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The immunology and neurobiology of multiple sclerosis

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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.

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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.

Loss of peripheral tolerance

1 Thymus

Escape of autoreactive T cells into the periphery

Blockade of CD25 may result in greater IL-2 availability for NK cell activation and subsequent T cell suppression

2 Break-down of peripheral tolerance owing to defects in T_{Reg} cells and/or resistance of autoreactive cells to suppression

Daclizumab, NK cell, IL-2, CD25 (IL-2Rα), CD52, Alemtuzumab, MHC class II, T_{Reg} cell, DC, TCR, CNS antigen, Activated autoreactive T cell, DMF, GLAT and IFNβ

3 Activation of autoreactive T cells can be mediated by novel autoantigens, release of sequestered CNS antigens, molecular mimicry or bystander signals

T_H17 cell, T_H1 cell, $CD8^+$ T cell, Memory B cell, BCR, Autoreactive B cell, CD20, $CD4^+$ T cell, Rituximab, Fingolimod, S1PR, Autoreactive T cell, Lymph node egress, Mitoxantrone and teriflunomide

Endothelial cell, Monocyte, Cognate antigen, Perivascular DC or macrophage, T cell, IFNs and other cytokines, chemokines, granzymes, perforin and matrix metalloproteinases, CNS infiltration

4 Immune cells can infiltrate from parenchymal blood vessels by crossing the blood–brain barrier as this breaks down and, to a lesser extent, from meningeal vessels via the subarachnoid space or from the choroid plexus across the blood–cerebrospinal fluid barrier

CNS antigen, VCAM1, α4β1 integrin, T_H cell, Vessel activation, Natalizumab, CNS blood vessel, Subarachnoid space, Pial basement membrane, Astrocyte, Glia limitans

Early disease

5 Infiltrate dominated by macrophages and $CD8^+$ T cells

Laquinimod, $CD8^+$ T cell, Macrophage, $CD8^+$ T cell, B cell, T_H1 cell, $CD8^+$ MAIT T cell, T_H17 cell, Plasma cell, Perivascular immune cell accumulation

6 Immune cells and activated CNS-resident microglia and astrocytes promote demyelination, as well as oligodendrocyte and neuroaxonal injury, through direct cell contact-dependent mechanisms and the production of pro-inflammatory cytokines, chemokines and antibodies

IFNγ, GM-CSF and IL-17, Antibody, Complement, Activated astrocyte, Myelinated axon segments, Activated microglial cell, CCL2, IFNγ, IL-12 and IL-23, Fingolimod, $CD8^+$ T cell, TCR, MHC class I, Erythropoietin may promote neurogenesis and neuronal differentiation while inhibiting apoptosis and inflammation, Neuron, Myelin fragment, Damaged oligodendrocyte, Oligodendrocyte, Neuroaxonal injury, Demyelinated axon segments

BDNF, which is secreted by neurons and glia in the CNS, may mediate neuroprotection and regeneration, although it may also have a detrimental effect via its action on astrocytes

Endocannabinoid-mediated protection against excitotoxicity

OPCs become activated and can remyelinate demyelinated axon segments

Late disease

Later in the disease course, immune cell infiltration wanes. However, chronic CNS-intrinsic inflammation persists.

In this milieu, oligodendrocytes are damaged and remyelination may fail. Various factors may inhibit OPC proliferation or differentiation and, in the absence of sufficient neuroprotection and repair, neurodegenerative processes prevail.

OPC, Notch signals and hyaluronan, Further microglial cell recruitment and activation, Persistence of chronic CNS-intrinsic inflammation, Loss of connectivity, Glutamate and NO, Myelin debris, GM-CSF and CCL2, Damaged astrocyte, ROS and RNS, FDC, Formation of tertiary lymphoid-like structures in the meninges promotes damage to the glia limitans and astrocytes, Clonal expansion of B cells

1. Redistribution of ion channels to maintain ion homeostasis

VGCC, TRPM4, VGSC, Myelin, Proteolytic enzyme activation, Ca^{2+}, Na^+, Cell swelling, Demyelinated axon segment, Na^+/Ca^{2+} exchanger, Na^+/K^+ ATPase, ASIC1, H^+, pH and ionic imbalance

2. Somal and nuclear mechanisms

Autophagy, translation inhibition and ER-associated protein degradation, Death receptor ligand (e.g. FASL, TNF or TRAIL) released from activated glia or immune cells, Death receptor, Apoptosis, Mitochondrion damage, Ca^{2+} and caspase activation, ER stress, ROS and RNS, Nucleus, DNA damage, Necrosis

3. Excitotoxicity

ROS, Presynaptic terminal, Mitochondrion damage, Lipid peroxidation, Glutamine, ↑ Glutaminase, Glucose transporter, EAAT3, Glutamate, ROS, NMDAR, AMPAR, Increased release and decreased reuptake of glutamate by neurons and glia, leading to excessive stimulation of NMDARs and AMPARs, EAAT1 or EAAT2, VGCC, Na^+, Ca^{2+}, Postsynaptic compartment, mGluR, Prolonged elevation of calcium ion concentration, Apoptosis

4. Axonal transport dysfunction

Cargo (mitochondria, vesicles, proteins or RNA), Energy deficiency and metabolic stress, Motor proteins, Microtubule

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, IFNβ, 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).

Normal white matter → Demyelination → OPC activation → OPC recruitment (remyelination fails at this stage if OPCs are absent) → OPC differentiation and myelin sheath formation (remyelination fails at this stage if OPCs cannot differentiate)

OPC, Demyelinated axon segment, Damaged oligodendrocyte, Activated OPC

- Positive regulators: CCL2, ET1, FGF, PDGF, SEMA3F, SOX2
- Negative regulators: SEMA3A

- Positive regulators: activin A, antimuscarinic agents, clobestasol, ET2, glutamate, miconazole, RXR, THR and VDR
- Negative regulators: CSPGs, hyaluronan, LINGO1, myelin debris, the Notch pathway, SEMA3A, WNT pathway

Abbreviations

AMPAR, α-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; $CD8^+$ MAIT cell, $CD8^+$ 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_H cell, T helper cell; THR, thyroid hormone receptor; TNF, tumour necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; T_{Reg} 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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The authors declare no competing interests.
Edited by Olive Leavy and Darran Yates; copyedited by Natasha Bray; designed by Patrick Morgan, Simon Bradbrook and Hannah Procter.

http://www.nature.com/posters/ms
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Produced with support of a medical education grant from Biogen.