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# Oligodendrocyte/myelin injury and repair as a function of the central nervous system environment

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**Abstract**

Multiple sclerosis is a chronic neurologic disorder considered to result from relatively selective immune mediated injury of central nervous system (CNS) myelin and/or its cell of origin, the oligodendrocyte (OGC). Constituents of both the innate and adaptive immune systems are potential contributors to this process. Endogenous (microglia) and infiltrating (macrophages, dendritic cells) constituents of the innate immune system serve as sensors of events occurring within the CNS; their response to such events underlies the extent of their interaction (chemoattraction, antigen presentation) with the components of the adaptive immune system (αβ T cells, B cells) and ultimately the extent of the resultant inflammatory response. Constituents of both the innate and adaptive immune system can serve as effectors of tissue injury. The susceptibility of specific types of neural cells to injury further reflects the extent to which immune mediators modulate expression of crucial molecules (adhesion molecules, receptors) involved in effector–target interactions. Ongoing interactions between the constituents of the immune system themselves and between these constituents and neural cells are important determinants of disease recurrence and/or progression. Conversely, these interactions also impact on the mechanisms involved in target protection and repair.


*Keywords:* Multiple sclerosis; Microglia; Innate immunity; Oligodendrocytes/myelin; Demyelination/remyelination

## 1. Introduction

Multiple sclerosis (MS) is a neurologic disorder that characteristically evolves its course over many years. The most usual initial clinical manifestation is an acute or subacute neurologic deficit reflecting dysfunction within the CNS, followed over subsequent days or weeks by substantial recovery. Both the initial and subsequent exacerbations correlate with times of immune activation, usually exposure to infections. The magnetic resonance imaging (MRI) defined correlate of such events is a new lesion that may enhance if gadolinium has been administered systemically. The pathologic correlate of the lesion is a T cell dominated inflammatory perivascular response with both lymphocytes and macrophages extending into the parenchyma. Within the tissue, there is destruction of myelin with relative but not absolute sparing of axons. New lesions resolve to variable extents but may reappear including with enhancement during subsequent relapses. Serial MR studies using specialized techniques such as MR spectroscopy or magnetization transfer imaging (MTR) indicate the involvement of the "normal appearing" white matter (NAWM) even in the early phase of disease and that subsequent new lesions are biased to occur where such NAWM changes are most apparent [1]. In the later phases of the disease, the neurologic deficit appears to accumulate progressively even in absence of clear-cut relapses. The chronic active MS lesion, characteristic of the later disease phase features macrophage dominated tissue destruction with loss of both myelin and oligodendrocytes (OGCs) and axons, associated with a prominent gliotic reaction. These pathologic features underlie the postulate that immune mediated mechanisms underlie the development of the disease. Currently, there are no animal models of a similar disease occurring spontaneously in out-bred animals raised in "dirty" environments. This report focuses on the interactions between the constituents of the immune system and the CNS that can contribute to the tissue injury and repair that characterize MS, and how these interactions are themselves modulated by the CNS environment.

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## 2. Initiation of the MS disease process

The currently favored postulate is that MS is triggered by immune responses directed against myelin or its cell of origin, the OGC. Observations from both clinical disorders and experimental models indicate that the initial events leading to immune mediated CNS demyelination can occur either within the systemic compartment or within the CNS. The syndrome of post vaccination encephalomyelitis (or ADEM) that can complicate immunization with vaccines containing neural tissue illustrates the former sequence of events and can be re-produced in animals by systemic administration of CNS tissue, crude white matter or myelin, or purified myelin antigens or peptides. The animal disorder is referred to as experimental autoimmune encephalomyelitis (EAE). Speculation remains that exposure to virus contained peptide sequences that have homology to myelin components, an occurrence referred to as molecular mimicry [2], may trigger the autoimmune response in MS. Prototypes of immune mediated demyelinating disorders initiated by events within the CNS compartment are provided by the experimental chronic neurologic disorders arising in mice consequent to intra-cerebral infection with corona and Theiler murine encephalomyelitis viruses. Disease relevant autoreactive T cells develop as result of antigen release consequent to the initial viral induced tissue injury [3]. Such T cell sensitization could occur either within the CNS or in regional lymph nodes since antigens released within the CNS can be transported from the CNS to regional lymph nodes.

The extent of inflammation in the active MS lesions indicates that there must be substantial recruitment of systemic immune cells, lymphocytes and monocytes, from the systemic compartment into the CNS. Such recruitment would require that the cells cross the BBB and enter an environment that would promote their persistence and function. The actual transmigration across microvessels is dependent on active molecular interactions involving chemoattraction and adhesion. Products released by microglia and astrocyte, both of which extend foot process to the microvessels, can modulate the permeability properties of the blood brain barrier [4]. Animal based studies indicate that T cells accessing the CNS from the systemic compartment will persist in the CNS only if presented with the antigen they can recognize by competent antigen presenting cells (APCs).

The process of competent antigen presentation requires two signals, namely antigen presentation to the T cells receptors of antigen in context of major histocompatibility molecules (MHC) (class II for CD4 T cells; class I for CD8 T cells) and a second set of molecules referred to as co-stimulatory molecules, prominent amongst which are CD80/86 that interacts with CD28/CTLA-4 and CD40 that interacts with CD154. The perivascular microglia are the cell type that in situ most prominently expresses both MHC and co-stimulatory molecules and in vitro are highly competent antigen presenting cells [5]. Dendritic cells are likely also present in the perivascular space. Within the CNS parenchyma, the microglia can express MHC class II and co-stimulatory molecules [6]. Microglia are constituents of the innate immune system and as such serve as sensors for "stranger" (derived from exogenous agents such as viruses or bacteria) or "danger" (derived from injured or dying tissue) signals in the environment [7]. In context of MS, the microglia also interact with invading immune cells and their products. The above signals can amplify or suppress the state of activation of the microglia, and thus be important determinants of whether microglia will or will not promote a persistent neuroinflammatory response. The invading immune response in MS also results in entry into the CNS of innate immune cells (monocytes/macrophages, dendritic cells) that can participate in the process of antigen presentation.

## 3. Basis of selective OGC/myelin injury in MS

In this section, we will consider how the relative selectivity of OGC/myelin injury could be conferred either by the properties of the immune effector cells or molecules that are present in the active lesions or by those of the targets and how these properties may be influenced by the CNS environment.

## 4. Effector determined selective tissue injury

The antigen receptors expressed by constituents of the adaptive immune system, namely immunoglobulin (Ig) itself for antibody producing cells (B cell lineage) and αβ receptor chains (αβ TcR) for T cells have a high degree of diversity, consequent to the process of rearrangement of the genes that contribute to their structure. This diversity would allow for recognition of a vast array of target specific determinants.

## 5. Antibody mediated immune responses

The Ig deposited in the lesions of MS patients and recovered from the cerebrospinal fluid (CSF) includes antibodies that react with myelin components. These can be directed at protein, carbohydrate or lipid moieties. In vitro studies have not yet, however, shown that serum or CSF from MS patients selectively and specifically induces injury of myelin producing cells even in presence of complement (reviewed in [8]). Myelin/OGC antibody could also contribute to selective tissue injury by directing cells of the innate immune system present in the inflammatory environment of MS lesions to specific targets. Members of the innate immune system including γδ T cells, NK cells and microglia/macrophages can all effect tissue injury by release of an array of mediators but due to their limited receptor heterogeneity, would not be expected to recognize targets with the specificity of the adaptive immune system constituents. These cells all express Fc receptors that can bind with the Fc portion of Ig molecules that are bound via their variable regions to specific targets.

This process whereby non-specific effector responses could be directed to a specific target is referred to as antibody dependent cell cytotoxicity (ADCC).

## 6. αβ T cell mediated responses

Myelin reactive CD4 αβ T cells, particularly those with a Th1 phenotype, are the cell type usually used to adoptively transfer EAE and implicated as initiating the neuroinflammatory response in MS. Although such cells are shown to possess cytotoxic potential (reviewed in [9]), in vitro studies to date, indicate that human OGCs do not express MHC class II molecules and are not susceptible to MHC class II restricted lysis by myelin reactive CD4 T cells. A caveat is that such myelin reactive CD4 T cell when exposed to pro-inflammatory cytokines can be induced to up-regulate expression of molecules associated with non-specific cytotoxic cells (NK cells) and mediate non-MHC restricted target cell lysis. CD8 T cells, the classic cytotoxic cell population, are prominent in components of MS lesions. OGCs derived from the adult human CNS express MHC class I molecules that can be recognized by CD8 T cells. Our studies using CD8 T cells reactive to a specific peptide sequence of myelin basic protein (MBP) indicates that such cells can induce MHC class I restricted cytotoxicity of OGCs [10].

## 7. Target determined selective tissue injury

Active MS lesions contain a number of cell bound and soluble molecules that are capable of inducing tissue injury but lack the capacity to recognize cell lineage specific "markers". Selective target injury could still result dependent on whether such effectors acted by interaction with specific receptors that may be expressed only by selected cell types. Ligands for "death domain" containing receptors belonging to the tumor necrosis factor (TNF) receptor superfamily present in MS lesions include fas ligand, TRAIL and TNF itself. Such receptors are up-regulated in response to pro-inflammatory cytokines [11]. We have observed that human OGCs, especially when exposed to interferon (IFN)γ, express fas and undergo caspase dependent cell death within 4–6 h following exposure to fas ligand or activating anti-fas antibody. Fetal human CNS derived cortical neurons were resistant to fas signaled injury in vitro, a finding we attributed to reduced fas expression on these cells. Susceptibility to injury can also reflect intra-cellular properties including the signaling cascades induced by receptor engagement and/or the activity of cell survival genes. Fetal human CNS derived astrocytes express fas but are resistant to fas signaled injury [12]. Our studies suggest that such resistance can reflect either failure of fas engagement to initiate the caspase cascade or the presence of inhibitory molecules that block the cascade from completing the death program. Human OGCs become susceptible to TRAIL mediated cell death only if protein synthesis is blocked with cyclohexamide or if they receive an initial insult as we have modeled by introducing sublethal levels of p53 into these cells [13,14]. Progenitor OLGs appear to be more susceptible to TNF mediate compared to their mature counterparts [15]. Progenitor and adult OLGs also appear to differ with regard to expression of glutamate receptors [16].

## 8. Recovery from immune mediated injury

Functional recovery following an MS relapse likely reflects multiple factors. These include active or passive termination of the inflammatory response with reduction in soluble mediators. Functional MRI based studies indicate that cerebral re-organization also occurs. Histologic and MR based studies further document that remyelination does occur in the early inflammation dominated MS lesions. Most experimental data suggest that remyelination in the CNS is derived from progenitor cells that enter the lesion site and mature into myelin forming cells. Multi-potential and glial restricted progenitor cells have been detected in the adult human CNS, including in the region of MS lesions [17,18]. The injured CNS environment contains a multitude of molecules that can positively or negatively impact on the capacity of progenitor cells to survive, differentiate and migrate into lesion sites (reviewed in [19]). Immune mediators also can negatively or positively contribute to progenitor mediated remyelination. Progenitor cells may be selective targets of immune derived effector molecules including specific antibodies and glutamate [16,20]. Conversely, microglia/macrophages may play an integral role in removing tissue debris that inhibits the repair process [21]. The infiltrating immune response may further contain progenitor cells that can provide trophic support for neural progenitor cells [22]. Antibodies are described that can promote myelin formation or regeneration. Most tend to be of germ line origin rather than having undergone Ig gene rearrangement [23].

## 9. Recurrence of the disease process

A hallmark of the active MS lesion is the presence of microglia and macrophages that contain myelin debris, indicating that these cells can take up released myelin products. Such products could then be processed, transported in conjunction with MHC molecules to the cell surface, and be presented to lymphocytes present in the inflammatory milieu. This sequence of events could lead to an expansion of the array of myelin antigens to which the immune system is sensitized, a phenomenon referred to as determinant spreading. CNS released antigens can also be transported back to regional lymph nodes resulting in recurrent and expanded immune activation in the systemic compartment. Determinant spreading could also contribute to the wide diversity of the human myelin directed T cells found in MS patients,

adding to the complexity of using specific antigen or T cell receptor directed therapies.

## 10. Progression of the disease process

The pathologic features of the more chronic MS lesions include extensive destruction of OGCs/myelin associated with a microglia/macrophage rather than lymphocyte dominated immune response. Such pathology can reflect repeated immune mediated injury of both OGCs/myelin and axons. As previously mentioned, we found that oligodendrocytes made to over-express p53 are more susceptible to TRAIL and fas ligand mediated injury [14]. We further found that p53 is over-expressed in oligodendrocytes in MS lesions that feature prominent OGC cell death. P53 can be up-regulated by an array of insults including ischemia, infection, and trauma. We postulate that such up-regulation may reflect initial sublethal injury of these cells making them very susceptible to subsequent insults that can lead to lethal injury. The chronic MS lesion also features extensive axonal loss that could reflect either direct immune mediated injury or the consequences of the loss of myelin on the trophic factor requirements and physiologic properties of axons [24].

## 11. Consequences of systemic immunotherapies in the neurobiologic aspects of the MS disease process

Current therapies for MS are all administered systemically and are aimed at interrupting immune mediators involved in mediating the disease process. Therapies are most effective in the early disease phase that features frequent inflammatory lesion formation and ineffective in the late progressive disease phase. Interferons up-regulate expression of many genes including those involved in immune regulation. Amongst these is TRAIL which if absent results in autoimmune disorders in animals. TRAIL, however, is also shown to be capable of mediating neuronal and OGC injury [25,26]. Glatiramer acetate (GA) therapy results in generation of GA reactive T cells that are polarized toward the Th2 phenotype. We have shown that both Th1 and Th2 polarized T cells can transmigrate across a brain endothelial cell barrier [27]. Properties of such cells that could impact on tissue injury and repair would include their capacity to produce trophic factors and to promote microglia/macrophage mediated clearance of tissue debris [21,22]. The T cells implicated in the process of "protective autoimmunity" are mainly of the Th1 phenotype [28]. Intense immune-suppression regimens employed in experimental protocols that require subsequent immune stem cell rescue have been shown both to prevent subsequent disease relapses and to induce early loss of brain volume [29]. Recent experience showing that natalizamab, at least when used in combination with other imunomodulators, can result in activation of usually quiescent viruses (JC virus/progressive multi-focal leukoencephalopathy) indicates the importance of physiologic immune surveillance within the central nervous system.

## 12. Conclusion

The interaction of the constituents of the immune system with those of the nervous system is a dynamic process that can contribute to the injury or recovery processes that characterize MS. Therapeutic interventions targeting these interactions will need to continue to consider both the physiologic and pathologic aspects of such interactions.

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