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Multiple Sclerosis

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Introduction

Multiple sclerosis (MS) is the most prevalent chronic inflammatory disease of the central nervous system (CNS), affecting >2 million people worldwide (~400,000 in the United States),[1] and currently incurable. It is punctuated by fully or partially reversible episodes of neurological disability, usually lasting days to weeks. Typical presenting syndromes include, but are not limited to, monocular visual loss due to optic neuritis, limb weakness or sensory loss due to transverse myelitis, double vision due to brainstem dysfunction, or ataxia due to a cerebellar lesion.[2] After typically 10–20 years, many of those affected develop a "progressive" clinical course, eventually manifesting impaired mobility and cognition; ~15% have a progressive course from onset. More than a dozen disease-modifying medications are available to reduce the frequency of transient episodes of neurological disability and limit the accumulation of focal white matter lesions on MRI. No medication fully prevents or reverses progressive neurological deterioration, characterized most commonly by impaired ambulation, loss of bladder control, and slowed cognitive processing, but whether disease-modifying medications can delay clinical progression is controversial.[3–5] The annual economic cost in the United States is ~$10 billion.[6]

Pathology

The pathological conception of MS as a disseminated "plaque-like sclerosis" was established ~150 years ago; indeed, the demonstration of dissemination – in space (disease-related changes in multiple CNS regions, including white matter, gray matter, brainstem, spinal cord, and optic nerve; Figure 1) and time – forms the cornerstone of MS diagnosis. Our understanding of the details of that pathology, and especially how it evolves over time,

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has been revolutionized with modern techniques such as immunohistochemistry and magnetic resonance imaging (MRI).

MS lesions can appear throughout the CNS and are most easily recognized in the white matter as focal areas of demyelination, inflammation, and glial reaction. Evidence from MRI and pathology (biopsies and autopsies) indicates that the earliest stages of white matter demyelination (known as “early active white matter lesions”) are heterogeneous[7] and evolve over the course of months. Interestingly, regardless of the particular immunological pattern of early demyelination (Figure 2), analysis of active lesions, over both time and space, suggests that a single immune-effector mechanism dominates in each person.[8] Consistent with this notion is the observation that plasma exchange, which removes pathogenic antibodies from the circulation, ameliorates relapses that are refractory to initial treatment with glucocorticoids only in patients whose active lesions contain immunoglobulin and complement,[9] and that cerebrospinal fluid (CSF) profiles differ by lesion pattern.[10] The identification of noninvasive biomarkers that correlate with active lesion patterns will facilitate the design of personalized therapeutic strategies, as current MS treatment algorithms may not adequately address the underlying pathogenic heterogeneity of this complex disease.

What determines the long-term fate of a given lesion – whether inflammation resolves or “smolders,” or whether it remyelinates – is not well understood. Recent data from longitudinal imaging studies suggest that lesions that form in younger people may repair more effectively,[11] consistent with preclinical work indicating that age strongly modulates immune-mediated regenerative processes.[12,13] What remains unclear is whether lesions can remyelinate years after a smoldering lesion is established and whether remyelinated lesions have heightened susceptibility to recurrent demyelination. High-resolution, ultrahigh-field (7-tesla) MRI shows promise as a tool for noninvasive lesion staging,[14] and future studies should investigate the relationship between lesion outcomes and clinical status.

Myelin is not exclusive to white matter, and demyelination in MS also involves gray matter.[15–17] About half of cortical lesions are perivascular. Often, the inflamed vessel is near the leukocortical junction, and demyelination affects both gray and white matter; sometimes, a small penetrating cortical vein is involved, and only central cortical layers are affected. Cortical lesions are less inflammatory than their white matter counterparts and have substantially less blood-brain-barrier (BBB) permeability.[18]

The remaining cortical lesions do not arise from a single cortical vessel but rather appear to proceed inward from the pial surface of the brain. In autopsies after decades of disease, most such lesions are inactive, in contrast to subpial lesions from early MS, which are inflammatory and topographically associated with diffuse and focal leptomeningeal inflammatory aggregates (especially when captured in biopsies).[17] Subpial lesions can be extensive and are often found on flanking cortical banks within a sulcus, strongly suggesting a leptomeningeal origin. Leptomeningeal inflammation can organize into self-sustaining structures akin to tertiary lymphoid follicles.[19] Although MRI supports an association between leptomeningeal inflammation and subpial cortical demyelination,[20] robust detection

methods are lacking; the natural history of such lesions – and their responsiveness to therapy – remain unknown.

Spinal cord lesions are a major source of clinical disability. Perivascular and circumferential demyelination is often highly inflammatory and can involve gray matter.[21] Spinal cord atrophy results from focal inflammatory demyelination and remote neuroaxonal degeneration.[22] It is detectable by MRI, and the cross-sectional area of the spinal cord is therefore a promising outcome measure for clinical trials.[23,24]

Part of the CNS, the optic nerve is also a major target in MS, and loss of the contiguous retinal ganglion cells is well documented.[25] Retinal damage can be assessed in vivo by optical coherence tomography,[26] which shows, remarkably, substantial thinning of the retinal nerve-fiber and ganglion cell layers despite their lack of myelin. Thinning results from injury to axons in the optic nerve, which are derived from retinal ganglion cells, and which succumb to a dying-back process following retrobulbar inflammatory demyelination in acute optic neuritis. Recent studies clearly show concomitant retinal ganglion cell loss[27] even in the absence of clinical optic neuritis, presumably reflecting either subclinical optic nerve inflammation or retrograde trans-synaptic degeneration.

Epidemiology

It is not known whether MS has a single or multiple causes, and rarely (if ever) has a specific etiological trigger been identified. Nonetheless, various genetic and environmental risk factors have been demonstrated (Figure 3).[28] For unknown reasons, roughly three-quarters of people with MS are women, as is common in diseases that are considered autoimmune. Those with an affected first-degree relative have 2–4% risk for developing MS (compared to ~0.1% in the general population), and concordance in monozygotic twins is 30–50%. Genome-wide association studies, based on samples assembled from thousands of people with MS and matched controls, have identified >200 gene variants that raise the risk of MS, of which the most significant remains the human leukocyte antigen DRB1*1501 haplotype (odds ratio~3). Most risk alleles are associated with immune-pathway genes, consistent with the notion that autoimmune mechanisms are paramount in the development of clinical MS. To date, no validated genetic risk factor is known to influence clinical course, a limitation that reflects the difficulty in measuring disease severity in a disease that evolves over decades.

On the environmental side, major risk factors include geographical latitude (higher incidence in more temperate climates), which may reflect seasonal changes in sunlight exposure influencing vitamin D levels or pathogens prevalent in these regions, although a genetic contribution is possible as well. Tobacco exposure, obesity, and mononucleosis are also associated with enhanced risk for developing MS. Mononucleosis results from infection by Epstein-Barr virus in the post-pubertal population, and only a minority of people with a history of mononucleosis (and a tiny minority of all those infected with the nearly ubiquitous Epstein-Barr virus) eventually develop MS. Viruses other than Epstein-Barr have been suggested as potential causes of MS or MS-related disease activity, but none has been definitively proven. Some of these may act as molecular mimics, whereas others may

interfere with mechanisms that normally limit self-reactive cells. Differential susceptibility is reflected in the mouse model for MS, experimental autoimmune encephalomyelitis (EAE), such that specific myelin antigens are required to induce EAE in different strains of mice.[29] Along these lines, an interesting set of experiments showed that components of the intestinal microbiome can also strongly influence the propensity to develop EAE, especially in genetically predisposed strains with transgenes for myelin recognition by B and T cells,[30] and evidence for a similar phenomenon in MS patients is beginning to emerge.[31,32] Overall, the mechanisms by which genetic polymorphisms and environmental exposures raise the risk of developing MS remain the subject of intense investigation.

Pathogenesis

Tissue damage in MS results from a complex and dynamic interplay between the immune system, glia (myelin-making oligodendrocytes and their precursors, microglia, and astrocytes), and neurons (Figure 4). Although there is debate about whether the root cause of MS is intrinsic to the CNS or extrinsic, studies in animal models, particularly EAE in mice and marmosets, together with analysis of immune cells and their products in CSF and blood of humans, have disclosed a critical role for adaptive immunity.[29] However, despite the fact that some disease-modifying therapies first shown to ameliorate EAE eventually reached clinical practice, differences between EAE and MS are myriad and have a variety of causes, including the genetic and environmental heterogeneity of human beings relative to laboratory mouse strains, as well as a complex immune process in MS that clearly involves T cells (the major driver of EAE) as well as B cells, antibodies, and cells of the innate immune system (as described below). Moreover, although some animal models show clinical progression, none recapitulates the spectrum of critical pathological features of MS.[33] Genetic data suggests that the pathogenesis of MS shares important features with a variety of non-CNS autoimmune diseases.[34]

On the T-cell side, both helper (CD4+) and cytotoxic (CD8+) T cells have been described in MS lesions: CD4s are more concentrated in the perivascular “cuff,” whereas CD8s are widely distributed within the parenchyma.[35] Drugs that limit T-cell access to the CNS can reduce or eliminate new MS lesions. However, T cells reactive to myelin antigens have been observed in similar proportions in individuals with and without MS, suggesting either that these cells are dysfunctional in MS or that other immune factors also play critical roles.

Due to the early and dramatic success of B-cell-depleting antibodies in limiting MS lesion formation and clinical disease activity, there is renewed attention on the role of B cells.[36] It has long been known that the CSF of most people with MS harbors unique antibodies (“oligoclonal bands”) produced within the CNS. There is evidence that the antibody-producing function of B-lineage cells is important in some MS lesions.[7] However, due to the rapidity of the clinical response to B-cell depletion (as early as 8–12 weeks), even before the reduction of circulating immunoglobulin, it seems more likely that other functions of B cells, including antigen presentation to helper T cells and cytokine production, are more relevant.

Cells of the innate immune system are especially important in MS pathogenesis.[37] Blood-borne macrophages infiltrate active MS lesions and remove myelin debris and inflammatory byproducts; classically and alternatively activated macrophages, as well as mixed populations, have been described in these lesions. Microglia, the primary endogenous phagocytes of the CNS, are abundant in MS lesions, but whether their role is pathogenic or protective – or both – remains uncertain.[38] Microglial activation has been observed in the white matter of MS autopsy specimens, often remote from established lesions,[39] and may represent the earliest stage of lesion development (as is the case in animal models[40]). Once activated, microglia and macrophages are pathologically indistinguishable, but recent progress using gene-expression technology has opened the door to unraveling their separate contributions, potentially enabling targeted therapy development.[41] Studies in animals have suggested that monocyte/macrophage populations strongly influence myelin regeneration.[13,42]

Disturbance in the blood brain barrier is an important step in the development of white matter lesions, which show evidence of gadolinium extravasation early in their development. Abnormal vascular permeability precedes inflammatory demyelination in animal models[40] and potentially in MS.[43] Provocative studies in mice have shown that leakage of a key plasma protein (fibrinogen),[44] or even secretion of a bacterial toxin,[45] can trigger inflammatory demyelination by a cascade that involves microglial activation and subsequent adaptive immunity. In early MS lesions, vessels near the lesion center become permeable to gadolinium, which then diffuses passively into enlarged interstitial spaces; days later, the central breach in the blood brain barrier begins to repair, while small capillaries at the lesion edge become permeable – perhaps as part of the early wound-healing process.[46] Leptomeningeal inflammation can also contribute to vascular permeability, but this appears to be a chronic process.[20]

Glial cell biology

Acute MS plaques demonstrate activation of astrocytes and microglia and sometimes caspase-independent oligodendrocyte apoptosis.[7] Microglia are prominent in white matter lesions but are less activated in gray matter.[18] Importantly, microglia play dual roles, sometimes mediating inflammation but in other circumstances promoting repair by clearance of myelin debris.[47] In gray matter, microglia may limit damage through pruning of dysfunctional synapses that express classical complement cascade proteins (C1Q and C3). This pruning process may become pathological if activated astrocytes promote aberrant expression of complement at synapses, thereby accelerating degeneration.[48] Since astrocytes are a major component of the MS plaque, they are well positioned to enhance inflammation by releasing effector molecules, but they may also limit damage by taking up glutamate, providing metabolic support to axons, and maintaining the blood brain barrier.[49]

An under-emphasized but surprisingly common cell (~10% of all CNS cells) is the oligodendrocyte precursor cell, which expresses the proteoglycan NG2.[50] Oligodendrocyte precursor cells can differentiate into oligodendrocytes and are present even late in life,[51] but in MS they are often arrested at the plaque edge, or they may differentiate into premyelinating oligodendrocytes but fail to wrap myelin.[52] Thus, promoting

oligodendrocyte precursor cell differentiation is an attractive strategy to enhance endogenous remyelination, but this must be balanced against the potential of oligodendrocyte precursor cells to respond to cytokines and thereby participate in inflammation themselves.[53,54] Furthermore, oligodendrocytes may become dysfunctional even without dying, causing tissue damage through loss of trophic support to axons; whether such dysfunctional oligodendrocytes can participate in repair is unclear.

Axon biology

Although relative axonal sparing in the face of profound demyelination is a hallmark of MS pathology, axonal transections are frequent, especially acutely.[55] Studies with 2-photon microscopy in animal models have begun to elucidate relevant cellular and molecular processes, some potentially reversible.[56] In chronically demyelinated lesions, denuded axons remain vulnerable and can degenerate slowly; possible mechanisms include impaired axonal transport, mitochondrial dysfunction, and increased energy demands related to upregulation of ion channels.[57] Importantly, adaptive immunity – critical for new white matter lesion formation – is much less prominent in the slow neurodegeneration of progressive MS, highlighting the importance of glial activation and secondary mechanisms of injury.

Biomarkers

The most important diagnostic and prognostic MS biomarker – particularly early in the disease course – is MRI, which is currently the only technique that can interrogate the entire CNS in vivo. Unfortunately, the slow rate of progression in time frames relevant for clinical monitoring or clinical trials, together with heterogeneous pathogenic mechanisms and the impracticality of directly sampling CNS tissue (as opposed to blood or cerebrospinal fluid), have limited biomarker development for progressive MS.

Magnetic resonance imaging

By MRI, Inflammatory demyelination is easily visible, as are blood brain barrier changes that accompany its early development. Figure 1 shows the in vivo MRI appearance of lesions in the periventricular white matter (A), thalamus and brainstem (D), spinal cord (E), and optic nerve (F). Since 2000, MRI has been the key diagnostic test when individuals present with a clinical syndrome suggestive of MS, and the most recent criteria[58] – when applied carefully[59] – allow accurate diagnosis with a single scan. MRI diagnostic criteria are revised as new data accumulate, and standardized protocols for routine use have been proposed.[60,61] MRI is also critical in the development of new disease-modifying therapies, as new lesions are an order of magnitude more frequent than clinical relapses.[62] Indeed, the effect on new lesion formation by MRI in small proof-of-concept studies strongly predicts the effect on relapses in definitive trials.[63] Furthermore, MRI findings consistent with MS have been observed in healthy individuals scanned for other purposes (such as research), and up to 50% of individuals with this so-called “radiologically isolated syndrome” ultimately develop clinical MS, sometimes with a primary progressive course.[64,65]

Neurodegeneration in MS is best captured on MRI by measuring the size of the brain or spinal cord. An abnormally low “brain parenchymal fraction” – a measure of brain size

relative to intracranial capacity – can be taken as surrogate evidence of prior disease-related brain atrophy. In cohort studies, CNS atrophy has been documented even before clinical presentation.[66,67] Atrophy complements lesion-based biomarkers,[68] and proof-of-concept clinical trials using atrophy as primary outcome have begun to appear.[69,70] Recent studies of CNS atrophy have focused on specific gray matter structures (neocortex, thalamus).[71–73]

As conventional MRI biomarkers have not achieved strong correlation with clinical status on a population level, likely due to the heterogeneous presentation and course of MS and to the inherent variability of clinical measures, there has been a trend toward the use of imaging to investigate MS pathology and pathogenesis, including perivascular inflammation, cortical and spinal cord lesion development, myelin loss and regeneration, innate immune activation, leptomeningeal inflammation, and network function.[14] Such research has been facilitated by the advent of 7-tesla MRI, and to a lesser extent molecular tracers detectable by positron emission tomography. A particularly exciting innovation has been the use of optical coherence tomography to assess the retina rapidly at micron-level resolution. Retinal ganglion cell axon loss results in easily detectable retinal thinning, which importantly tracks with MRI changes in the brain[74] and can predict disability evolution on a cohort level.[75]

Blood and cerebrospinal fluid

Clonal expansion of immunoglobulin-secreting B cells and plasma cells in the CNS results in the characteristic finding of CSF-specific oligoclonal bands.[76] While the targets of these immunoglobulins are probably multifaceted, their presence implies a CNS-restricted immune response. However, the specificity of oligoclonal bands for MS is poor, and infections can cause the same pattern. Currently, no externally validated blood immune marker has adequate sensitivity and specificity to be used for MS diagnosis, probably reflecting the genetic and environmental heterogeneity of MS. CSF and serum neurofilament light chains are promising in their ability to reflect axonal pathologic processes in the CNS at the cohort level,[77] and there is ongoing interest in various types of noncoding RNA molecules that can affect gene expression.[78] Whether these approaches are useful in individuals remains unclear.

Therapies

As of October 2017, the US Food and Drug Administration has approved 15 medications for modifying the course of MS: 5 preparations of interferon beta; 2 preparations of glatiramer acetate; the monoclonal antibodies natalizumab, alemtuzumab, daclizumab, and ocrelizumab (the first B-cell targeted therapy); the chemotherapy mitoxantrone; and the small-molecule oral agents fingolimod, dimethyl fumarate, and teriflunomide. Dalfampridine has been approved as a symptomatic therapy to improve walking speed. It is beyond the scope of this article to discuss the relative benefits, risks, modes of action, and routes of administration of these various medications (though some targets are depicted in Figure 4), except to say that all are approved for relapsing-remitting MS and reduce, to various extents, the likelihood of developing new white matter lesions, clinical relapses, and stepwise accumulation of disability. Based on the ability of several of these medications to delay a formal diagnosis of MS following an initial attack, there has been a general move toward early treatment, though

as discussed above, the long-term value of this approach with respect to preventing progressive MS remains uncertain. The recent approval of ocrelizumab for primary progressive MS is a promising step, but the reasons for ocrelizumab's ability to slow progression[79] remain uncertain. Another important trend has been to escalate treatment with a target of "no evidence of disease activity," as evidenced by absence of new lesions, relapses, disability progression and, more recently, tissue atrophy;[80,81] however, it is doubtful that MS can be fully arrested with current therapies. Several incipient multicenter studies will compare early intensive treatment with more conventional treatment escalation approaches.

Small-scale studies have shown that immunoablation followed by autologous hematopoietic stem cell transplantation may be a highly durable and effective – and increasingly safe – therapy.[82] The tolerability and high efficacy of B-cell modulating therapies is a welcome development, though opportunistic infections can occur rarely, and post-marketing studies will need to monitor long-term side-effects. There are early-stage efforts to interfere with specific T-cell populations thought to drive MS, stemming from data that certain key subsets of helper T cells, including those that express both interferon-gamma and interleukin-17, are important.[83,84] Such approaches may involve specific inhibition, clonal deletion, or tolerization. Prior attempts at targeting cytokines have been unsuccessful[85] or even deleterious,[86] probably due to incomplete understanding of the roles of different forms of cytokines and their receptors, as well as compensatory pathways. The innate immune system has not been specifically targeted in large-scale MS trials, and given the high likelihood that this system can be both protective and deleterious, such efforts must be approached cautiously. Nonetheless, the ubiquity of innate immune cells in and around MS lesions underscores the need for further research.

Beyond the immune system, a great deal of work has revolved around tissue repair and protection. On the repair side, small studies have preliminarily reported mixed results for therapies that promote endogenous remyelination through various pathways.[87] Interestingly, based on preclinical data including in vitro screens and testing in models such as EAE, several approved drugs (targeting, for example, nuclear hormone receptor, histaminic, cholinergic (muscarinic), and adrenergic pathways) are being tested for remyelination or myelin protection. Transplantation of neural or oligodendrocyte precursor cells into the brain is effective in animal models, but well-designed clinical trials have not been undertaken in MS, and it is likely that promotion of endogenous remyelination will prove more fruitful and feasible, especially if the inhibitory factors inherent in the MS plaque can be overcome.[52] A challenge for remyelination trials is the lack of a robust, easily deployable biomarker of success. Visual evoked potentials have been used in small studies, but standardization is difficult and technical variability high. The specificity of high-resolution imaging-based markers for myelin regeneration remains questionable. Nevertheless, MRI is highly sensitive to changes in myelin, and such sensitivity can be exploited in early proof-of-concept trials.[88]

Axonal protection is actively being examined. Results from initial clinical trials of a wide variety of drugs have been published or reported, with several medium-to-large studies currently underway.[89] There is an emerging consensus that slowing the rate of cerebral or spinal cord atrophy is a feasible goal, which at the proof-of-concept stage can be undertaken

in several hundred people over a 1–2-year period.[90] However, definitive proof of neuroprotection – an elusive goal in many neurological conditions – awaits larger studies with clinical endpoints.

Conclusions and future directions

Meaningful advances in basic immunology, myelin biology, and neuroscience, together with a global focus on halting progressive accumulation of disability,[91] have opened the promise of a multipronged understanding of, and therapeutic attack on, MS. At the same time, a renewed focus on lesion development and repair – more broadly conceived to include lesions in white matter, gray matter, and leptomeninges – should ultimately unify lines of research, particularly on the side of fluid and imaging biomarkers and clinical outcomes, which have sometimes strayed too far from the causative biology. The richest conception of MS will allow appreciation of common pathology, which, in the setting of variable triggers and clinical courses, makes MS among the most heterogeneous, and remarkable, of all neurological disorders.

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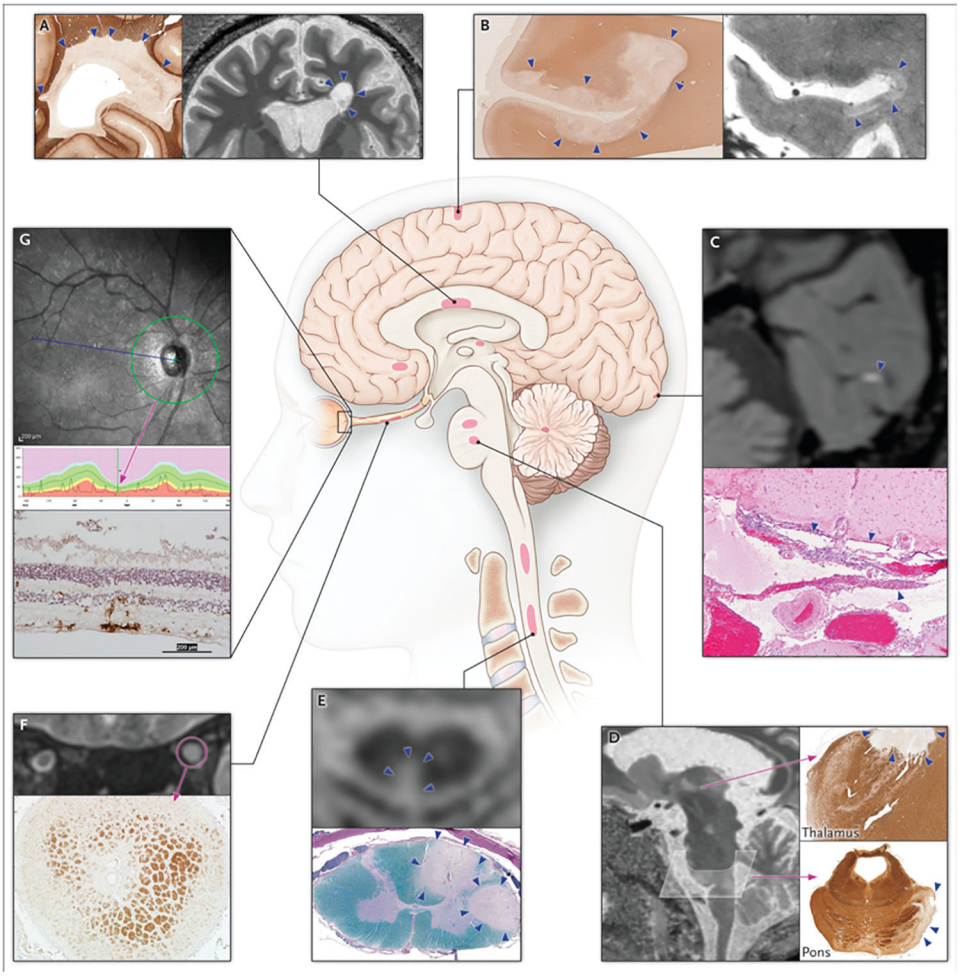

Figure 1. Topography of multiple sclerosis lesions.

Schematic of lesion location, calling out imaging and pathological examples, in the (A) periventricular white matter; (B) subpial cortex; (C) leptomeninges; (D) thalamus and pons; (E) spinal cord; (F) optic nerve; and (G) retina. (A, B, D) 7-tesla MRI of a 40-year-old woman with relapsing-remitting MS, with similar pathological findings (in different cases) highlighted by immunohistochemistry directed against myelin proteolipid protein. (C) 3-tesla post-gadolinium MRI of a 35-year-old woman with secondary progressive MS, with corresponding pathological findings in the meninges of a different case (hematoxylin and eosin stain). (E) 3-tesla MRI of a 60-year-old woman with relapsing-remitting MS and corresponding pathological findings in a different case (Luxol fast blue-periodic acid Schiff stain). (F) 3-tesla MRI of a 31-year-old woman with relapsing-remitting MS and corresponding pathological findings in a different case (anti-proteolipid protein immunohistochemistry). (G) Spectral-domain optical coherence tomography reconstruction showing thinning of the peripapillary retinal nerve fiber layer. The normal range of retinal thickness is shown in green, and for this particular individual (black line) the retina is thinner than 99% of control eyes. The bottom panel shows corresponding pathological findings in a different case (immunohistochemistry for Iba-1, a microglial marker, with hematoxylin counterstain). Lesions are denoted with arrows or circles.

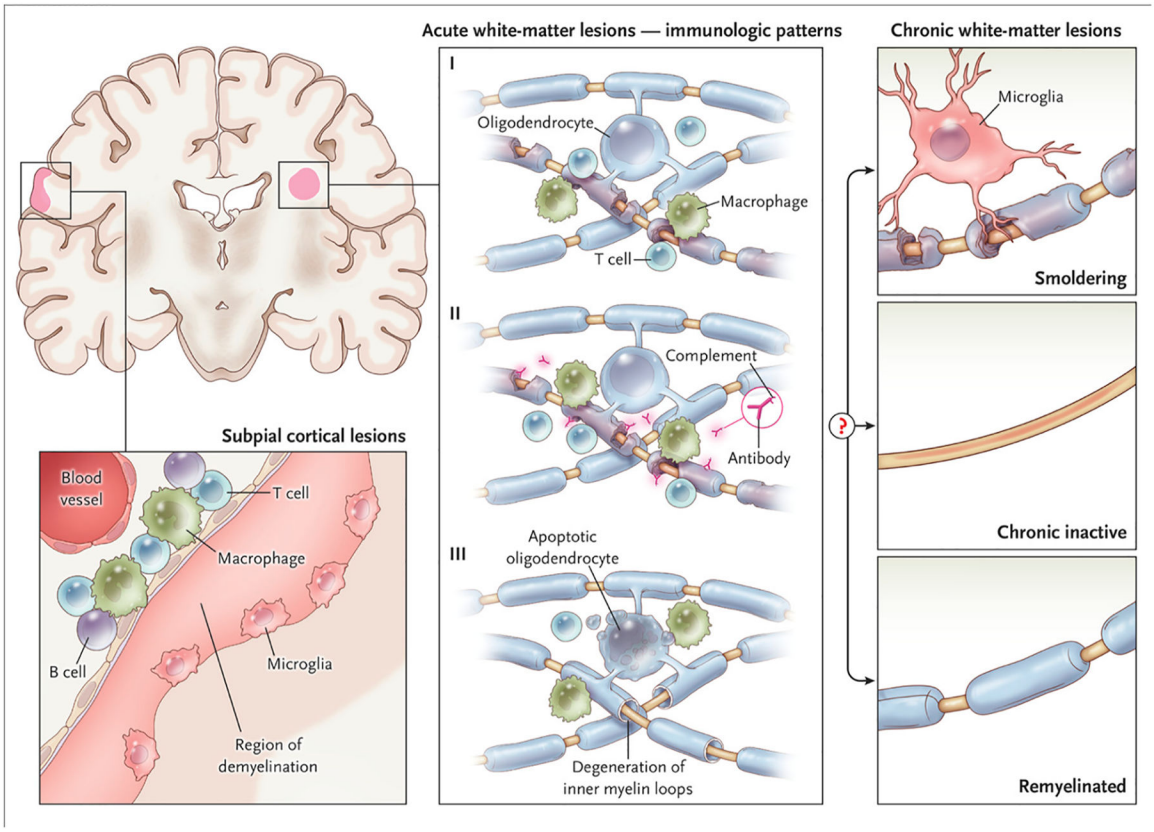

Figure 2. White and gray matter lesions.

Early active white matter demyelination falls into three major categories. The most common types (Patterns I and II) show a background of mononuclear phagocytes with perivascular and parenchymal T-cell infiltration; Pattern II is further distinguished by immunoglobulin and complement deposition. In ~25% of biopsied active lesions (Pattern III), oligodendrocyte apoptosis is accompanied by a “dying-back” oligodendrogliopathy, starting at the “inner tongue.” These lesions show resemble viral, toxic, and ischemic processes, and can be destructive. After the acute phase, factors that remain poorly understood determine whether surviving axons in a lesion are invested by a thin myelin sheath (“remyelinated”), whether inflammation resolves without remyelination (“chronic inactive”), or whether inflammation and slow myelin degeneration persist (“smoldering”). Smoldering lesions are most common in progressive MS. The subpial cortical lesion, which is also more common in progressive MS, is characterized by demyelination of the superficial cortex, possibly associated with inflammation in the overlying leptomeninges and sparse microglia at the border between demyelinated and myelinated neuropil.

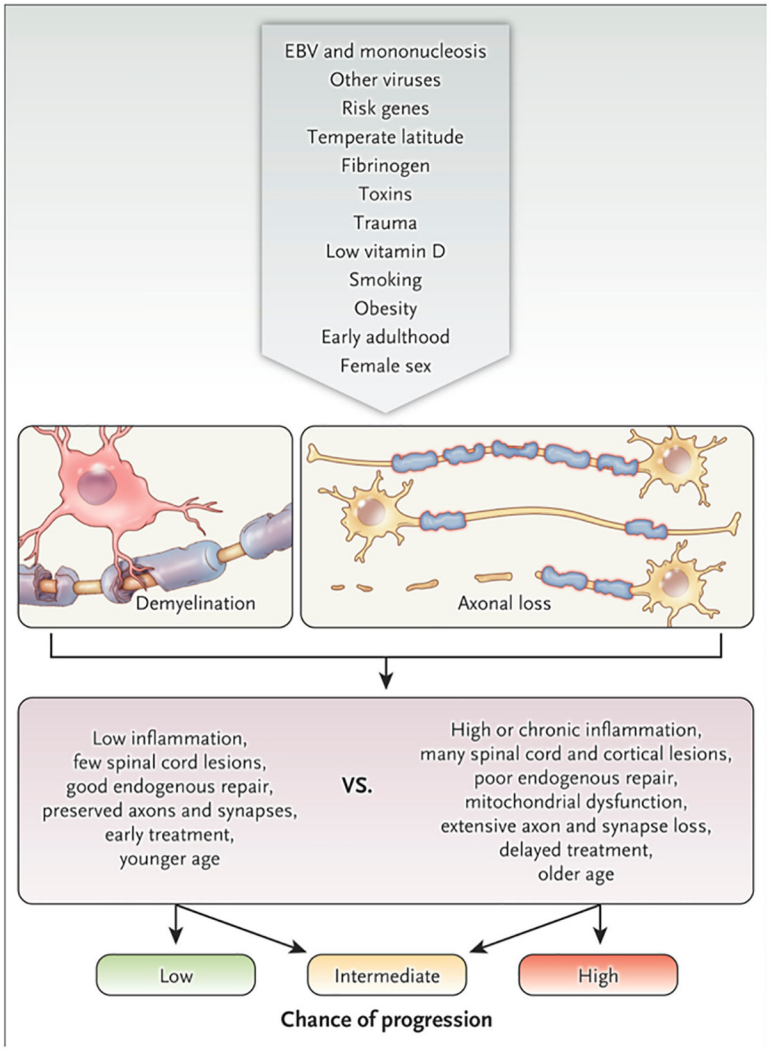

Figure 3. Risk factors, triggers, modifiers, and disease courses.

It is exceedingly unlikely that multiple sclerosis will ultimately be attributed to a single cause. Rather, the genetic and environmental factor or combination of factors that predispose to and initiate the disease, and that modify its course, are highly diverse from one person to the next. The top row of the figure depicts the funneling of proposed factors, for which varying levels of evidence exist, into the development of inflammatory, demyelinating lesions with heterogeneous axonal loss (second row). The third row lists features of the lesions and their consequences that are generally salutary or deleterious and that modify the chance of progression (bottom row).

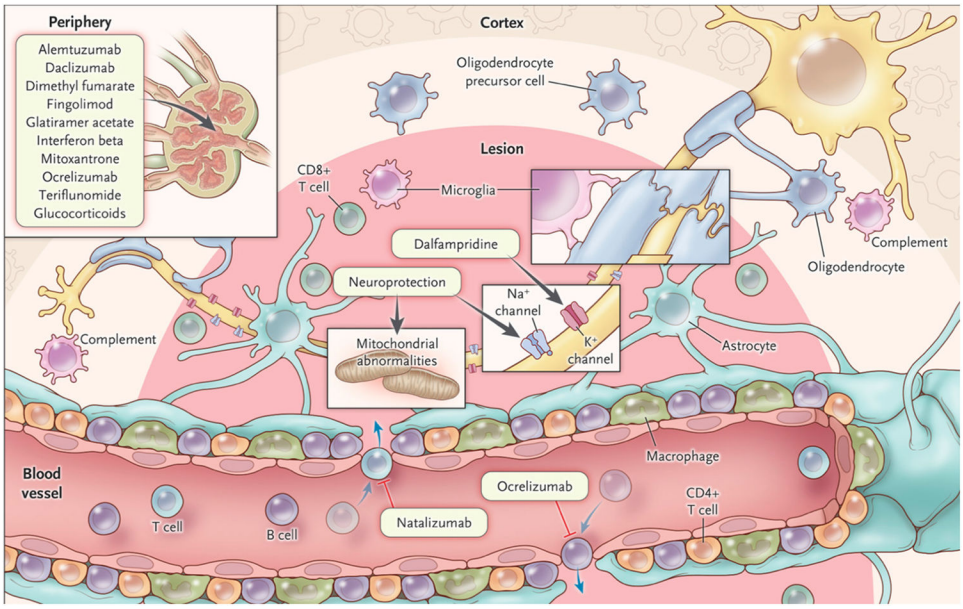

Figure 4. Cells, molecules, and therapies.

Simplified schematic depiction of major cell types within white matter MS lesions, along with several current and promising therapeutic targets in the central nervous system and in the periphery. More detailed descriptions can be found in the text.