Pathogenesis of multiple sclerosis

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Purpose of review

The aim of this article is to describe recent observations regarding the basis for the initiation and disease evolution of multiple sclerosis.

Recent findings

A current debate is where and what initiates the neuroinflammatory reaction that characterizes the acute multiple sclerosis lesion. Immune sensitization to neural antigens could develop within the systemic compartment consequent to exposure to cross-reacting, possibly viral derived, peptides (molecular mimicry). Although CD4 T cells are considered central to initiating central nervous system inflammation, the actual extent and specificity of tissue injury reflects the array of adaptive (CD8 T cells and antibody) and innate (microglia/macrophages) immune constituents present in the lesions. Neuropathologic studies indicate that lethal changes in neural cells (oligodendrocytes) could also be the initiating event, reflecting as yet unidentified acquired insults (e.g. exogenous virus or reactivated endogenous retrovirus) or intrinsic abnormalities ('neurodegenerative' hypothesis). Recurrence or persistence of the disease process can reflect events occurring at multiple sites including expansion of the immune repertoire in response to neural antigens transported to regional lymph nodes (determinant spreading), especially if immune regulatory mechanisms are defective; alterations in blood–brain barrier properties consequent to initial cellular transmigration; and participation of endogenous (microglia, astrocytes) or long lived infiltrating cells (macrophages, B cells in ectopic germinal centers) in regulating and effecting immune functions within the central nervous system. Accumulating neurologic deficit reflects the balance between injury and repair; the latter also being negatively or positively (trophic support and clearance of tissue debris) impacted by inflammatory processes.

Summary

Understanding the full spectrum of multiple sclerosis presents a continuing challenge for both immunology and neurobiology.

Keywords

autoimmunity, multiple sclerosis, myelin, oligodendrocytes

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Abbreviations

BBB	blood–brain barrier
CNS	central nervous system
CSF	cerebrospinal fluid
EAE	experimental autoimmune encephalomyelitis
MHC	major histocompatibility
MS	multiple sclerosis

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Introduction

In this article we will consider emerging observations that reflect on the entire clinical spectrum of multiple sclerosis (MS), from its typical relapsing remitting initial course onset to its evolution into a progressive disorder. These observations provide new insights into the disease pathogenesis but also raise new questions and challenges.

Basis of disease initiation

The pathologic lesions that best correlate with acute clinical exacerbation of disease, feature foci of inflammation associated with active myelin degradation and phagocytosis. An ongoing issue is whether this neuroinflammatory reaction is initiated within the immune system or in response to primary events impacting on the neural cells.

Immune initiated disease hypothesis

This long favored hypothesis in MS implicates that autoreactive T cells generated in the systemic compartment access the central nervous system (CNS) where they persist and induce an inflammatory cascade that results in the injury of previously normal neural tissues. The animal model for this sequence is experimental autoimmune encephalomyelitis (EAE) which is initiated by systemic immunization with neural auto-antigens or by transfer of neural antigen sensitized T cells. The various EAE models show marked heterogeneity with regard to topography of lesions and extent of demyelination/axonal disruption, indicating the need to define mechanisms linking neuroinflammation and actual tissue injury [1].

Initial studies regarding the frequency and properties of disease relevant immune constituents focused on $CD4^+$ T cells, the cell type most used to adoptively transfer EAE. The apparent increased frequency of $CD4^+$

myelin reactive cells in the peripheral blood of MS patients compared with healthy donors seems to be derived from the memory T cell implicating prior sensitization with disease relevant antigens [2]. Affinity based studies suggest that the most relevant peptide regions may be different than those previously emphasized [3•], although our studies of MS patients immunized with an altered peptide ligand for MBP 83–99 show that such patients can generate a prolonged immune response (>3–4 years) to this peptide [4]. Peptide library based studies [5] indicate that myelin reactivity in many cases actually reflects cross reactivity with exogenous peptides, supporting the concept that initial immune sensitization in MS results from exposure to exogenous agents: a phenomenon known as molecular mimicry.

CD8 T cells in the blood, cerebrospinal fluid (CSF) and in the lesions have an even more restricted heterogeneity of T cell receptors than do CD4 T cells, consistent with their participation in an antigen restricted response [6•,7]. Antigen restricted target recognition by CD8 and CD4 T cells would be major histocompatibility (MHC) restricted. MHC class I, but not class II expression by neural cells seems to be a common occurrence under inflammatory or stress conditions [8], implicating CD8 T cells in the injury process [9]. Note that activated T cells, as found in MS lesions, can acquire non-MHC restricted cytotoxic capability mediated against neurons/axons and myelinating cells [10•,11,12].

Myelin directed antibodies can contribute to the extent of tissue injury (demyelination) in experimental models of MS, but to date not initiate such disorders [13]. Disease relevant antibodies are present in lesions in at least some MS sub-types. Myelin specific antibodies can also be identified in the blood and CSF, although consensus is lacking regarding actual frequency or contribution to disease course or phenotype [14,15•]. Phenotypic and molecular studies of B cells recovered from the CSF early in the course of MS indicate that these cells are clonally expanded and antigen reactive, although the precise antigens remain to be defined [16,17•]. Antibody bound specifically (via Fab region) to neural cells could interact via their Fc portions with Fc receptor bearing cells (microglia/macrophages), thus directing the potential injury mediators produced by the latter toward a specific target.

Neural initiated disease hypothesis

This hypothesis implicates that events within the CNS initiate the MS disease process. A frequent speculation is that an acquired acute or persistent infection of neural cells could result in release of tissue antigens that in turn would provoke a disease relevant autoimmune response. The chronic inflammatory demyelinating disease induced by Theiler murine encephalomyelitis virus provides an example of such a disease development sequence. A role of direct infection-mediated cytotoxic neural injury would seem less likely given the apparent positive rather than negative effects of intense immunosuppression on lesion formation in MS. Other mechanisms whereby acquired infections could impact on MS include molecular mimicry responses, perturbing systemic immune regulatory properties, as might occur with Epstein–Barr virus infection of B cells [18] or MS retrovirus [19,20], and modulating immune related properties of glial cells via toll like receptor signaling [21]. Expression of persistent virus within the CNS could reflect a response to inflammation, an issue raised with regard to detection of human herpes virus-6 and human endogenous retroviruses (HERVs) in MS tissues [22,23•]. Increased expression of HERVs in astrocytes can result in release of mediators cytotoxic to oligodendrocytes [23•].

Barnett and Prineas [24•] observed that changes in oligodendrocytes (caspase independent apoptosis) can be the initial events in formation of an acute MS lesion, serving to recruit an initial innate (microglia) and subsequently adaptive (T cell) immune response. The basis for the oligodendrocyte apoptosis is not defined but could reflect a primary cell injury, consistent with the previous discussion regarding CNS virus infection or other insults including trauma, or ischemia. In response to this report, Trapp [25] questioned 'whether the inflammatory demyelination is central to the pathogenesis of MS or is part of a cascade of adaptive immune responses that evolved as a critical component of tissue repair'. Therapies which deplete all circulating T cells in MS patients, such as intense immunosuppression requiring stem cell rescue or lympholytic anti-T cell monoclonal antibody (Campath-1) are associated with complete elimination of new inflammatory lesion formation [26•,27]. Inherited disorders resulting in myelin disruption, particularly adrenoleukodystrophy, can feature a robust inflammatory response but to date there is little evidence that the disease course is altered by immunomodulatory therapy [28].

Basis of disease recurrence and progression

Recurrent or persistent disease could reflect events that occur in the systemic immune system, at the blood–brain barrier (BBB), and in the CNS. Polymorphisms in an array of genes (*MHC class II*, *NOS2A*, *CCR5δ*, *CTL-A4*, *APOE-ε4*) that impact on these parameters and that influence development and course of MS continue to be identified [29–32].

Systemic immune related events

Serial studies of peripheral blood T cells indicate that there is an expansion of the repertoire of antigens recognized over time (epitope and determinant spreading

[33]). In the intense immunosuppression/stem cell rescue cohort there is recovery over time of an even broader myelin reactive T cell repertoire raising the questions of whether and where memory cells persist or of where new antigen is being presented [26•]. A number of factors could contribute to ongoing systemic immune reactivity. Neuroantigens can be transported from the CNS to cervical lymph nodes [34•] via lymphatics that originate in the region of the olfactory bulb and reach peripheral lymphatic structures through the cribriform plate of the nasal bone. Activated T cells may have reduced requirements for co-stimulatory signals to respond to antigen presentation, and may serve as their own antigen presenting cells [35•]. Circulating B cells in MS contain an increased proportion of activated memory cells that can serve antigen presentation functions and skew the T cell responses towards a specific cytokine profile [36•]. An inborn or acquired functional deficit in regulatory cells, $CD25^{+}CD4^{+}$ cells [37•] and NKCD95 cells [38,39], could further contribute to disease recurrence.

Blood–brain barrier related events

The properties of the BBB that actively regulate recruitment of leukocytes to the CNS (adhesion, chemoattraction) are themselves modulated during the process of neuroinflammation [40]. Leukocyte migration across BBB endothelial cells involves both paracellular (at intercellular contact points) and transcellular migration [41]. Carman *et al*. demonstrated that upon contact with leukocytes, endothelial cells reorganize their membranes, creating 'cuplike' microdomains enriched with ICAM-1 and VCAM-1 microvilli projections that surround the transmigrating leukocytes and allow the transendothelial passage of an intact leukocyte to the abluminal side of the endothelial cell, without damaging the barrier [42]. ICAM-1 signals via the Rho pathway to regulate the endothelial actin cytoskeleton and possibly the formation of microvilli structures that favors transcellular passage of leukocytes. We believe that anti-VLA-4 therapy (natalizumab) [43] primarily impacts on the movement of immune cells within the extracellular matrix (basal lamina) surrounding the BBB-endothelial cells rather than on migration of leukocytes across endothelial cells *per se*. This matrix is composed of collagen, fibronectin, entactin and laminin 8 and 10, each of which is known to be a potent ligand for integrins, such as VLA-4 (α4 integrin).

IFNβ and glatiramer acetate therapies also impact on BBB trafficking. In our in-vitro migration assay, IFNβ reduces the migration of monocytes [44] and of Th1 but not Th2 lymphocytes [45] through human brain endothelial cells. IFNβ also stabilizes BBB permeability and decreases the passage of soluble molecules across bovine brain endothelial cells [46]. Glatiramer acetate induces a significant increase in the migration of Th2 cells across human brain endothelial cells [45].

Central nervous system related events

Within the CNS parenchyma, microglia can serve as antigen presenting cells, a function dependent on their state of activation. Activation of microglia/macrophages, the major CNS phagocytes, is also an important determinant of their capacity to remove damaged tissues, a prerequisite for optimal tissue repair [47]. Activation is upregulated or downregulated by 'danger' (infection/immune related) or 'stranger' (tissue injury) signals derived from their environment [48]. Ingestion of apoptotic T cells downregulates activity, representing a potential means to terminate the initial inflammatory response [49]. T cell signaling of microglia/macrophage mediated via specific cell surface molecule interactions (CD40:CD154) and proinflammatory cytokines results in upregulation of molecules involved in chemoattraction and antigen presentation. Ingestion of myelin debris, especially if opsonized with immunoglobulin, activates microglia [50]. Stressed or injured neurons release an array of cyclic nucleotides that can interact with purinergic receptors expressed on microglia, resulting in release of proinflammatory cytokines [51].

Although none of the currently approved therapies for MS directly accesses the CNS, Kim *et al*. [52•] showed that T cells polarized toward the Th2 cytokine, as can be achieved with glatiramer acetate, can impact on antigen presenting cells in the systemic compartment (monocytes) or CNS (microglia) so that naïve T cells to which they present antigen will be biased towards a Th2 phenotype. Minocycline (now in clinical trials for MS) [53] was shown to downregulate microglia activity in both neuroinflammatory and neurodegenerative disease models [54]. Other cells identified within the inflamed CNS and that can contribute to antigen presentation include dendritic cells and blood-borne monocytes that could have the capacity to convert into dendritic cell-like cells when migrating into the CNS [44,55,56].

A hallmark of MS is the persistence of intrathecal immunoglobulin production, the majority of which does not seem to be neural specific. Ectopic lymphoid follicle-like structures with active germinal centers, now a recognized feature of the meninges in secondary progressive MS, provide a potential source of ongoing B cell responses that need not be disease antigen specific [57•,58•]. One speculates whether these meningeal structures underlie some of the recently observed pathology in superficial gray matter regions [59]. Specific antibodies may be generated subsequent to tissue injury as for example antineurofilament antibodies which presumably arise secondary to axonal injury in secondary progressive MS patients [60] and antibodies reactive with intracellular molecules (ribonucleoproteins) presumably reflecting

leakage of intracellular neuronal proteins [61]. Their role in subsequent disease course remains to be shown.

The above observations all contribute to the changing view regarding the CNS as being a site of immunological privilege. Following an initial immune reaction within the brain, a cascade of immunological phenomena can be triggered that favor the perpetuation of antigen specific reactivity and the formation of follicle-like structures within the CNS, leading to the chronic breach of this immune privilege. Conversely, active mechanisms can suppress such responses; they may also be subject to therapeutic modulation.

The basis of the continued tissue injury and loss over time in MS continue to be defined. The lesions associated with the late progressive phases of MS seem more dominated by microglia/macrophage response than by lymphocytic infiltrates. We postulate that the accumulating tissue loss could reflect the impact of multiple recurrent insults with initially injured cells being more susceptible to subsequent effector molecules (multiple hit hypothesis). We found that human oligodendrocyte overexpressing p53 *in vitro*, as occurs in response to an array of insults and as seen *in situ* in MS tissues, makes them more susceptible to TRAIL and fas mediated injury [62]. Chronic demyelination itself impacts on axonal survival as a result of redistribution of sodium channels that permit calcium influx [63•,64•].

Progression of disease due to failure of repair/regeneration

Initial recovery from injury in MS may reflect at least in part progenitor cell dependent regenerative processes. Such cells may themselves be affected by the disease process. Selectivity of progenitor cell injury has been linked with their expression of maturation related surface molecules or receptors that determine their functional responses to specific antibodies [65,66], potential injury mediating molecules (glutamate) present in MS lesions [67,68], and trophic factors such as a low affinity p75 receptor for proNGF [69–71].

Conclusion

Our opinion is that a T cell guided immune response, whether induced by systemic molecular mimicry responses or antigen release from events within the CNS, remains a central event in the initiation of the acute MS lesions, consistent with observations that therapeutically targeting these cells or their access to the CNS favorably impacts on the disease course. The endogenous or infiltrating innate immune constituents play a central role in determining whether immune responses will persist or recur in the CNS. The functional properties of these cells are themselves subject to regulation by signals derived from the immune mediators and neural cells impacted by the disease process. Persistence of activated innate immune system cells in cooperation with long-lived adaptive immune system cells (antibody producing plasma cells) could result in chronic neural injury with or without recurrent T cell infiltration. This would be consistent with observations regarding failure of systemic immunotherapies to impact on the progressive phases of MS. The precise patterns of tissue injury seen amongst cases and over time would reflect the combination of effectors present.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 Kawakami N, Lassmann S, Li Z, *et al.* The activation status of neuroantigen-specific T cells in the target organ determines the clinical outcome of autoimmune encephalomyelitis. J Exp Med 2004; 199:185–197.

2 Wulff H, Calabresi PA, Allie R, *et al.* The voltage-gated Kv1.3 K(+) channel in effector memory T cells as new target for MS. J Clin Invest 2003; 111:1703–1713.

3 • Bielekova B, Sung MH, Kadom N, *et al.* Expansion and functional relevance of high-avidity myelin-specific CD4+ T cells in multiple sclerosis. J Immunol 2004; 172:3893–3904.

This provides a new insight into defining the properties of autoreactive T cells likely to be most disease relevant.

4 Kim HJ, Antel JP, Duquette P, *et al.* Persistence of immune responses to altered and native myelin antigens in patients with multiple sclerosis treated with altered peptide ligand. Clin Immunol 2002; 104:105–114.

5 Zhou D, Hemmer B. Specificity and degeneracy: T cell recognition in CNS autoimmunity. Mol Immunol 2004; 40:1057–1061.

6 • Skulina C, Schmidt S, Dornmair K, *et al.* Multiple sclerosis: brain-infiltrating CD8+ T cells persist as clonal expansions in the cerebrospinal fluid and blood. Proc Natl Acad Sci U S A 2004; 101:2428–2433.

This emphasizes potential role of antigen reactive CD8 T cells as contributors to the MS disease process.

7 Crawford MP, Yan SX, Ortega SB, *et al.* High prevalence of autoreactive, neuroantigen-specific CD8+ T cells in multiple sclerosis revealed by novel flow cytometric assay. Blood 2004; 103:4222–4231.

8 Hoftberger R, Aboul-Enein F, Brueck W, *et al.* Expression of major histocompatibility complex class I molecules on the different cell types in multiple sclerosis lesions. Brain Pathol 2004; 14:43–50.

9 Zang YC, Li S, Rivera VM, *et al.* Increased CD8+ cytotoxic T cell responses to myelin basic protein in multiple sclerosis. J Immunol 2004; 172:5120–5127.

10 • Nitsch R, Pohl EE, Smorodchenko A, *et al.* Direct impact of T cells on neurons revealed by two-photon microscopy in living brain tissue. J Neurosci 2004; 24:2458–2464.

These authors used an emerging technology to visualize the capacity of T cells to interact and induce neuron/axon injury.

11 Giuliani F, Goodyer CG, Antel JP, Yong VW. Vulnerability of human neurons to T cell-mediated cytotoxicity. J Immunol 2003; 171:368–379.

12 Antel JP, McCrea E, Ladiwala U, *et al.* Non-MHC-restricted cell-mediated lysis of human oligodendrocytes in vitro: relation with CD56 expression. J Immunol 1998; 160:1606–1611.

13 Aboul-Enein F, Bauer J, Klein M, *et al.* Selective and antigen-dependent effects of myelin degeneration on central nervous system inflammation. J Neuropathol Exp Neurol 2004; 63:1284–1296.

14 Mathey E, Breithaupt C, Schubart AS, Linington C. Commentary. Sorting the wheat from the chaff: identifying demyelinating components of the myelin oligodendrocyte glycoprotein (MOG)-specific autoantibody repertoire. Eur J Immunol 2004; 34:2065–2071.

15 • Lennon VA, Wingerchuk DM, Kryzer TJ, *et al.* A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004; 364:2106–2112.

This provides evidence of an immunologic response that distinguishes these entities; its role in disease pathogenesis will be defined.

16 Qin Y, Duquette P, Zhang Y, *et al.* Intrathecal B-cell clonal expansion, an early sign of humoral immunity, in the cerebrospinal fluid of patients with clinically isolated syndrome suggestive of multiple sclerosis. Lab Invest 2003; 83:1081–1088.

17 • Haubold K, Owens GP, Kaur P, *et al.* B-lymphocyte and plasma cell clonal expansion in monosymptomatic optic neuritis cerebrospinal fluid. Ann Neurol 2004; 56:97–107.
These findings support the postulate of an antigen restricted humoral immune response at the early stages of MS.

18 Alotaibi S, Kennedy J, Tellier R, *et al.* Epstein-Barr virus in pediatric multiple sclerosis. JAMA 2004; 291:1875–1879.

19 Perron H, Garson JA, Bedin F, *et al.* Molecular identification of a novel retrovirus repeatedly isolated from patients with multiple sclerosis. The Collaborative Research Group on Multiple Sclerosis. Proc Natl Acad Sci U S A 1997; 94:7583–7588.

20 Nowak J, Januszkiewicz D, Pernak M, *et al.* Multiple sclerosis-associated virus-related pol sequences found both in multiple sclerosis and healthy donors are more frequently expressed in multiple sclerosis patients. J Neurovirol 2003; 9:112–117.

21 Rivest S. Molecular insights on the cerebral innate immune system. Brain Behav Immun 2003; 17:13–19.

22 Rotola A, Merlotti I, Caniatti L, *et al.* Human herpesvirus 6 infects the central nervous system of multiple sclerosis patients in the early stages of the disease. Mult Scler 2004; 10:348–354.

23 • Antony JM, van Marle G, Opii W, *et al.* Human endogenous retrovirus glycoprotein-mediated induction of redox reactants causes oligodendrocyte death and demyelination. Nat Neurosci 2004; 7:1088–1095.
This presents a mechanism (involving astrocyte activation) whereby expression of these endogenous viruses during MS can contribute to tissue injury.

24 • Barnett MH, Prineas JW. Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. Ann Neurol 2004; 55:458–468.
Raises the issue of early oligodendrocyte injury as the precipitating event in lesion formation; this results in recruitment of an innate (microglia) and then adaptive (lymphocyte) response.

25 Trapp BD. Pathogenesis of multiple sclerosis: the eyes only see what the mind is prepared to comprehend. Ann Neurol 2004; 55:455–457.

26 • Sun W, Popat U, Hutton G, *et al.* Characteristics of T-cell receptor repertoire and myelin-reactive T cells reconstituted from autologous haematopoietic stem-cell grafts in multiple sclerosis. Brain 2004; 127(Pt 5): 996–1008.
This raises the issues of where and why autoreactive T cells reappear after intense immunoablation in MS.

27 Coles A, Deans J, Compston A. Campath-1H treatment of multiple sclerosis: lessons from the bedside for the bench. Clin Neurol Neurosurg 2004; 106:270–274.

28 Nowaczyk MJ, Saunders EF, Tein I, *et al.* Immunoablation does not delay the neurologic progression of X-linked adrenoleukodystrophy. J Pediatr 1997; 131:453–455.

29 Barcellos LF, Begovich AB, Reynolds RL, *et al.* Linkage and association with the NOS2A locus on chromosome 17q11 in multiple sclerosis. Ann Neurol 2004; 55:793–800.

30 Silversides JA, Heggarty SV, McDonnell GV, *et al.* Influence of CCR5 delta32 polymorphism on multiple sclerosis susceptibility and disease course. Mult Scler 2004; 10:149–152.

31 Enzinger C, Ropele S, Smith S, *et al.* Accelerated evolution of brain atrophy and ''black holes'' in MS patients with APOE-epsilon 4. Ann Neurol 2004; 55:563–569.

32 Dyment DA, Ebers GC, Sadovnick AD. Genetics of multiple sclerosis. Lancet Neurol 2004; 3:104–110.

33 Achiron A, Gurevich M, Friedman N, *et al.* Blood transcriptional signatures of multiple sclerosis: unique gene expression of disease activity. Ann Neurol 2004; 55:410–417.

34 • Karman J, Ling C, Sandor M, Fabry Z. Initiation of immune responses in brain is promoted by local dendritic cells. J Immunol 2004; 173:2353–2361.
This helps to define how antigen that is released in the CNS is taken up, processed, and transported to regional lymph nodes.

35 • Lovett-Racke AE, Rocchini AE, Choy J, *et al.* Silencing T-bet defines a critical role in the differentiation of autoreactive T lymphocytes. Immunity 2004; 21:719–731.
This advances knowledge regarding the development of autoreactive T cells.

36 • Duddy ME, Alter A, Bar-Or A. Distinct profiles of human B cell effector cytokines: a role in immune regulation? J Immunol 2004; 172:3422–3427.
This emphasizes the role that B cells can play in determining the inflammation mediating properties of T cells.

37 • Viglietta V, Baecher-Allan C, Weiner HL, Hafler DA. Loss of functional suppression by CD4+CD25+ regulatory T cells in patients with multiple sclerosis. J Exp Med 2004; 199:971–979.
The authors present support for the postulate that recurrent immune activity in MS may reflect altered function of immune regulatory mechanisms.

38 Takahashi K, Aranami T, Endoh M, *et al.* The regulatory role of natural killer cells in multiple sclerosis. Brain 2004; 127(Pt 9):1917–1927.

39 Antel J, Owens T. Multiple sclerosis and immune regulatory cells. Brain 2004; 127(Pt 9):1915–1916.

40 Biernacki K, Prat A, Blain M, Antel JP. Regulation of cellular and molecular trafficking across human brain endothelial cells by Th1- and Th2-polarized lymphocytes. J Neuropathol Exp Neurol 2004; 63:223–232.

41 Wong D, Prameya R, Dorovini-Zis K. In vitro adhesion and migration of T lymphocytes across monolayers of human brain microvessel endothelial cells: regulation by ICAM-1, VCAM-1, E-selectin and PECAM-1. J Neuropathol Exp Neurol 1999; 58:138–152.

42 Carman CV, Springer TA. A transmigratory cup in leukocyte diapedesis both through individual vascular endothelial cells and between them. J Cell Biol 2004; 167:377–388.

43 Miller DH, Khan OA, Sheremata WA, *et al.* A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2003; 348:15–23.

44 Seguin R, Biernacki K, Rotondo RL, *et al.* Regulation and functional effects of monocyte migration across human brain-derived endothelial cells. J Neuropathol Exp Neurol 2003; 62:412–419.

45 Prat A, Biernacki K, Antel JP. Th1 and Th2 lymphocyte migration across the human BBB is specifically regulated by interferon β and copolymer-1. J Autoimmunity (in press).

46 Kraus J, Ling AK, Hamm S, *et al.* Interferon-beta stabilizes barrier characteristics of brain endothelial cells in vitro. Ann Neurol 2004; 56:192–205.

47 David S, Lacroix S. Molecular approaches to spinal cord repair. Annu Rev Neurosci 2003; 26:411–440.

48 Matzinger P. The danger model: a renewed sense of self. Science 2002; 296:301–305.

49 Chan A, Seguin R, Magnus T, *et al.* Phagocytosis of apoptotic inflammatory cells by microglia and its therapeutic implications: termination of CNS autoimmune inflammation and modulation by interferon-beta. Glia 2003; 43:231–242.

50 Williams K, Ulvestad E, Waage A, *et al.* Activation of adult human derived microglia by myelin phagocytosis in vitro. J Neurosci Res 1994; 38:433–443.

51 Chakfe Y, Seguin R, Antel JP, *et al.* ADP and AMP induce interleukin-1beta release from microglial cells through activation of ATP-primed P2X7 receptor channels. J Neurosci 2002; 22:3061–3069.

52 • Kim HJ, Ifergan I, Antel JP, *et al.* Type 2 monocyte and microglia differentiation mediated by glatiramer acetate therapy in patients with multiple sclerosis. J Immunol 2004; 172:7144–7153.
This demonstrates that the properties of antigen presenting cells in the periphery and the CNS can themselves be modulated by interaction with T cells whose own properties (Th1 versus Th2) have been modified by a therapeutic agent.

53 Metz LM, Zhang Y, Yeung M, *et al.* Minocycline reduces gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. Ann Neurol 2004; 55:756.

54 Yong VW, Wells J, Giuliani F, *et al.* The promise of minocycline in neurology. Lancet Neurol 2004; 3:744–751.

55 Suter T, Biollaz G, Gatto D, *et al.* The brain as an immune privileged site: dendritic cells of the central nervous system inhibit T cell activation. Eur J Immunol 2003; 33:2998–3006.

56 Plumb J, Armstrong MA, Duddy M, *et al.* CD83-positive dendritic cells are present in occasional perivascular cuffs in multiple sclerosis lesions. Mult Scler 2003; 9:142–147.

57 • Serafini B, Rosicarelli B, Magliozzi R, *et al.* Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. Brain Pathol 2004; 14:164–174.
This presents neuropathologic data (formation of germinal centers) that provide an explanation for the basis for chronic antibody production in the CNS in MS.

58 • Corcione A, Casazza S, Ferretti E, *et al.* Recapitulation of B cell differentiation in the central nervous system of patients with multiple sclerosis. Proc Natl Acad Sci U S A 2004; 101:11064–11069.
This presents neuropathologic data (formation of germinal centers) that provide an explanation for the basis for chronic antibody production in the CNS in MS.

59 Bo L, Vedeler CA, Nyland HI, *et al.* Subpial demyelination in the cerebral cortex of multiple sclerosis patients. J Neuropathol Exp Neurol 2003; 62:723–732.

60 Ehling R, Lutterotti A, Wanschitz J, *et al.* Increased frequencies of serum antibodies to neurofilament light in patients with primary chronic progressive multiple sclerosis. Mult Scler 2004; 10:601–606.

61 Sueoka E, Yukitake M, Iwanaga K, *et al.* Autoantibodies against heterogeneous nuclear ribonucleoprotein B1 in CSF of MS patients. Ann Neurol 2004; 56:778–786.

62 Wosik K, Antel J, Kuhlmann T, *et al.* Oligodendrocyte injury in multiple sclerosis: a role for p53. J Neurochem 2003; 85:635–644.

63 Craner MJ, Newcombe J, Black JA, *et al.* Molecular changes in neurons in • multiple sclerosis: altered axonal expression of Nav1.2 and Nav1.6 sodium channels and Na+/Ca2+ exchanger. Proc Natl Acad Sci U S A 2004; 101: 8168–8173.
This indicates a mechanism by which demyelination in the CNS can lead to axonal dysfunction and loss.

64 Bechtold DA, Kapoor R, Smith KJ. Axonal protection using flecainide in • experimental autoimmune encephalomyelitis. Ann Neurol 2004; 55:607–616.
This indicates a therapeutic approach to prevent the axonal injury described by Craner *et al.* [63•].

65 Cid C, Alvarez-Cermeno JC, Camafeita E, *et al.* Antibodies reactive to heat shock protein 90 induce oligodendrocyte precursor cell death in culture. Implications for demyelination in multiple sclerosis. FASEB J 2004; 18:409–411.

66 Niehaus A, Shi J, Grzenkowski M, *et al.* Patients with active relapsing-remitting multiple sclerosis synthesize antibodies recognizing oligodendrocyte progenitor cell surface protein: implications for remyelination. Ann Neurol 2000; 48:362–371.

67 Follett PL, Deng W, Dai W, *et al.* Glutamate receptor-mediated oligodendrocyte toxicity in periventricular leukomalacia: a protective role for topiramate. J Neurosci 2004; 24:4412–4420.

68 Wosik K, Ruffini F, Almazan G, *et al.* Resistance of human adult oligodendrocytes to AMPA/kainate receptor-mediated glutamate injury. Brain 2004; 127(Pt 12):2636–2648.

69 Petratos S, Gonzales MF, Azari MF, *et al.* Expression of the low-affinity neurotrophin receptor, p75(NTR), is upregulated by oligodendroglial progenitors adjacent to the subventricular zone in response to demyelination. Glia 2004; 48:64–75.

70 Althaus HH. Remyelination in multiple sclerosis: a new role for neurotrophins? Prog Brain Res 2004; 146:415–432.

71 Hempstead BL, Salzer JL. Neurobiology. A glial spin on neurotrophins. Science 2002; 298:1184–1186.