Mechanisms of Virus-Induced Demyelination and Remyelination

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Animal models of virus-induced demyelination and remyelination have provided one important piece of evidence to suggest that multiple sclerosis is the result of immunopathology induced by a virus. These models provide the framework to study the potential interaction between the immune system, persistent viruses, and glial cells. This review will address major mechanisms considered to be important in the pathogenesis of virus-induced demyelination including:

1. Direct viral cytopathologic effects on oligodendrocytes
2. Virus-induced autoimmune demyelination
3. "Bystander" demyelination
4. Immune-mediated alteration of viral tropism for oligodendrocytes
5. Immune-mediated destruction of persistently infected oligodendrocytes.

Each mechanism will be illustrated by various examples of virus infection. Special emphasis will be given to Theiler’s murine encephalomyelitis virus (TMEV)-induced demyelination, a model that exemplifies many potential mechanisms of myelin destruction. In addition, the factors that control new myelin formation after virus-induced demyelination will be discussed.

DEMYELINATION

Direct Cytopathology of Oligodendrocytes by Virus

One of the best examples of a virus causing demyelination by direct lytic infection of the myelin-producing cell is the JHM virus, a neurotropic strain of mouse hepatitis virus. This coronavirus produces demyelination in susceptible BALB/c mice within the first week of infection. Demyelination in this model is not temporally related to the presence of perivascular inflammatory cells, and immunosuppression with cyclophosphamide fails to diminish demyelination in the mouse, strongly suggesting that
immune mechanisms are not involved. The virus can infect neurons and astrocytes, but oligodendrocytes appear to be the principal target. Experiments by Powell and Lampert demonstrated oligodendrocytes containing intracisternal virions. Virus buds from cytoplasmic vacuoles, leading to pathologic alterations of oligodendrocytes, which then result in abnormal glial connections with myelin sheaths and syncytia formation.

A characteristic feature of JHM-induced demyelination is the rapid recovery of infected animals, resulting from proliferation of surviving oligodendrocytes and remyelination of previously demyelinated axons. Myelin sheaths are almost completely restored within 2 to 3 months of infection. Prominent remyelination, observed with this model, indicates that oligodendrocytes within the central nervous system (CNS) have an intrinsic capacity for myelin repair, even when primary injury is directed at the myelin-producing cell. As will be discussed, the extent of remyelination in this model may indicate that immune mechanisms are not important in JHM-induced demyelination.

Papovaviruses also appear to cause demyelination by direct injury of oligodendrocytes. The JC virus, a member of the papovavirus family, causes progressive multifocal leukoencephalopathy in immunosuppressed patients. This rare demyelinating disease was seen in patients with lymphoma and leukemia, but it has emerged as an important complication of human immunodeficiency virus (HIV) infection. Pathologically, it is characterized by multiple patches of noninflammatory demyelination without relation to blood vessels. Infected oligodendrocytes are easily recognized by their enlarged nuclei containing papovaviruses. Astrocytes are transformed and develop bizarre, hyperchromatic nuclei. Recent experiments using in situ hybridization clearly demonstrated the remarkable propensity of this virus for oligodendrocytes.

**Virus-Induced Autoimmune Demyelination**

An attractive hypothesis in virus-induced demyelination is that virus infection can trigger a destructive host immune response to self antigens. A basis for this idea comes from observations in patients with postinfectious encephalomyelitis in which perivascular demyelination develops 2 to 3 weeks after virus infection including measles or vaccinia infection and, to a lesser extent, varicella or rubella infection. The pathologic features closely resemble those of acute experimental autoimmune encephalomyelitis. This finding raises the possibility that viruses can cause primary damage to oligodendrocytes or myelin sheaths, or both. This then results in the release of "self" myelin antigens that would be recognized as foreign by immunocytes. This hypothesis would be supported by the demonstration of cellular or humoral immune responses, or both, to myelin antigens after virus infection and by passive transfer of pathologic abnormalities into naive recipients by immune serum or lymphocytes.

Probably the best example of virus-induced autoimmune demyelination is coronavirus infection in rats. Watanabe et al. inoculated rats with a murine coronavirus and observed late demyelinating disease characterized by perivascular lymphoid infiltration. Early in the disease, viral antigen was found primarily in glial cells in association with small demyelinating plaques. As the animals recovered from the initial infection, late demyelinating disease developed and was associated with intense inflammatory infiltrates. Lymphocytes from infected rats were sensitized against myelin basic protein (MBP) and virus antigen. Lymphocytes from Lewis rats recovering
from infection were cultured in vitro in the presence of myelin basic protein and injected intravenously in naive syngeneic rats. In a few days, mild clinical disease and perivascular inflammatory infiltrates resembling EAE developed. Interestingly, demyelination was not detectable.

Thus far, autoimmune demyelination has not been confirmed in any other viral model. This hypothesis was tested in the demyelinating disease induced by Theiler's virus (TMEV), a picornavirus that results in chronic immune-mediated demyelination. Barbano and Dal Canto failed to produce demyelination in vitro when isogenic organotypic brain cultures were exposed to serum or splenocytes from mice persistently infected with TMEV. In addition, disease could not be transferred into naive recipients when splenocytes from infected mice were incubated with myelin basic protein. The studies agree with those of Lampert et al. who concluded that MBP-sensitized cells are not elicited in TMEV infection. Also, Miller et al. showed that class II-restricted autoimmune responses against syngeneic spinal cord homogenate or MBP are not demonstrable in susceptible SJL/J mice. Finally, experiments using sensitive immunoblotting techniques failed to demonstrate within cerebrospinal fluid an immune response to myelin antigens. Thus, data do not support a critical role for autoimmune demyelination in TMEV disease.

One other model in which autoimmune demyelination remains a possibility, however, is the late phase of canine distemper virus (paramyxovirus) encephalitis. This natural disease in dogs is characterized by central nervous system symptoms and signs in the acute viral phase. Similar to measles virus, the acute syndrome can cause lymphopenia to develop in dogs. Intracellular virus in the absence of inflammatory cells has been demonstrated in acute demyelinating lesions. In contrast, the late demyelinating disease is associated with perivascular cuffs of inflammatory cells, and antimyelin antibodies develop before the onset of symptoms. Thus far, demyelination has not been obtained in rodents infected with the canine distemper virus, making it very difficult to formally test the autoimmune hypothesis in this model.

Bystander Demyelination

Considerable thought has been given to the concept that myelin may be injured "nonspecifically" as a result of an immune response within the nervous system, and it would help explain why different viruses may result in myelin destruction. This hypothesis suggests that T cells, macrophages, or both, in reacting to a viral antigen, secrete factors that cause demyelination. For example, myelin is vulnerable to neutral proteases, including plasminogen activator, which can be secreted by activated macrophages. Some experiments suggest that demyelination can occur after local injection of purified protein derivative in the spinal cord of animals previously sensitized to this antigen. However, other similar experiments failed to show a "bystander effect" in the peripheral nervous system. It is possible that "bystander" demyelination may be important in augmenting myelin destruction, especially in a host with latent hypersensitivity to myelin.

The bystander hypothesis was considered by Clatch et al. to explain demyelination induced by Theiler's virus. They propose that as a consequence of persistent virus infection, TMEV-specific precursor delayed hypersensitivity (DTH) cells are triggered to expand within the brain. These cells release lymphokines which would lead to recruitment of activated macrophages. Factors released by DTH cells or macrophages
would then nonspecifically destroy myelin. In support of this hypothesis is the close relation between skin DTH response and susceptibility to TMEV infection. Also, virus persists within macrophages in the CNS which may predispose to bystander demyelination.\textsuperscript{23} Whether this factor contributes significantly to TMEV-induced disease is not yet clear, but there are data to suggest that this may not be the primary mechanism. (1) TMEV-induced demyelinating disease is controlled in part by genes within the major histocompatibility complex.\textsuperscript{27-29} However, the disease maps within the H-2D region which controls class I-restricted immune responses. If DTH-mediated bystander demyelination were important, restriction to class II genes could be hypothesized. (2) Treatment of TMEV-infected mice with aminomethylcyclohexane carboxylic acid (AMCHA), ε-amino caproic acid (EACA), and p-nitrophenyl guanidino benzoate (NPGB), which are inhibitors of plasminogen activators and other neutral proteases, fail to suppress TMEV demyelination, even though they diminish demyelination in EAE.\textsuperscript{30} Also, pepstatin, an acid protease inhibitor that interferes with cathepsin D, fails to diminish TMEV demyelination.\textsuperscript{30} (3) Cyclosporin A fails to diminish demyelination once the disease process is established,\textsuperscript{30} indicating that effectors dependent on the production of interleukin-2 are not involved in myelin destruction during late disease. (4) Susceptibility to demyelination does not correlate with proliferative responses of class II-restricted viral antigens.\textsuperscript{24} (5) Demyelination occurs in nude mice that are deficient in DTH type responses.\textsuperscript{31,32} (6) Demyelinating disease can be suppressed by treatment with mAb to Lyt2 (directed at class I-restricted T cells), whereas mAb to L3T4 (directed at class II-restricted T cells) increases demyelination.\textsuperscript{33} (7) Finally, bystander demyelination runs counter to most human neuropathologic observations, because demyelination is not present in most inflammatory responses to CNS viruses.\textsuperscript{34} This finding suggests that the presence of primary demyelination in the context of inflammation implies a more specific cellular or humoral reaction directed against virus, myelin, or oligodendrocytes.

**Immune-Mediated Alteration of Viral Tropism for Glial Cells**

Nitayaphan \textit{et al.}\textsuperscript{35,36} proposed a unique hypothesis in which immune cells could change the surface structure of a virus so that it has more propensity to infect myelin-producing cells. Using Theiler's virus to test this concept, they found that proteases secreted by macrophages can cleave one of the major structural proteins of TMEV (VP1) and thereby disrupt an epitope important in neutralization.\textsuperscript{35,36} This could promote viral persistence and subsequent infection of oligodendrocytes. Serum from mice with early disease is less effective in neutralizing VP1-cleaved virus than VP1-uncleaved virus. Therefore, immune cells could be critical in demyelination by producing factors that change the structural properties of viruses rather than in mediating disease.

This hypothesis may apply to visna infection in which virus is able to escape host defense mechanisms. This retrovirus causes a slow natural disease of sheep involving the lungs and the CNS.\textsuperscript{37} Pathologically, there is subacute encephalitis in which virus antigen is found primarily in macrophages and demyelination is associated with inflammatory infiltrates.\textsuperscript{38} A unique aspect of the disease is the failure to neutralize virus by serum as a result of viral "antigenic drift."\textsuperscript{39} Virus isolates from sheep years after infection are antigenically different from input virus. It is possible that factors secreted by macrophages may alter virus and contribute to subsequent "antigenic drift."
Immune-Mediated Destruction of Persistently Infected Oligodendrocytes

Humoral or cellular immune mechanisms may play a role in injuring oligodendrocytes that have been infected by virus. This hypothesis implies the expression of viral antigens or viral-induced "novel" antigens on the surface of myelin-producing cells. Humoral mechanisms may interact with virus antigens on oligodendrocytes, resulting in immunoglobulin-directed killing, injury by complement, antibody-dependent cell-mediated cytotoxicity, or activation of macrophages through binding of Fc receptors. Cellular immune mechanisms would depend on the recognition of processed viral polypeptides or intact structural viral protein by class II- or class I-restricted T cells in the context of major histocompatibility complex (MHC) glycoproteins.

An example of humoral-mediated destruction of infected oligodendrocytes is subacute sclerosing panencephalitis. This persistent measles virus infection is characterized by infection of neurons and oligodendrocytes. A constant feature of the disorder is high titers of anti-measles antibody in the spinal fluid and brain of infected patients. Lysis of infected oligodendrocytes is associated with antibodies that bind to the nucleocapsid of the virus. Studies in tissue culture have suggested a mechanism by which virus persists in the presence of a competent immune response. If virus antigens are expressed on the cell surface, then lysis of infected cells occurs in the presence of antibody and complement. However, if measles-infected cells are cultured in the presence of antibody without complement, antigens are "modulated" off the cell surface, rendering the cell resistant to subsequent immunopathology. Once the antibody is removed, the persistently infected cell will begin to express viral antigens on the surface so that it is once again susceptible to injury by complement and antibody. Thus, the relative concentration of antibody to measles virus or complement, or both, determines if virus will persist in the nervous system or if oligodendrocytes will be killed.

Theiler's murine encephalomyelitis virus infection may prove to be the result of immune-mediated injury of persistently infected oligodendrocytes. Pathologically, the CNS is characterized by perivascular demyelination in association with mononuclear cellular infiltrates. During the first 2 weeks of infection the infiltrates consist primarily of macrophages and class II-restricted T cells (helper and delayed hypersensitivity cells), but as the demyelinating disease progresses (after 21 days of infection), class I-restricted T cells (cytotoxic and suppressor cells) gradually become more numerous. In every example, demyelination is preceded by perivascular inflammation. In addition, immunosuppression by cyclophosphamide, antilymphocyte serum, and monoclonal antibodies to Ia diminishes the extent of demyelination. Also, Ia antigens are expressed on astrocytes, oligodendrocytes, and endothelial cells after persistent virus infection, suggesting that the demyelinating process is the result of immune mechanisms.

There is, however, strong evidence that oligodendrocytes are infected persistently by virus. Ultrastructural immunoperoxidase experiments have demonstrated virus antigens within oligodendrocytes. Paracrystalline arrays of virus were demonstrated within oligodendrocytes of neonates infected by the WW strain of TMEV. The virus readily infects oligodendrocytes in tissue culture, and virus antigens can be detected on the surface of these cells. Finally, in situ hybridization studies showed a direct correlation between the presence of viral RNA in the white matter and demyelinating lesions. Simultaneous immunoperoxidase and in situ hybridization assays have shown that 25-40% of cells expressing viral RNA are also expressing antigenic markers specific for oligodendrocytes. Approximately 10% of infected cells are microglia and...
macrophages and 5-10% are astrocytes. The identity of the remainder of the cells has not been determined.

There are also strong immunogenetic data that one of the genes that determines susceptibility and resistance to TMEV demyelinating disease maps within the MHC. Infection of nonrecombinant $H-2$ congeneic strains on a common background showed that mice with $s$, $f$, $p$, $r$, $v$, or $q$ haplotypes on C57BL/10 background develop demyelination, whereas mice with $b$, $k$, or $d$ haplotypes are resistant. Infection of mouse strains with congeneic recombinant haplotypes demonstrated that the $D$ region of the $H-2$ complex determines susceptibility. In addition, the susceptible and resistant gene was mapped to the $3'$ end of $D'$ by using mice with mutations within the $D$ region genes. Because the $D$ region controls class I-restricted immune responses, it suggests an important role of T cells in clearing virus (resistance) or in contributing to demyelination (susceptibility).

Rodriguez et al. proposed a hypothesis of immune-mediated demyelination that incorporates the beneficial response to immunosuppression, virus persistence in oligodendrocytes, and the immunogenetic data. This hypothesis suggests that resistance to disease is an active immunologic process. In genetically resistant mice, viral replication may be limited by class I-restricted T cells in the context of $H-2D$ gene products, by natural killer cells (preliminary observations by P. Leibson), or by neutralizing antibody to virus. In genetically susceptible mice, virus antigens may fail to be recognized by T cells in association with class I MHC antigens so that virus is not cleared from the CNS and persists in oligodendrocytes. Antibody to virus may fail to neutralize infection, either because it occurs too late or because antigens are sequestered in the cytoplasm.

Once oligodendrocytes become infected, viral infection may directly induce demyelination, which would explain the presence of demyelination in nude mice without a T-cell response. However, in immunocompetent mice, antigens not normally expressed by oligodendrocytes may appear on the cell surface and provide the target for an immune response. The nature of the antigen on the cell surface remains to be determined. It may represent a polypeptide on the surface that resides primarily in an unprocessed form within the cytoplasm. Alternatively, the surface antigen may be a "novel" host-derived protein induced by viral infection. Injury to the oligodendrocytes may occur by humoral mechanisms directed at this antigen or by class I- or class II-restricted T cells recognizing the antigen in the context of MHC glycoproteins. Recent experiments showing suppression of demyelination with monoclonal antibodies to Lyt-2 suggest that class I-restricted cells may be one important effector in the demyelinating phase of disease.

REMYELINATION

The factors that control the extent of remyelination after viral-induced demyelination are being evaluated. Some viral infections are characterized by extensive and almost complete myelin repair (i.e., JHM virus infection), whereas in others the extent of remyelination is variable and incomplete (i.e., TMEV). Several factors have been considered to explain the extent of new myelin formation after demyelinating conditions, as follows:

1. Degree of oligodendroglial injury or infection
2. Propensity for oligodendroglial proliferation
3. Extent of astroglial "scarring"
4. Intensity of inflammatory response
5. Alteration of demyelinated axon surface
6. Host genetic factors

Of greatest importance is to determine if the original demyelinating process is the result of immune mechanisms. Those disorders in which immune mechanisms play a primary role (chronic experimental autoimmune encephalitis or Theiler's virus) are characterized by abortive attempts at remyelination. In contrast, disorders with minimal immunopathology (JHM infection and cuprizone toxicity) show almost completely remyelinated lesions, suggesting that immune factors may be critical in determining the degree of remyelination.

Experiments by Dal Canto and Lipton using the DA strain of TMEV in SJL mice demonstrated abortive attempts at CNS remyelination as early as 21 days after infection. Remyelination was somewhat more prominent in the late phase of chronic infection and was associated with a marked astroglial response. In contrast, experiments with a more attenuated WW strain of TMEV with outbred Swiss male mice resulted in greater remyelination by Schwann cells or oligodendrocytes.

Lang et al. undertook a series of experiments in an attempt to promote remyelination after Theiler's virus-induced demyelination. With the observations of Raine and Traugott in mind, a series of experiments were performed to test the hypothesis that immune factors contribute to the extent of remyelination following infection with the DA strain of TMEV. Lang et al. found that DAV-infected mice treated by injections of MBP plus galactocerebroside in incomplete Freund's adjuvant (IFA) had areas of extensive remyelination. Similar results were obtained with infected mice injected with spinal cord homogenate (SCH) plus IFA. These results were similar to those of Raine and Traugott in promoting remyelination in guinea pigs with chronic EAE.

Rodriguez et al. tested the hypothesis that new myelin formation observed in infected mice treated with myelin components is the result of a humoral factor. Normal syngeneic SJL/J mice were divided into three groups and injected subcutaneously in the flank with a 1-mg dose of SCH in IFA, phosphate-buffered saline (PBS) in IFA (1:1), or PBS alone. Serum was collected and passively transferred into mice chronically infected with DA virus. Of interest is that TMEV-infected animals treated with serum from mice given SCH had extensive areas of remyelination that were 6 to 11 times greater than those in the control groups (Fig. 1). Oligodendrocytes were clustered in groups, suggesting proliferation. The addition of SCH sera to oligodendrocytes grown in tissue culture resulted in three- to fivefold proliferation as measured by the incorporation of tritiated thymidine. This finding suggests that a factor is present in the sera of mice immunized to SCH that promotes new myelin formation and proliferation of oligodendrocytes. The identity of the factor remains to be determined. Preliminary studies suggest that the active factor is in the immunoglobulin fraction of sera. In addition, lymphokines may be important in triggering oligodendrocytes to divide and myelinate.

SUMMARY

Viral models of demyelination and remyelination provide important clues to the pathogenesis of multiple sclerosis. Determining the precise viral polypeptides recognized by T cells during the demyelinating process will be important in understanding.
FIGURE 1. Extensive remyelination by oligodendrocytes in the spinal cord of an SJL/J mouse infected with the DA strain of TMEV (6 months) and treated for 1 month with sera from a mouse hyperimmunized to spinal cord homogenate (SCH sera). Note three oligodendrocytes (O) making contact with newly synthesized myelin in the area of remyelination. New myelin formation in the CNS is characterized by abnormally thin myelin sheaths compared to axon diameter (star). One demyelinated axon that has not undergone remyelination is shown by the arrow. The area of remyelination in mice treated with SCH sera was significantly greater ($p < 0.01$) than that in mice treated with control sera. Similar areas of remyelination were seen in TMEV-infected mice treated with a purified IgG preparation of SCH sera. (Reduced by 35%)
the mechanisms of viral-induced myelin destruction. Isolation, purification, and characterization of factors that promote remyelination and proliferation of oligodendrocytes may provide hope in the treatment of patients with chronic demyelinating disorders.

ACKNOWLEDGMENT

I wish to thank Kathryn A. Jensen for helping to prepare this manuscript.

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