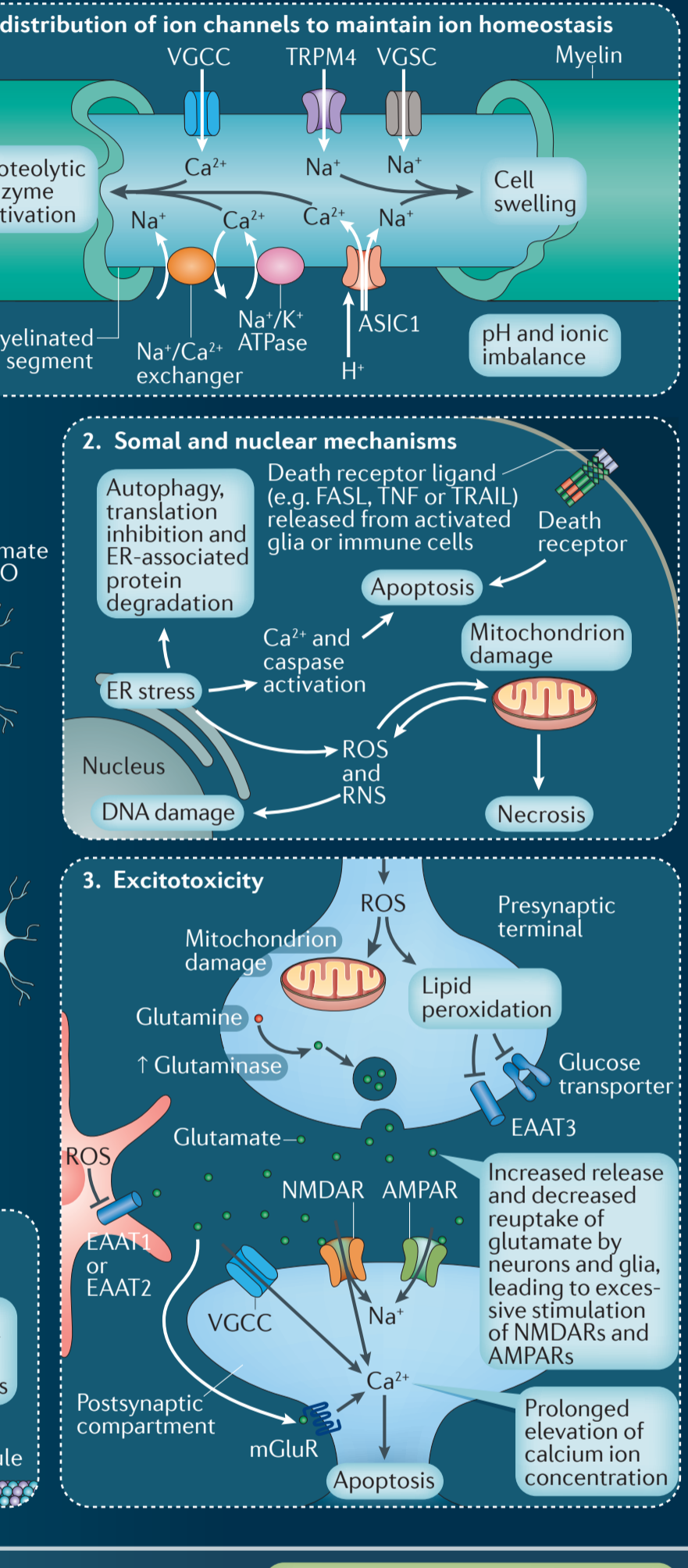
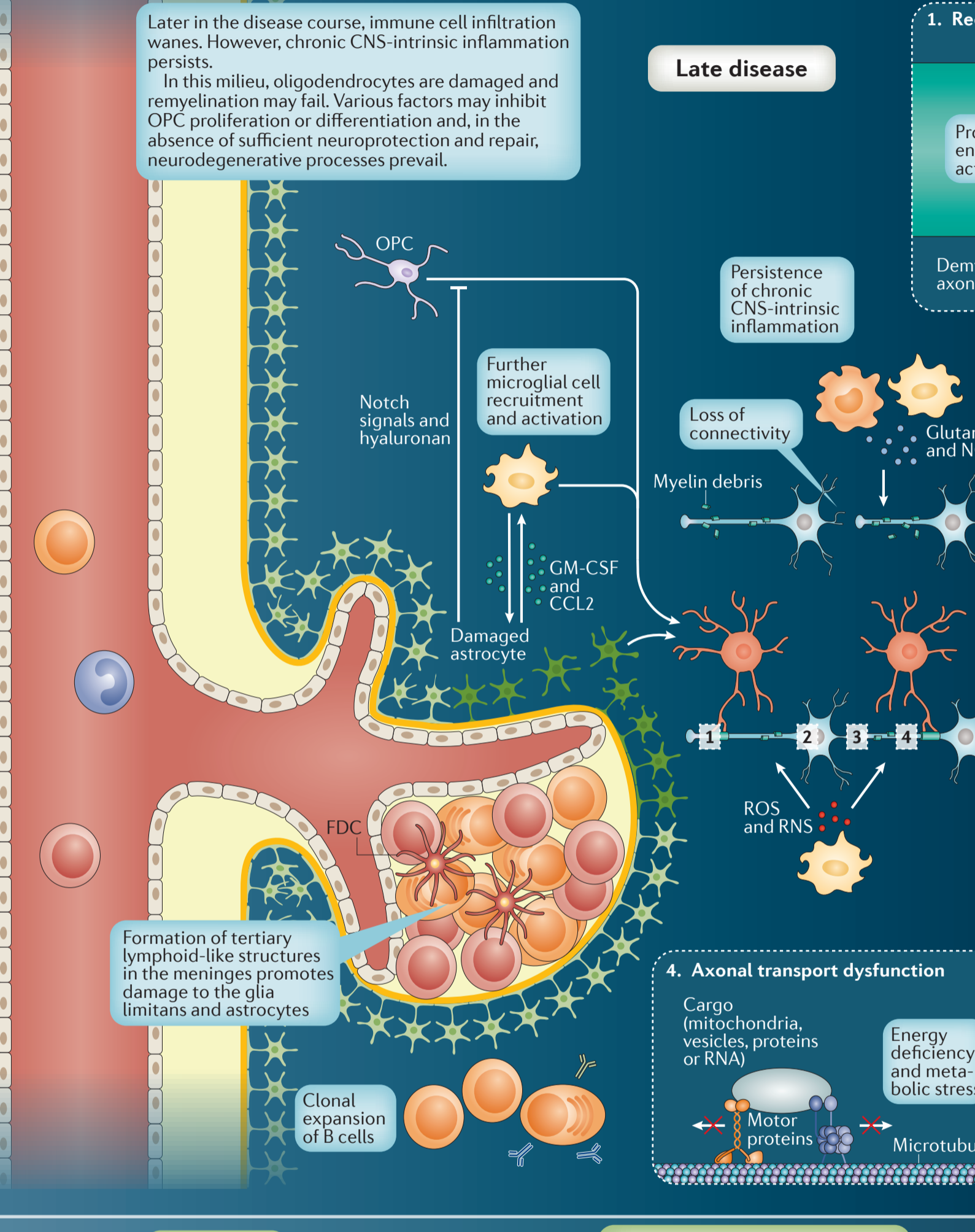
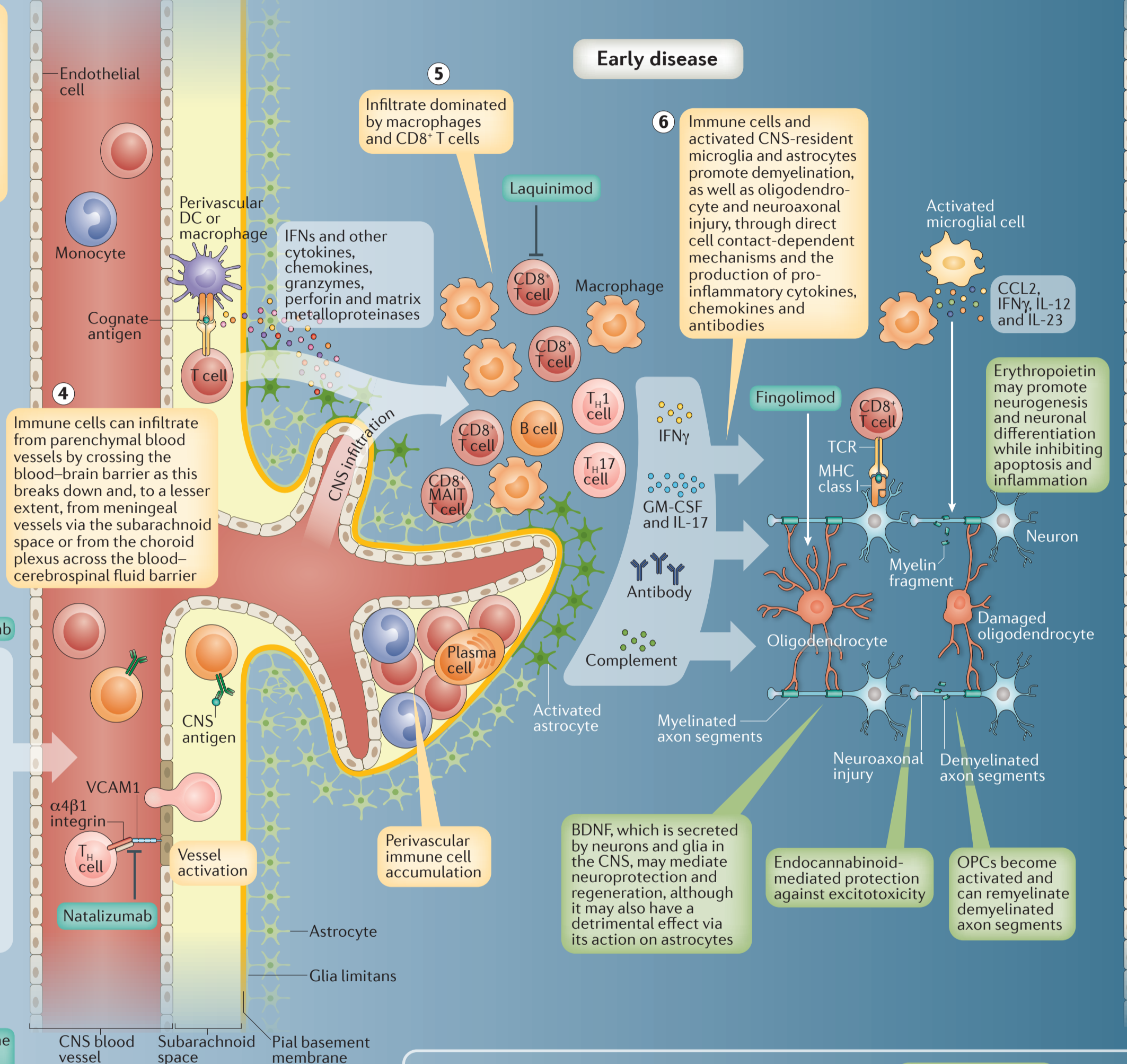
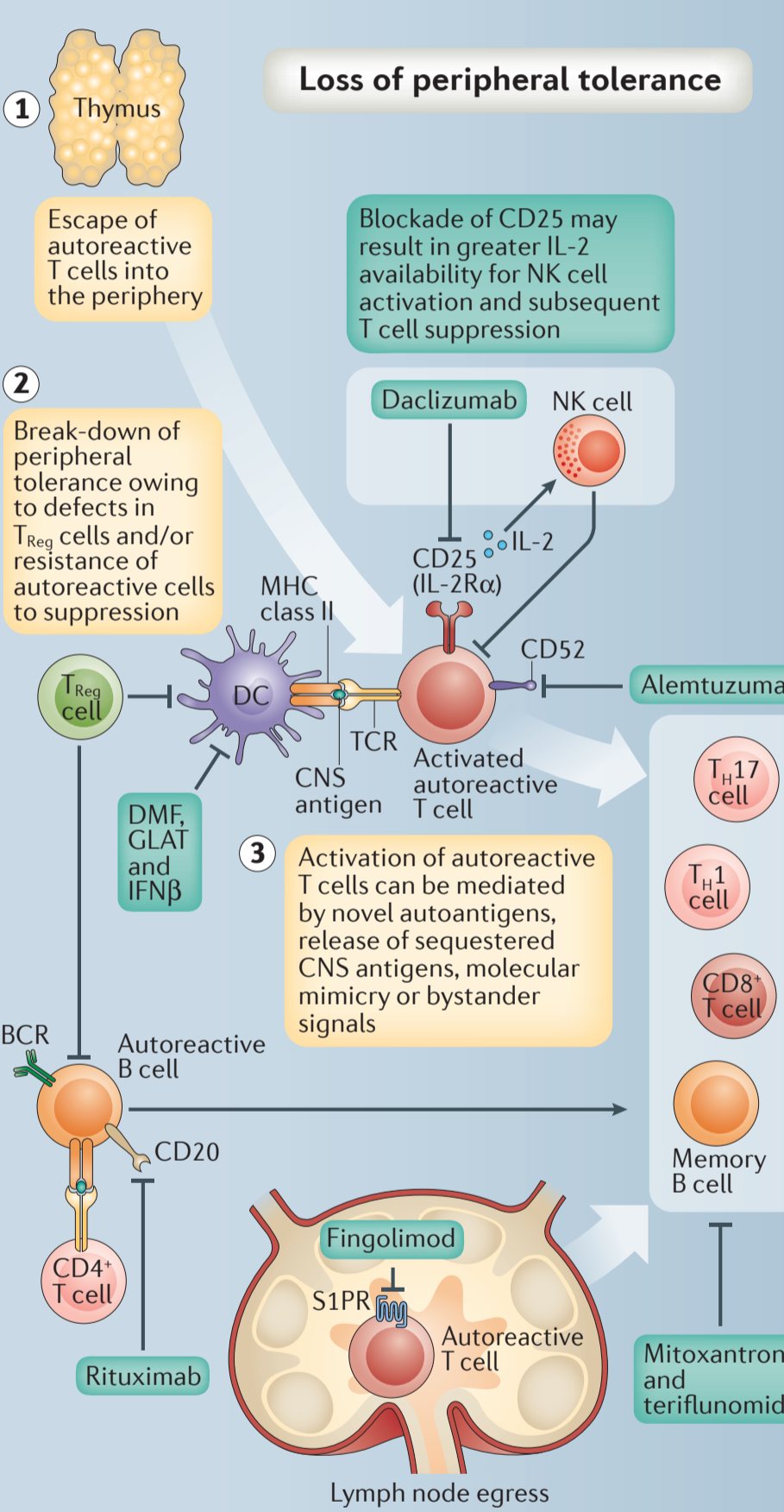


Multiple sclerosis (MS) is a neuroinflammatory disease of the central nervous system (CNS). The disease is characterized by a considerable heterogeneity of disease course and clinical manifestations — which can include visual and sensory disturbances, motor impairments, pain, fatigue and cognitive deficits. However, most individuals with MS show a progressive accumulation of disability in the later stages of the disease. Disease onset usually occurs at around 30 years of age and most people with the condition have a near-normal life expectancy: thus, MS is a chronic debilitating disorder. Here, we summarize

key immune and nervous system cell types and molecules that are involved in the pathophysiology of MS. We delineate the roles of innate and adaptive immune cells, in the periphery and within the CNS, and we provide an overview of how the relative contributions of immune and nervous system components change over time as the chronic neurodegenerative damage to the CNS ultimately overwhelms neuroprotective and/or neuroregenerative mechanisms. We also highlight the sites of action of currently available drugs, where known, and therapeutic strategies that are under investigation.

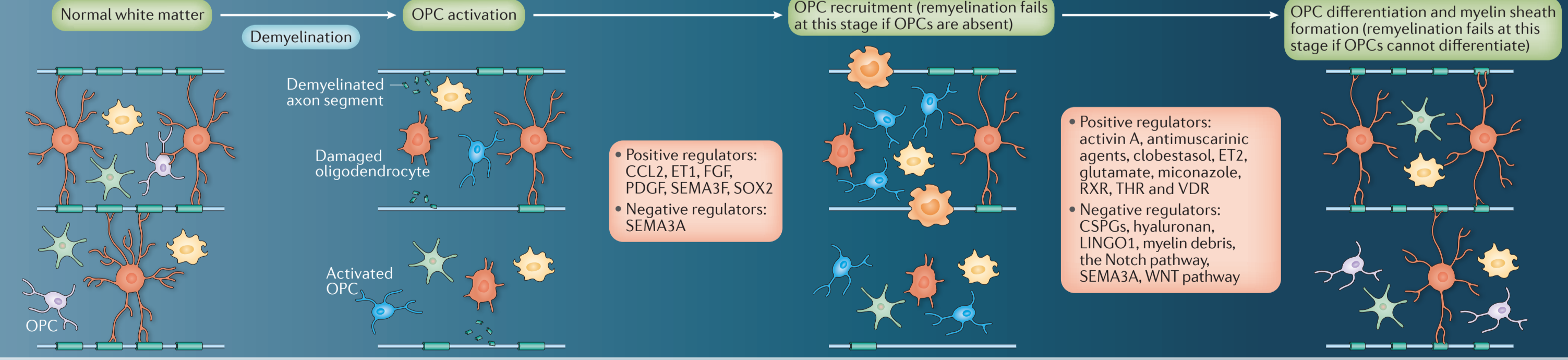
MS is thought to arise when an aberrant immune response is mounted against CNS antigens as self-tolerance mechanisms break down in the periphery, potentially owing to a combination of genetic and environmental factors. Following activation in the periphery, CNS-directed autoreactive T cells, along with antigen-presenting cells such as DCs, infiltrate the CNS, where they drive focal inflammation and tissue damage. Various mechanisms are induced to mitigate neural tissue injury. Remyelination, which depends on the survival of oligodendrocyte progenitor cells (OPCs), is thought to actively reverse damage to the myelin sheath.



**Therapeutic targets**  
Most drugs that are either currently available or in Phase III clinical trials for the treatment of MS are immunomodulatory. The exact modes of action for many of these drugs have not been fully elucidated; however, these agents are thought to prevent immune cell egress from secondary lymphoid organs (fingolimod), regulate peripheral immune cell activation (for example, IFN $\beta$ , GLAT, mitoxantrone, teriflunomide, alemtuzumab, daclizumab and rituximab), prevent immune cells from crossing the blood-brain barrier (natalizumab) or, potentially, suppress inflammation in the CNS through possible direct effects on oligodendrocytes and immune cells (fingolimod and laquinimod) or through anti-oxidant effects (DMF).

These therapeutics all have efficacy in treating the earlier phases of MS. To date, however, no drugs have been shown to be effective at slowing the later, progressive accumulation of disability in a Phase III trial. Therefore, there is a need for drugs with non-immunological targets within the CNS, such as sodium channel blockers, which are currently in clinical trials. The complexity of MS pathophysiology suggests that combinatorial therapy for the modulation of multiple disease mechanisms — both immunological and neurological — is likely to be of greatest benefit, and thus the continued study of these mechanisms is crucial for the establishment of improved therapeutic options for MS.

**Remyelination and its points of failure**  
Following demyelination, microglia and astrocytes become activated, resulting in activation of nearby OPCs. The release of mitogens and pro-migratory factors by reactive astrocytes and inflammatory cells (mainly microglia and monocyte-derived macrophages) leads to the proliferation of OPCs and their migration to the demyelinated area. The recruited OPCs differentiate into remyelinating oligodendrocytes, a process that involves axon engagement and the formation of a myelin sheath. Macrophages also facilitate remyelination by removing myelin debris, which contains inhibitors of OPC differentiation. Remyelination failure can occur because of a failure of OPC recruitment or, more frequently, because of a failure of differentiation. The most promising remyelination-promoting agents aim to target positive regulators of differentiation (such as RXR agonists) or negate inhibitors of differentiation (such as antibodies against LINGO1).



**Abbreviations**  
AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ASIC1, acid-sensing ion channel 1; BCR, B cell receptor; BDNF, brain-derived neurotrophic factor; CCL2, CC-chemokine ligand 2; CD8<sup>+</sup> MAIT cell, CD8<sup>+</sup> mucosa-associated invariant T cell; CNS, central nervous system; CSPG, chondroitin sulphate proteoglycan; DC, dendritic cell; DMF, dimethyl fumarate; EAAT, excitatory amino acid transporter; ER, endoplasmic reticulum; ET, endothelin; FASL, Fas ligand; FDC, follicular dendritic cell; FGF, fibroblast

growth factor; GLAT, glatiramer acetate; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LINGO1, leucine rich repeat- and immunoglobulin domain-containing 1; mGluR, metabotropic glutamate receptor; MHC, major histocompatibility complex; MS, multiple sclerosis; NK cell, natural killer cell; NMDAR, N-methyl-D-aspartate receptor; NO, nitric oxide; OPC, oligodendrocyte precursor cell; PDGF, platelet-derived growth factor; RNS, reactive nitrogen species; ROS, reactive oxygen species;

RXR, retinoid X receptor; S1PR, sphingosine 1-phosphate receptor; SEMA, semaphorin; TCR, T cell receptor; T<sub>H</sub> cell, T helper cell; THR, thyroid hormone receptor; TNF, tumour necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; T<sub>reg</sub> cell, regulatory T cell; TRPM4, transient receptor potential cation channel subfamily M member 4; VCAM1, vascular cell adhesion molecule 1; VDR, vitamin D receptor; VGCC, voltage-gated calcium channel; VGSC, voltage-gated sodium channel.

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