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Insights Into the Molecular Pathogenesis of Progression in Multiple Sclerosis

Potential Implications for Future Therapies

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Despite recent advances in the diagnosis and treatment of multiple sclerosis, we still lack a consensus regarding the causes, pathogenesis, and mechanisms of disease progression. Current evidence indicates that multiple sclerosis is an inflammatory neurodegenerative disorder in which both adaptive and innate immunity play important roles in initiation and maintenance of the disease. Recent evidence supports the notion of molecular pathologic abnormalities beyond the plaques and dysfunction of neurons in normal appearing areas, in addition to the multifocal demyelination and axonal loss, as important features that may underlie early reversible changes in the disease. Chronic failure of remyelination, axonal regeneration, and neuronal dysfunction may contribute to disease progression. This article discusses the emerging molecular evidence for the progression of multiple sclerosis with particular focus on alterations in the local central nervous system microenvironment of neural and glial cells. The molecular pathways leading to structural and functional neurodegeneration and those that prevent regeneration need to be identified in order to design new therapeutic strategies that can halt or even reverse disease progression. *Arch Neurol. 2006;63:25-33*

Multiple sclerosis (MS) affects 1 million people worldwide and is the leading cause of neurological disability in young adults.[1] The disease has substantial personal and economic costs. It is an immune-mediated demyelinating and neurodegenerative disease of the central nervous system (CNS). Initially, more than 80% of patients experience a relapsing-remitting form of disease, characterized by exacerbations of neurologic deficits with periods of symptom remission. After several years, a high proportion of patients enter a secondary progressive phase characterized by irreversible deficits and neurodegeneration. About 10% of patients exhibit a primary progressive form of the disease from onset.[1]

There is substantial evidence that immune dysregulation plays an important role in the disease process in MS.[2] Thus, current therapies for MS are immunomodulatory and have been effective in decreasing relapse rates but seemingly far less effective in preventing disease progression, defined as an accumulation of neurologic disability. Pathologically, neuronal and axonal loss as well as demyelination are observed in MS lesions, and they likely contribute to disease progression. In addition, evidence of remyelination can be seen in "shadow plaques"; however, a pronounced failure of remyelination occurs as the disease progresses.[3-5]

Although MS treatment has advanced significantly in the past 10 years, several pressing questions remain unanswered. First, there is a weak correlation between standard magnetic resonance imaging findings and clinical symptoms. In particular, there is a discrepancy between T2 lesion load and clinical disability. Some of the discrepancy has been resolved by the use of specialized magnetic resonance imaging techniques such as diffusion tensor imaging that reveal pathological changes in normal appearing white matter.[6,7] In ad-

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dition, differences in radiological patterns between MS subtypes may also contribute to this dissociation.[7,8] To more definitively understand the evolution of MS pathologic abnormalities during the disease course, more sensitive imaging techniques and validation of these techniques by correlation of radiological with pathological findings are required.

Second, what determines the clinical outcome of benign vs malignant disease? This question requires investigation of the genetic modifiers that control immune response on the one hand and capacity for repair on the other and is currently being addressed through large-scale genetic studies. Of direct clinical relevance is the third question, that of responders vs nonresponders to therapy. This question is being addressed by several investigators through gene expression profiling of peripheral blood mononuclear cells from patients before and after start of therapy to determine the mechanisms of therapy and gene profiles that may have predictive value for response to therapy.[9] Fourth, the major challenge facing clinicians today is to determine the mechanisms of disease progression and how to prevent it. Here, we focus on the emerging evidence of the contributions of resident neural cells to disease progression in MS with attention to neuroglial interactions. For reviews of the immunological aspects associated with disease progression, consult previous articles in the ARCHIVES.[10,11]

CHRONIC ABNORMALITIES IN THE CELLULAR AND MOLECULAR MICROENVIRONMENT IN THE PLAQUES AND BEYOND AS SUBSTRATE FOR PROGRESSION

The current model of MS pathogenesis suggests that autoreactive T cells, B cells, myelin-specific autoantibodies, and macrophages enter the CNS and initiate demyelination and irreversible axonal loss that accumulate in chronic lesions by direct damage and in normal appearing white matter as a result of wallerian degeneration.[12] However, this model alone cannot explain disease progression, given the complexities of immune-neural interaction in the CNS and the heterogeneity of pathologic abnormalities in patients with MS.[13] It is likely that immune and neural dysregulation within the CNS is as critical in MS pathogenesis as the peripheral immune response and might also influence disease outcome and progression.

Evidence of Molecular Activation of Astrocytes and Microglia as "Effector" Cells in Chronic Pathogenesis in MS

Astrocytes and microglia respond to environmental cues from neural cells and immune cells, establishing a rich network of connections that can regulate the local cytokine environment during normal homeostasis and in disease. It was initially suggested that astrocytes might act as antigen presenting cells in the CNS, but in humans this role is still unclear. However, alterations in the regulation of glutamate by astrocytes are observed in MS lesions. Degradation of glutamate is mediated by glutamine synthetase and glutamine dehydrogenase, and these have been found to be reduced in MS lesions.[14] Similarly, glial transporters responsible for uptake of glutamate by astrocytes are also decreased in MS lesions,[14] suggesting an increase in extracellular concentration of glutamate that may be toxic to oligodendrocytes and neurons. However, the timing and the relative contribution of excitotoxicity to the overall pathological picture is not known.[14,15] In addition, factors produced by astrocytes may inhibit remyelination. An example of this is Jagged, a Notch ligand, which is up-regulated after exposure to transforming growth factor β and has been shown to reduce oligodendrocyte progenitor cell (OPC) maturation.[16] However, in the model of cuprizone-mediated demyelination, Stidworthy et al[17] found that the lesions remyelinate completely despite abundant expression of Jagged in glial cells and Notch in OPCs. Furthermore, ablation of Notch in OPCs did not change the rate of remyelination in this model.[17] This discrepancy may relate to differences in the species studied, but the role of Jagged-Notch in inhibiting remyelination needs further study. Furthermore, astrocytes may produce cytotoxic compounds in MS. It was recently shown that astrocytes produce syncytin, a human endogenous retrovirus encoded glycoprotein that is toxic to oligodendrocytes and produces neuroinflammation.[18] In addition, based on the accumulated evidence from pathological studies in humans and animal models, chronically activated parenchymal and perivascular microglia appear to be important in the disease process because complete eradication of microglia decreases substantially experimental autoimmune encephalomyelitis (EAE).[19] There are numerous reports of microglia-induced neurotoxicity in vitro and evidence of microglia activation in the CNS. However, a direct role for microglia in neuronal dysfunction in vivo is less well established. **Table 1** lists the molecules that have been dysregulated in microglia and astrocytes in patients with MS.

Evidence of Molecular Dysregulation of Neurons as "Afferent" Cells in Chronic Pathogenesis in MS

Neuronal cell loss and apoptosis of small numbers of neurons are present in demyelinated cortical MS lesions.[20] Human T cells can induce apoptosis of human fetal neurons in vitro[21]; however, few T cells are seen in these areas. The degree of neuronal apoptosis observed in MS is not sufficient to explain the progression and severity of the disease, so in addition to cell death, it appears that a large number of neurons or axons in normal appearing white and gray matter in MS may also be dysfunctional. The studies supporting this notion report alteration in genes that participate in transcriptional regulation and inflammation,[6,7,22-24] such as increased expression of 5-lipoxygenase and caspase 1; alterations in the distribution of sodium and calcium channels in pathological specimens,[25,26] such as the N-type Ca^{2+} channel; and decreased expression of metabolism-related genes, such as cAMP (cyclic adenosine

Table 1. Molecules Found Dysregulated in Microglia and Astrocytes of Patients With Multiple Sclerosis

Molecule	Function
	Microglia/Macrophages
Increased	
iNOS	Produces oxidative stress
GRM8	Induces nonneurotoxic activation of microglia
CXCL1	Chemokine attraction of infiltrating immune cells
CXCR2	CXCL1 receptor, mobilization of activated microglia
GRM2	Glutamate receptor, metabotropic 2
mGluR1	Activation is associated with neuroprotection and secretion of BDNF by microglia
IL-10, IL-10R, and IL-4R	Anti-inflammatory
Oncostatin M	Proinflammatory cytokine
IL-6	Induces neurodegeneration
CCR2, CCR3, CCR5, and MIP1 α	Migration
Leukotriene A_4 hydrolase	Leukotriene metabolism, proinflammatory
5-lipoxygenase	Proinflammatory
MCP1	Migration
RelA	NF-kappa b member, proinflammatory
TNF α	Cytotoxic cytokine, induces neural cell death in vitro
Calpain	Protease, degrades myelin
TGF β1 and TGF β2	Anti-inflammatory
Annexin-2 tetramer	Apoptosis
NgR	Activated by myelinolysis
FasL	Proapoptotic molecule, induces apoptosis in Fas+ oligodendrocytes
Nav1.6	Increases phagocytic activity of microglia; phenytoin blocks microglia activation
Decreased	
IGFBP-2	Growth factor
	Astrocytes
Increased	
14-3-3 protein	Increased CSF levels are associated with an increase of disease progression
mGluR4 and mGluR8	Excitotoxicity
Syncytin	Induces oligodendrocyte toxicity
Jagged-1	Inhibits oligodendroglia differentiation
mGluR5 and mGluR2/3	Glutamate receptors involved in excitotoxicity
IL-10, IL-4, IL10R, and IL4R	Th2 cytokines, anti-inflammatory
Oncostatin M	Proinflammatory molecule
iNOS	Induces oxidative stress
CCR3 and GRO-α	Migration, attraction of infiltrating cells
IP-10	CXCR3 ligand
IL-8	Migration
Alpha beta cristallin	Immunomodulation
CCR5	Migration
TNF α	Cytotoxic
IL-6	Neurotoxic
MHC-II	Antigen presentation
Calpain	Activates proteases, digests myelin
IGFBP-1	Growth factor
C5a	Complement associated with inflammation
IGF-1	Growth factor
Tenascin-R	Extracellular matrix
TGF β1	Anti-inflammatory molecule, activates the expression of oligodendroglial inhibitor Jagged-1
TGF β2, TGF β3, TGF βR1, and TGF βR2	Anti-inflammatory molecules
Annexin-2 tetramer	Apoptosis
NgR	Activated by myelin degradation
MCP-1, MCP-2, and MCP-3	Migration
BAFF	TNF-related molecules
Tenascin-C	Extracellular matrix
Decreased	
Neuregulin	Axonal support

Abbreviations: BAFF, B-cell activating factor belonging to tumor necrosis factor family; BDNF, brain-derived neurotrophic factor; C5a, complement component 5a; CCR, chemokine (c-c motif) receptor; CSF, cerebrospinal fluid; CXCL, chemokine (c-x-c motif) ligand; CXCR, chemokine (c-x-c motif) receptor; FasL, Fas ligand; GRM, glutamate receptor metabotropic; GRO-α, growth regulated gene-alpha; IGF, insulinlike growth factor; IGFBP, IGF binding protein; iNOS, inducible nitric oxide synthase; MCP, monocyte chemoattractant protein; mGluR, metabolic glutamate receptor; MHC, major histocompatibility complex; MIP1 α, macrophage inflammatory protein-1 alpha; Nav1.6, voltage-gated sodium channel; NF, neurofilament; NgR, Nogo receptor; RelA, v-rel reticuloendotheliosis viral oncogene homolog A; TGF, transforming growth factor; Th2, T helper 2; TNF, tumor necrosis factor.

monophosphate) response element binding protein 1, sterol delta-7 reductase, aspartoacylase, and epsin-2.[23] Thus, neurons and oligodendrocytes outside the lesions may become chronically dysfunctional and, in the presence of subtle but persistent chronic inflammation from activated glial cells and the failure of protective mechanisms,[27-29] result in progressive impairment and susceptibility to structural loss of axons and cell death (Table 1). **Table 2** summarizes the molecular pathways in neurons, oligodendrocytes, and progenitors that were found to be dysregulated in patients with MS.

What Are the Mechanisms That May Contribute to Neuronal and Axonal Dysfunction?

Chronic Demyelination Itself. Substantial axonal loss has been reported in the spinal cord[30-33] as well as in the corpus callosum and optic nerve of patients with MS,[34] and factors such as demyelination itself have been implicated. The integrity of axons is dependent in part on the integrity of the myelin sheath,[35] and an intact myelin sheath protects the axon from immune-mediated damage.[36] Mice lacking proteolipid protein and humans with mutation in the proteolipid protein gene develop axonal swellings and degeneration.[37] Both proteolipid protein and myelin-associated glycoprotein[38] are believed to be essential for delivering myelin-derived trophic signals to axons.[38]

Direct Damage by Inflammatory Cells. In addition to demyelination, there is strong evidence that direct interaction with inflammatory cells plays a critical role in the induction of axonal damage. The presence of macrophages/microglia as well as $CD8^+$ T cells in MS lesions has been correlated with axonal injury.[32] Soluble mediators such as complement,[39] antibodies,[40] and various cytokines[41,42] are critical components of the immune inflammatory process and either individually or in concert have been implicated in axonal degeneration, neuronal dysfunction,[43] and oligodendrocyte cell death, but some cytokines may have neuroprotective effects[44] that may be exploited therapeutically. Inflammatory mediators can indirectly promote degeneration by up-regulating excitotoxic receptors on oligodendrocytes and neurons.[15] Astrocyte-derived tumor necrosis factor α regulates the strength of synaptic transmission by modulating the expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors[45] that are involved in excitotoxicity. These molecular changes are present in normal appearing white matter[23,24,46] and can also be seen in normal aging brain[47] and may be sustained in the absence of obvious inflammation.[23] The exact role of tumor necrosis factor α is very complex; although known to be neurotoxic for neurons, oligodendrocytes, and their progenitors in vitro,[48] in vivo blockade of tumor necrosis factor α resulted in worsening of MS, suggesting a yet-to-be-defined protective role of tumor necrosis factor α[49] or a role in remyelination in vivo.[50]

Oxidative Stress and Neuronal Gene Expression. Oxidative stress may also contribute to neuronal dysfunction and axonal loss.[51] Activated macrophages and microglia[51] and astrocytes[52] produce inducible nitric oxide synthase and nitric oxide, which are associated with oxidative damage to mitochondrial DNA in chronic active MS plaques, ultimately leading to cell dysfunction and death.[53] Furthermore, experimental evidence shows that electrically active axons exposed to high concentrations of nitric oxide have enhanced susceptibility to persistent conduction block and axonal degeneration.[36,54] In addition, a decrease in expression of several neuronal genes, such as synaptosomal-associated protein 25, glycine receptor, lissencephaly-related protein, γ-aminobutyric acid receptor, and Neuro D, has been reported by 2 independent groups,[46,55] possibly mediated by chronic oxidative damage in susceptible genes[47,53] (Table 2). Thus, reduction of oxidative stress early in the disease course may ultimately prevent chronic damage.[56]

Impact of Simultaneous Pathologic Abnormalities in the Progression of Disease. Our current perception that MS is a disease with 2 different temporally distinct phases, an inflammatory and a neurodegenerative phase,[57] needs to be reevaluated because recent observations reveal that both phases can occur simultaneously.[22,28-30] N-acetyl aspartate (NAA) is a metabolite localized almost exclusively in neurons and neuronal processes in the mature brain.[58] The resonance intensity of NAA therefore provides an index of neuronal integrity and can be measured by spectroscopy; a decrease in the NAA peak correlates with axonal and neuronal damage in MS and stroke.[28,29] In MS, a decrease in NAA can be found early in the disease and provides evidence of early neuronal and axonal damage[59] but can also be seen with alterations in neuronal metabolism without structural damage as shown in other neurological disorders.[60] Consequently, abnormalities of NAA can be found in regions far from the local demyelinating areas of the brain, reflecting dysfunction of axons in projection pathways[61] that may be the substrate of wallerian degeneration.[22,26] Central nervous system homeostasis is maintained by local oxygen supply and pH control; it is thus not surprising that inflammation may jeopardize the delicate homeostatic balance, as described by Lassmann,[62] who found ischemic-like changes in a subset of MS lesions.

Unlike stroke or other neurodegenerative diseases that have a regional preponderance, MS is characterized by multiple "hits" involving various locations within the CNS at different times. Each subsequent hit initiates focal areas of damage and more widespread areas of oxidative stress dysfunction, leading to the initiation of progression and neurodegeneration.

We suggest that the substrate for chronic neurodegeneration in MS is initiated long before any widespread structural damage. Neuronal dysfunction in normal areas characterized by metabolic and molecular changes may occur during the initial attacks.[23,24,46] Because this process may be preventable, we need to learn more about this initial stage

Table 2. Molecules Found Dysregulated in Neurons and Oligodendroglial Cells of Patients With Multiple Sclerosis

Molecule	Function
Neurons	
Increased	
mGluR1	Glutamate receptor, excitotoxicity
α-Tubulin, β-Tubulin, and double cortin	Cytoskeleton
Reticulon	Inhibits axonal regeneration
Dynamim- and synaptosome-associated proteins	Synaptic protein
Nav1.2 and Nav1.6	Associated with axonal degeneration
Na^+/Ca exchanger	Increases Na^+ influx with increase in Ca^{2+} influx, inducing axonal degeneration
Reticulocalbin	Calcium binding proteins
Decreased	
Neuroregulin	Axonal support; reduction causes hypomyelination and reduced nerve conduction velocity
NCAM	Axonal pathfinding
IG-2 receptors	Growth factor
Neuro D	Transcription factor
ChaT	Cholinergic enzyme neurotransmission
CRE-BP1	Neuronal survival
Presenilin	Multifunctional molecule associated with neuronal survival, neurogenesis
Potassium channel Kv 2.1 and GABA receptor α	Neurotransmission
Pentraxin 1	Synaptic recycle
GAP-43	Axonal regeneration and growth factor
SCG10	Required for neural cell growth, synapse formation
Synaptotagmin, synaptobrevin 1-2, and synapsin	Synaptic proteins
Oligodendroglial Cells	
Increased	
Notch1 and Hes5	Inhibit oligodendrocyte differentiation
PTPRZ1	Expressed in remyelinating oligodendrocytes, promotes survival
ErbB2, ErbB3, and ErbB4	Promote oligodendrocyte differentiation
GGF-2	Oligodendrocyte growth factor
Olig-1	Oligodendrocyte differentiation
14-3-3 Protein	Associated with neural damage
Bcl-2	Associated with remyelinating lesion (survival)
CXCR1, CXCR2, and CXCR3	Migration
Alpha beta cristallin	Immune mediation
Fas antigen	Induces apoptosis
Decreased	
Myelin-associated glycoprotein, peripheral myelin protein 2, proteolipid protein, oligodendrocyte-myelin glycoprotein, and myelin-associated oligodendrocytic basic protein	Myelin synthesis
UDP-galactose ceramide galactosyl transferase	Metabolism of myelin

Abbreviations: Bcl-2, B cell CLL/lymphoma 2; ChaT, choline acetyltransferase; CRE-BP1, cAMP (cyclic adenosine monophosphate) response element binding protein 1; CXCR, chemokine (c-x-c motif) receptor; ErbB, x-erb-b2 erythoblastic leukemia viral oncogene homolog; GABA, γ-aminobutyric acid; GAP-43, growth associated protein 43; GGF-2, glial growth factor 2; Hes5, hairy and enhancer of split 5; Kv, potassium channel; mGluR1, metabolic glutamate receptor 1; Nav, voltage-gated sodium channel; NCAM, neural cell adhesion molecule; Notch1, notch member 1; Olig-1, oligodendrocyte transcription factor 1; PTPRZ1, protein tyrosine phosphatase–receptor type Z polypeptide 1; SCG10, superior cervical ganglia 10; UDP, uridine diphosphate.

and develop therapeutic strategies to prevent irreversible damage as soon as the diagnosis of MS is made.

Impact of Aging in the Progression of Disease. An important consideration when thinking about disease progression in MS is the possibility that normal brain aging may contribute or even precipitate the onset of progression. During "normal aging," a set of genes with central roles in synaptic plasticity, vesicular transport, and mitochondrial function have reduced expression after age 40 years.[47] This is attributed to DNA damage by oxidative stress in the promoter regions, resulting in reduced expression of selectively vulnerable genes involved in learning, memory, and neuronal survival.[47] Aging also has an adverse effect on remyelination, affecting recruitment and differentiation of OPCs in a model of demyelination.[63] Brain aging is a risk factor for other neurodegenerative diseases, including stroke and Alzheimer disease. Thus, it seems important to study the impact of aging on neuronal function in MS. An aging effect on progression of disease may contribute to the data of Confavreux et al[64] that showed variation in the time to reach an Expanded Disability Status Scale score of 4.0 among patients but consistency in the time to progress from the Expanded Disability Status Scale score 4.0 to 6.0. Data from an Italian cohort also suggests age-related onset of progression[65] in that clinical disability was influenced by the patient's age. Other genes associated with inflammation and aging such as apolipoprotein E ε4 have an impact on disease severity in MS.[66] Thus, it is possible that normal aging and other modifier genes could have a previ-

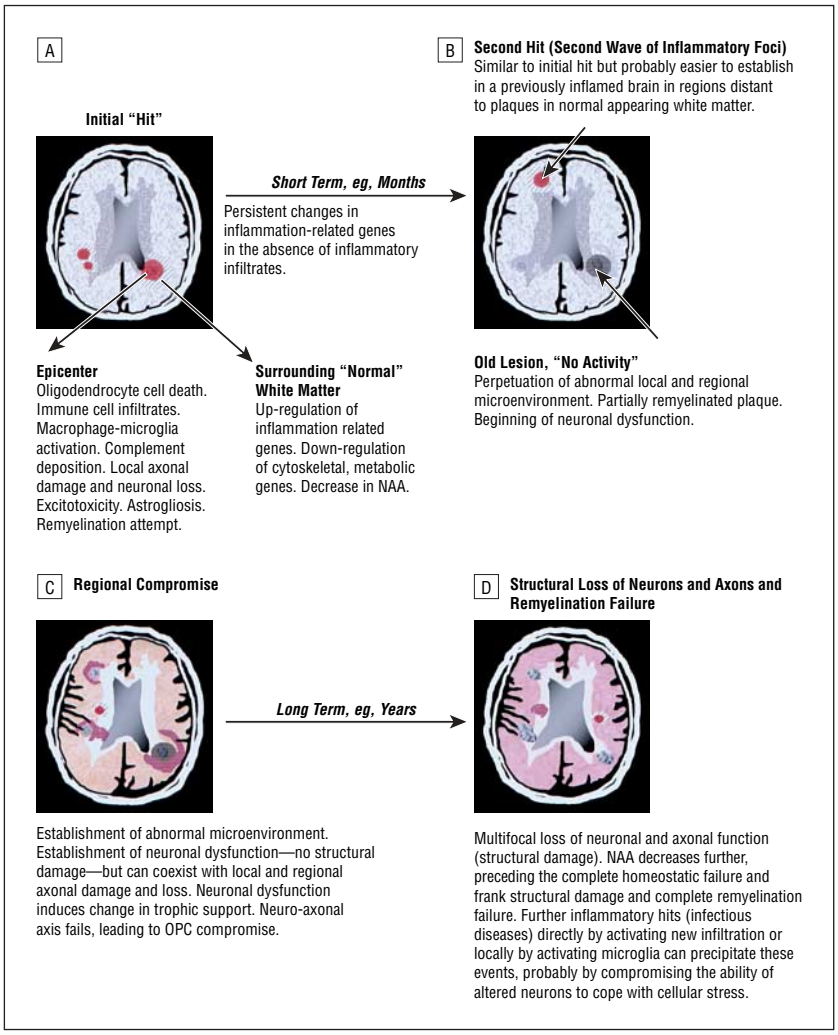

Figure. A pathophysiological working hypothesis for a model of progression in multiple sclerosis. The model is based on our current understanding of the disease pathologic abnormalities. The changing color of brain parenchyma signifies a transition from local dysfunction to a regional and then multifocal compromise. NAA indicates *N*-acetyl aspartate; OPC, oligodendrocyte progenitor cell.

ously unforeseen role as adjuvants of neurodegenerative changes in MS.

A Model for Progression. A model of the steps leading to disease progression is presented in the **Figure**. In this model, the initial hit mediated by immune cells and repeated bouts of inflammation results in a chronic abnormal microenvironment, leading to eventual regional compromise and brain dysfunction, which may contribute to disease irreversibility. In areas of plaques, inflammation mediated by adaptive and innate immunity initiates destruction of myelin and axons while outside the plaques, subacute and sustained inflammation is mediated by activated glia[67] that establish an abnormal microenvironment. Neuronal dysfunction occurs early and a new adaptive abnormal steady state in the neuron is established, represented by alteration of gene expression and function that may be worsened by aging. A new event near the original site of pathologic abnormality (a new lesion, infection, trauma) worsens inflammation and surpasses the adaptive capacity of neurons,[68] resulting in more neuronal dysfunction or cell autonomous axonal loss. New lesions in areas not previously affected multiply the regions with an abnormal microenvironment. Cell death in a dysregulated environment may further sustain inflammation by activated glia cells, resulting in a vicious cycle. At the same time, axonal loss and wallerian degeneration may contribute to distant areas of pathologic abnormality.[22] Because there is heterogeneity in MS lesions, different combinations of these events may contribute to progression in MS (Figure).

RELEVANCE TO THE STUDY OF NEUROSCIENCE

Potential Targets for Halting Progression and Increasing Regeneration

Restoring Neuronal Dysfunction. Current evidence suggests that the neurodegenerative component in MS is critical for the progression of disability.[31] Thus, novel therapies for MS should target not only the peripheral immune response but also the underlying mechanisms of dysregulated CNS inflammation and neurodegeneration and should promote repair and regeneration in the CNS. There are now therapies that can prevent exacerbations, but none forestall the progression of neurodegeneration, in part because of a lack of identification of the molecular pathways that mediate the chronic alteration of neurons and surviving oligodendrocytes. Neuronal dysfunction has been described in EAE. D'Intino et al[69] demonstrated a deficit in learning and memory performance in rats with EAE that correlated with a decline in choline acetyltransferase activity and nerve growth factor messenger RNA levels in the cortex, hippocampus, and basal forebrain neurons, without apparent cell loss. Furthermore, selective acetylcholinesterase inhibitors restored cognitive performance, choline acetyltransferase activity, and nerve growth factor messenger RNA expression in the rats with EAE.[69] Other potential targets include neuroprotective cytokines, such as leukemia inhibitor factor and ciliary neurotrophic factor, a cytokine that promotes neuronal survival and maturation of oligodendrocytes. Ciliary neurotrophic factor–deficient mice have more severe EAE with increased oligodendrocyte apoptosis and severe vacuolar dystrophy of myelin and axonal damage.[70] In addition, ciliary neurotrophic factor was reported to be neuroprotective in a model of optic neuritis,[71] and leukemia inhibitor factor promoted the survival of oligodendrocytes in EAE.[72]

Promotion of Remyelination. We also need therapies that promote effective remyelination. Adult brain contains neural stem cells and progenitors scattered throughout the CNS in regional pools, and these cells have the capability to engage in endogenous repair. The lack of effective repair in MS suggests that either the size or number of lesions overcome the capacity of endogenous precursor cells to repair the damage or that precursor cells could themselves be targets of the inflammatory pathologic process.[73]

How do we boost the repair potential of neural stem cells? One approach is to manipulate the molecular signals that control the differentiation of endogenous neural stem cells and OPCs while avoiding unwanted proliferation and tumorigenesis. Some of the molecular signal candidates may include the neuroregulin glial growth factor 2 and thyroid hormone that promote oligodendrocyte progenitor maturation and remyelination in a model of MS.[74,75]

Another approach is through transplantation of exogenous neural stem cells, an approach that eliminates the potential problem of the endogenous cells having a genetic predisposition to malfunction. The transplantation approach offers the added options of genetically modifying the cells ex vivo prior to transplantation to optimize remyelination and support axonal repair. Regardless of the strategy, more research is needed to understand the contributions of key molecules in differentiation and survival of progenitors during MS. For instance, the transcription factors Sox-10 (SRY box family member 10), Olig-1 and Olig-2 (oligodendrocyte transcription factor 1 or 2), and Nkx2.2 (NK2 transcription factor related, locus 2) participate in the response of progenitors to demyelination. Sox-10 is required for oligodendrogenesis,[76] and Nkx2.2 and Olig-2 positive cells proliferate and differentiate in response to a demyelinating insult.[77] Furthermore, Olig-1 is present in MS lesions and appears to have a critical role for effective remyelination in a model of MS.[78] Future work in the regulation of these genes during MS would offer ways to manipulate relevant molecular targets without inducing aberrant neurogenesis, gliogenesis, or tumorigenic proliferation.

Promotion of Axonal Regeneration. Axonal regeneration is another potential target for intervention. Injured oligodendrocytes and myelin exert negative signals for axonal regeneration; calpains (calcium-activated neutral proteinases) can degrade myelin proteins at physiological pH and are found in glia and inflammatory cells. Thus, neuronal self-repair and axonal regeneration may be impaired by negative signals released during myelin destruction. Among the products of myelinolysis, myelin-associated glycoprotein, myelin oligodendocyte glycoprotein, and Nogo inhibit axonal regeneration and are collectively called myelin-associated inhibitory factors.

Nogo is a member of the reticulon family, expressed by oligodendrocytes but not by Schwann cells, and inhibits axonal extension.[79] The Nogo receptor complex, composed of the Nogo-66 receptor 1, neurotrophin p75 receptor, and LINGO-1, represses axon regeneration upon binding to myelin-associated inhibitory factors. The binding of neurotrophin to its receptor, p75 neurotrophic tyrosinekinase receptor, abolishes activation of protein kinase C and the GTPase ras homolog gene family member A and decreases neurite outgrowth.[80] Nogo-66 is immunogenic and may play a role in EAE: antibodies to Nogo-66 protect from EAE,[81] and Nogo-66–derived peptides are encephalitogenic while other Nogo-66 epitopes induce protective Th2 cell lines.[82] Therapeutic targets to stimulate axonal regeneration include inhibitors of Nogo signaling and protein kinase C inhibitors.[83]

Challenges for MS Research

Current therapies address the inflammatory and immunological components of MS pathologic abnormalities, a strategy that is necessary to modulate the "nonpermissive environment" before contemplating neuroprotective and repair therapies. Interactions between the immune system and the CNS may lead to neurologic dysfunction but may also be necessary to initiate repair. One of the challenges in the next phase of therapeutic investigations is to dissect the positive vs negative neural-immune interactions and design selective therapies. Another challenge is how to measure the effects of neuroprotective therapies. Intrinsic challenges in MS include the relative unavailability of obtaining serial pathologic material, making it necessary to depend on novel imaging and modeling techniques.

RELEVANCE TO THE PRACTICE OF NEUROLOGY

There is evidence that the mechanism of progression in MS is related to chronic neuronal dysfunction within the lesions and in normal appearing areas outside the lesions in both the white matter and cortex as a result of chronic inflammation, oxidative stress, and microglia activation. While this article was under review, Kutzelnigg et al[84] reported a detailed study on the neuropathologic features of 52 MS cases, and their conclusions give additional support to our proposed model of progression. Therefore, the goals for MS therapy should include the following: the induction and maintenance of immunological tolerance toward self-antigens in the susceptible population, the promotion of remyelination, and the promotion of axonal regeneration but, more importantly, the prevention of axonal degeneration and neuronal dysfunction as soon as the diagnosis is made.

The current state of MS therapy has advanced significantly in the control of the inflammatory and immunologic aspects of MS that decrease relapses but are less effective in stopping progression. Therefore, we need now a concerted effort and interdisciplinary approach to study the molecular pathologic abnormalities of neural degeneration in MS to identify novel therapeutical targets.

We conclude with a quote from J. M. Charcot: "Disease is very old and nothing about it changes. It is we who change as we learn to recognize what was formerly imperceptible."

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