Critical Role for Protein Tyrosine Phosphatase SHP-1 in Controlling Infection of Central Nervous System Glia and Demyelination by Theiler’s Murine Encephalomyelitis Virus

Paul T. Massa,* Stacie L. Ropka, Sucharita Saha, Karen L. Fecenko, and Kathryn L. Beuler

Department of Neurology and Department of Microbiology and Immunology, Upstate Medical University, State University of New York, Syracuse, New York 13210

Received 25 February 2002/Accepted 17 May 2002

We previously characterized the expression and function of the protein tyrosine phosphatase SHP-1 in the glia of the central nervous system (CNS). In the present study, we describe the role of SHP-1 in virus infection of glia and virus-induced demyelination in the CNS. For in vivo studies, SHP-1-deficient mice and their normal littermates received an intracerebral inoculation of an attenuated strain of Theiler’s murine encephalomyelitis virus (TMEV). At various times after infection, virus replication, TMEV antigen expression, and demyelination were monitored. It was found that the CNS of SHP-1-deficient mice uniquely displayed demyelination and contained substantially higher levels of virus than did that of normal littermate mice. Many infected astrocytes and oligodendrocytes were detected in both brains and spinal cords of SHP-1-deficient but not normal littermate mice, showing that the virus replicated and spread at a much higher rate in the glia of SHP-1-deficient animals. To ascertain whether the lack of SHP-1 in the glia was primarily responsible for these differences, glial samples from these mice were cultured in vitro and infected with TMEV. As in vivo, infected astrocytes and oligodendrocytes of SHP-1-deficient mice were much more numerous and produced more virus than did those of normal littermate mice. These findings indicate that SHP-1 is a critical factor in controlling virus replication in the CNS glia and virus-induced demyelination.

Neurotropic viruses that infect astrocytes and myelin-forming oligodendrocytes often lead to demyelinating disease similar to that seen in multiple sclerosis (11, 43, 56). Demyelination in rodent models for multiple sclerosis results in inefficient saltatory conduction of nerve fibers with accompanying motor deficits and limb paralysis (61, 62). Recent research has centered on understanding the mechanisms responsible for virus-induced demyelination in these animals and the genetic susceptibility to disease (3, 7, 8, 12, 20, 29, 44, 48). These studies have indicated that damage to oligodendrocytes and myelin may occur by multiple distinct pathways. Depending on the particular virus, these pathways include direct cytopathic effects of the virus in oligodendrocytes, virus-induced inflammatory immune responses promoted by infected glia in the white matter, or molecular mimicry between virus and myelin antigens (43, 56, 57). In each of these responses, the activities of proinflammatory cytokines, interferons, and virus-induced genes play an important role in promoting or protecting against oligodendrocyte pathology (6, 40, 44, 45, 51, 65). Therefore, the regulation of these activities in central nervous system (CNS) cells may be particularly important in controlling virus replication and virus-induced demyelinating processes. However, many of the host genes that control virus infection and demyelination in the CNS through multiple intracellular signaling pathways have not been identified.

Virus-induced genes provide for a rapid innate response to control virus replication at the earliest stages of infection. The activities of virus-induced cellular proteins, including interferons, cytokines, and intracellular signaling molecules, are controlled at multiple levels to provide for modulation of the antiviral state and inflammation (9, 19, 30, 38, 42, 55). Although these regulatory pathways have been extensively studied, such mechanisms in neural cells have been less well studied and may be unique. For instance, it was recently reported that interferons protected CNS neurons from virus infection but were unable to stimulate the expression of major histocompatibility complex class I genes in these cells (36). Multiple mechanisms likely are responsible for mediating tissue-specific antiviral responses in the CNS, but one such regulatory mechanism appears to involve SHP-1, a cytosolic protein tyrosine phosphatase that controls interferon and virus-induced signaling in the glia (16, 34, 37, 38, 66).

SHP-1 has been characterized as a key functional modulator of cytokine responses in hematopoietic and neural cells (9, 17, 19, 34, 42). The physiological ramifications of SHP-1 loss in animals have been extensively studied by using two independent strains of mice with natural mutations in the SHP-1 gene (53). Moth-eaten (me/me) mice have a single nucleotide deletion mutation which generates a cryptic mRNA splice donor site, a resulting frameshift, and a complete loss of SHP-1 protein expression (53). Viable moth-eaten (me+/+;me−/−) mice have a T-to-A transversion mutation in a splice donor that leads to the usage of cryptic donors on either side of the mutation. This situation results in an in-frame deletion and an insertion in the mRNAs, which encode a slightly smaller or larger SHP-1 protein with activity reduced to approximately 10% that in normal mice. Moth-eaten animals display a number of well-characterized hematopoietic abnormalities (32, 52);
however, the regulatory role of SHP-1 in cells of epithelial origin, including glia, and the pathological consequences of SHP-1 loss in these cells have only recently been investigated (5, 16, 31, 42, 66, 67).

Massa and colleagues previously described the expression and functions of SHP-1 in astrocytes and oligodendrocytes, which represent the major macroglial populations of the CNS (34, 37, 38). By examination of glia from SHP-1-deficient mice (either moth-eaten or viable moth-eaten mice), they showed that SHP-1 controls gene expression induced by the proinflammatory cytokines gamma interferon (38) and interleukin-6 (34), both of which have been implicated in the pathogenesis of virus-induced demyelinating disease. Others have shown that SHP-1 also controls alpha/beta interferon signaling through alpha/beta interferon receptors in hematopoietic cells (9). Similar findings for oligodendrocytes have been reported elsewhere (P. T. Massa, S. L. Ropka, and S. Saha, abstract Immunology 12–16 May 2000, FASEB J. 14:A1084, 2000). Furthermore, there has been shown that SHP-1 controls the direct activation of NF-κB in astrocytes by viral mimetic double-stranded RNA (dsRNA) (37), which occurs as a consequence of the activation of the virus-inducible antiviral gene product double-stranded RNA-activated protein kinase (68). Taken together, these observations indicate that SHP-1 may control antiviral signaling pathways in the CNS glia. However, the biological significance of the regulation of virus-induced responses by SHP-1 has not been demonstrated. It was therefore of interest to determine whether SHP-1 controls the susceptibility of the CNS glia to infection by neurotropic viruses. To do this, we analyzed the susceptibility of SHP-1-deficient mice to a paralytic virus-induced demyelinating disease following infection with Theiler’s murine encephalomyelitis virus (TMEV) (2, 47, 49, 59, 69).

We found that astrocytes and oligodendrocytes of mice lacking SHP-1 are extremely susceptible to TMEV infection both in vivo and in vitro and that these mice are highly susceptible to TMEV-induced demyelinating disease. In vitro, astrocytes and oligodendrocytes of SHP-1-deficient mice had a higher rate of infection and produced larger amounts of virus. We therefore propose that the susceptibility of astrocytes and myelin-forming oligodendrocytes to TMEV infection is controlled by innate antiviral responses mediated by SHP-1 within the CNS glia.

MATERIALS AND METHODS

Mice. SHP-1-deficient moth-eaten (me/me) mice (C3HeB/FeJLe-a/a background) and their phenotypically normal littermates (designated +/- for either me/me or me/+ or me+/+) were produced from heterozygous breeding pairs obtained from Jackson Laboratories (Bar Harbor, Maine). Strain designations for heterozygous breeders are C3FLe.B6-a/a Hephm128r1 (stock no. 000225) for moth-eaten mice and C57BL/6 Hephm128r1 (stock no. 000811) for viable moth-eaten mice.

Glia cultures. Glial cultures containing astrocytes and oligodendrocytes were produced from newborn mice as previously described (38). Cerebral hemispheres were used for cultures, and cerebella were used to probe SHP-1 in Western immunobots to identify either moth-eaten or normal littermate mice. Genomic DNA was isolated from cerebellar tissue for verification of normal and mutant SHP-1 gene structures of moth-eaten mice as previously described (53). Brains from littermates of heterozygous breeding pairs having the moth-eaten mutation of the SHP-1 gene (either moth eaten or viable moth eaten) were dissected and mechanically dissociated for separate cultures. Cells in approximately 10 ml of Dulbecco modified Eagle medium (DMEM) containing 10% fetal bovine serum per brain were plated on 60-mm dishes on September 27, 2016 by guest

http://jvi.asm.org/ Downloaded from
step was followed by fixation and incubation with goat anti-mouse IgG conjugated to FITC. The cells were then permeabilized with 0.25% Triton X-100, incubated with anti-TMEV antibodies, and finally incubated with goat anti-rabbit antibodies conjugated to TRITC.

RESULTS

Increased paralysis in TMEV-infected SHP-1-deficient mice. Moth-eaten (me/me) mice and normal littermate mice (C3FeLe.B6 background) infected with attenuated TMEV strain BeAn 8386 by i.c. injection were monitored daily for clinical signs, including limb paralysis. Moth-eaten (me/me) mice first appeared lethargic at approximately 3 to 4 days after infection, while normal littermates remained healthy (Table 1). By day 10, a majority of infected moth-eaten mice displayed clinical signs of spastic limb paralysis that rapidly progressed to quadriplegia and a moribund state in all infected animals. In distinction, normal littermates were only partially susceptible, with a third of the animals developing paralytic disease but at

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No. of mice with spastic paralysis/no. tested</th>
<th>% of mice diseased</th>
<th>Onset</th>
<th>Infection of oligodendrocytes</th>
<th>Spinal cord demyelination</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/− (C3FeLe.B6-a/a)</td>
<td>19/58</td>
<td>33</td>
<td>4–5 wk</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>me/me (C3FeLe.B6-a/a)</td>
<td>10/10</td>
<td>100</td>
<td>5–10 days</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>+/− (C57BL/6J)</td>
<td>0/10</td>
<td>0</td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>me/me (C57BL/6J)</td>
<td>8/8</td>
<td>100</td>
<td>10–15 days</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

a +/-, phenotypically normal heterozygous (me+, and me+/+) and homozygous (+/+) at the SHP-1 locus.
b Infected (+/−) animals were age matched with paralyzed moth-eaten mice.

FIG. 1. Focal demyelinating lesions in dorsal cervical spinal cords of moth-eaten (me/me) mice at 5 days after i.c. inoculation with the attenuated BeAn 8386 strain of TMEV. Five-micrometer paraflin sections were stained with rat monoclonal antibody to MBP and labeled with FITC-conjugated secondary antibody. Sections were photographed with color film by double exposure under both FITC (green) and red fluorescence filter sets. Green fluorescence labels MBP. Red profiles above the background in panel D indicate autofluorescent red blood cells in focal hemorrhagic lesions in regions of demyelination in the parenchyma of the spinal cord. The dorsal funiculus of the cervical spinal cord is shown in either TMEV-infected (B and D) or sham-infected (A and C) normal littermate mouse (A and B) and me/me mice (C and D).
much later times after infection (4 to 5 weeks) (Table 1),
compared to their moth-eaten littermates. Like moth-eaten
mice, viable moth-eaten mice (me'/me') also showed complete
susceptibility to TMEV. However, their normal littermates
(C57BL/6 background) were entirely resistant for up to 6
months after infection (Table 1). Infected me'/me' mice
generally developed disease a few days later than me/me mice (10
to 15 days after infection).

**Immunohistochemical examination of demyelination in
moth-eaten mice.** The ability of TMEV to produce spastic limb
paralysis at early times after infection in moth-eaten mice was
surprising, because this type of paralysis is a relatively late
event in wild-type susceptible mice (27, 28, 60, 63). Because
limb spasticity suggested possible demyelination in the spinal
cords of moth-eaten mice (39), the ability of TMEV infection
to cause spinal cord demyelination was assessed with immu-
nohistological sections stained for MBP (Fig. 1 and 2). Unin-
fected moth-eaten mice showed the expected distribution of
MBP staining in white matter tracts of the spinal cord (Fig.
1C). In TMEV-infected moth-eaten mice, MBP staining was
sharply reduced in both white matter and gray matter, with
some white matter regions of both dorsal (Fig. 1D) and ventral
(Fig. 2A) tracts displaying extensive areas of focal demyelina-
tion. Some lesions were obviously hemorrhagic, with conspic-
uous red blood cells at the center of the lesions (Fig. 1D),
features not seen in normal littermate or uninfected moth-
eaten mice (Fig. 1A to C). In H+E-stained adjacent sections,
areas of demyelination showed considerable white matter cel-
lar infiltrates, especially in the vicinity of blood vessels (Fig.
2C). In contrast to what was seen in the spinal cord, no such
large areas of focal demyelination or inflammation were de-
tected in sagittal midline sections of the brain (data not
shown), indicating that the spinal cord was particularly sensi-
tive to virus-induced demyelination.

**Immunofluorescence identification of infected cells in spinal
cords and brains of TMEV-infected moth-eaten mice.** Inspec-
tion of the most severely demyelinated areas in adjacent sec-
tions of the spinal cord by using an antiserum to TMEV
showed numerous virus antigen-containing cells in both gray
matter and white matter regions (Fig. 2B). Some cells in the
gray matter could be morphologically identified as large dor-
sal horn motoneurons (Fig. 3 and 4). However, many oth-
er smaller cells containing TMEV antigens were scattered
throughout the spinal cord and could not be morphologically
identified. In the brain, many infected cells were detected in
the white matter (Fig. 5), but none were detected in distinct
neuronal layers in the cerebral cortex, hippocampus, or brain
stem nuclei (data not shown). Of particular note, almost all of
the TMEV antigen was localized to small cells in white matter
tracts, especially in the corpus callosum. Taken together, these
observations indicated that TMEV-infected cells in white mat-
ter regions occurred in both brains and spinal cords of SHP-
deficient animals and that demyelination was extensive in the
spinal cord in areas of TMEV infection.

To determine whether some of the small infected cells in the
spinal cord and brain white matter regions were glial cells,
sections were doubly labeled for TMEV and oligodendrocyte-
specific antigens. While cell bodies in the spinal cord were not
discernibly stained with MBP antibodies, many cells in the
spinal cord were doubly labeled for TMEV and oligoden-
drocyte-specific PLP, especially in areas of diffuse myelin in
demyelinating lesions (Fig. 3). In the brain, infected oligoden-
drocytes were doubly labeled for MBP and TMEV at the
interface of the corpus callosum and cerebral cortex, where
myelination was sparse enough to allow resolution of the cell
bodies in magnified micrographs (Fig. 5B). Nonetheless, not all
infected cells in the white matter were labeled with PLP or
MBP (Fig. 5). Many of these infected cells were doubly labeled
for GFAP in both the spinal cord (Fig. 4A and B) and the brain.
FIG. 3. Double immunofluorescence of TMEV (A, C, and E; FITC) and PLP (B, D, and F; TRITC) in the ventral cervical spinal cords of me/me (A to D) mice 5 days after inoculation with TMEV. (A and B) Doubly labeled cells (arrows) in the ventral funiculus at the interface between the white matter and the gray matter of the medial nuclei. A large motoneuron in the gray matter also contains TMEV antigen (arrowhead). (C and D) Doubly labeled cells (arrows) in a demyelinated region of the ventral funiculus adjacent to the ventral median fissure (*). (E and F) No TMEV antigens are seen in cervical spinal cords of +/- animals infected with TMEV.
(Fig. 4C and D), indicating that astrocytes were also productively infected in moth-eaten mice. In contrast, no infected cells were detected in the spinal cords or brains of age-matched normal littermate mice that had received TMEV inoculation (Fig. 3 and 4). Taken together, these data indicated that astrocytes and oligodendrocytes of SHP-1-deficient animals were particularly susceptible to TMEV infection and that TMEV rapidly spread from the brain to the glia in the spinal cord.
Virus spread and replication in moth-eaten mice. As noted above, TMEV-infected astrocytes and oligodendrocytes were detected in both brains and spinal cords of moth-eaten mice but not in infected normal littermate mice. We reasoned that the replication and spread of TMEV may be much greater in moth-eaten mice. Therefore, we assayed infectious virus in brains and spinal cords of moth-eaten and normal littermate mice after infection. For these studies, moth-eaten (me/me), viable moth-eaten (me+/me+), and normal littermate mice were infected i.c. with 1.5 × 10^3 PFU/brain. Normal littermates of viable moth-eaten mice had essentially no detectable infectious virus in the brain, on average (0.6 PFU/g of brain); however, diseased viable moth-eaten mice contained an average of 1.4 × 10^5 PFU/g of brain, constituting approximately a million more virus particles per gram of tissue than the levels found in normal mouse brain (Fig. 6A). Consistent with the latter results, viable moth-eaten mice had nearly 1,000-fold more virus particles per gram of tissue in the spinal cord than did normal littermates (Fig. 6B). Moth-eaten (me/me) mice also contained higher virus titers in brains and spinal cords than did their normal littermates (Fig. 6C and D). However, unlike normal littermates of viable moth-eaten mice (C57BL/6 background), normal littermates of moth-eaten mice (C3FeLe.B6 background) had substantial virus titers in both brains and spinal cords, indicating differences in background susceptibility, in agreement with the data in Table 1. Despite this level of virus replication, repeated immunohistochemical analysis was not able to detect virus antigen-containing cells in C3FeLe.B6 normal littermates, perhaps due to the lower sensitivity of this assay. Nonetheless, plaque assays indicated that both replication and spread of TMEV were clearly increased in the two strains of SHP-1-deficient mice, in accord with their increased susceptibility to clinical disease compared to the status of their normal littermates.

Analysis of TMEV infection of moth-eaten mouse glia in vitro. The increased infection of astrocytes and oligodendrocytes and the concomitant demyelination in SHP-1-deficient mice suggested a possible alteration in direct virus-oligodendrocyte interactions dependent on SHP-1 in these cells. To test this possibility, we analyzed TMEV replication in glial cell cultures containing astrocytes and oligodendrocytes produced from moth-eaten and normal littermate mice. Glial cell cultures were inoculated with 7.4 × 10^6 PFU of TMEV/ml (multiplicity of infection, 1.0) and then incubated for 3 days after inoculation. We first analyzed the numbers and types of glial cells infected by using double immunohistochemical analysis. To analyze oligodendrocyte infection, cultures were stained with oligodendrocyte-specific antibody to O1 antigens and subsequently for intracellular TMEV antigens. O1 antigen-positive oligodendrocytes expressing TMEV antigens were readily identified in both moth-eaten and normal littermate glial cell cultures (Fig. 7A); however, the number of oligodendrocytes...
infected was much higher (approximately 10-fold) in moth-eaten mouse cultures (Fig. 7B). Additionally, many O1 antigen-negative cells in moth-eaten mouse cultures contained TMEV antigens and had an astrocytic morphology. To ascertain whether these cells were astrocytes, cultures were doubly labeled for GFAP and TMEV antigens. Many GFAP-positive astrocytes were found to contain TMEV antigens in moth-eaten mouse cultures, but none were seen in normal littermate cultures (Fig. 8). Taken together, the immunofluorescence data showed that TMEV produced much more infection of O1 antigen-positive oligodendrocytes and GFAP-positive astrocytes in moth-eaten than in wild-type mouse glial cell cultures.

**Virus production in the glia of normal and moth-eaten mice.**

To ascertain whether moth-eaten mouse glial cells produced higher virus titers than normal littermate glial cells, infectious virus in supernatants and cell lysates from the above-described infected glial cell cultures was assessed at 3 and 6 days after infection. Mean virus titers (PFU per milliliter of supernatant) were significantly higher (approximately fivefold) in me/me mouse cultures than in normal littermate mouse cultures (Fig. 9). Analysis of lysates of infected cells at 3 days after infection indicated that the majority of the virus was cell associated in both me/me glia and normal littermate glia and that me/me glia contained significantly more virus particles than normal littermate glia. At 6 days after infection, the ratio between released virus and cell-associated virus was increased in both me/me and normal littermate glial cell cultures, indicating that a higher proportion of virus was being released from the cells as the infection progressed. Nonetheless, the difference in the amounts of released virus and cell-associated virus between me/me glia and normal littermate glia increased over time (Fig. 9). Taken together with the immunohistochemical data, these

![Graphs showing virus production in the glia of normal and moth-eaten mice.](http://jvi.asm.org/)

**FIG. 6.** TMEV titers in brains and spinal cords of infected me/me and me/me mice and normal littermate (+/− Control) mice. Brains (A and C) and spinal cords (B and D) were harvested from paralyzed viable moth-eaten (me'/me') (A and B) or moth-eaten (me/me) (C and D) animals along with age-matched sham-infected normal littermate animals (+/− Control). Error bars indicate standard errors of the means. Numbers in the histograms are for control PFU per gram of brain or cord where these cannot be read from the ordinate. Differences in the means between normal littermate mice and either moth-eaten or viable moth-eaten mice were significant (P < 0.0004) for both brains and spinal cords.
data indicated that moth-eaten mouse astrocytes and oligodendrocytes sustained a higher level of virus production than did the glia of normal littermates.

**DISCUSSION**

In the present report, we have shown that SHP-1 is a critical determinant in controlling virus replication in the glia of the CNS. Further, in vitro studies suggested that SHP-1 may control virus replication at least in part at the level of direct virus-cell interactions. However, the way in which SHP-1 may function to control virus replication in these cells and whether
direct virus-cell interactions controlled by SHP-1 fully account for increased virus growth in SHP-1-deficient mice in vivo are not known. To address possible alterations in virus-cell interactions, we are currently investigating multiple antiviral pathways that are likely to be affected by SHP-1 in the CNS glia in vitro. For instance, the role of an innate antiviral state including the interferon system has been shown to be critically important for controlling infection by TMEV in the CNS (12). Such studies may be relevant to the possible role of SHP-1 in controlling TMEV infection, because previous studies showed that SHP-1 altered STAT1 activation in response to interferons (9, 38, 42). One possibility is that increased induction of STAT1 enhances the expression of proapoptotic genes (22), which may increase virus replication in the CNS, as recently described for Sindbis virus infections of neurons (25). However, other distinct antiviral pathways may be directly affected by the loss of SHP-1 in the CNS glia. The role of SHP-1 in controlling NF-κB activation by dsRNA in astrocytes was recently described. It is known that NF-κB activation by dsRNA is mediated by the antiviral gene product double-stranded RNA-activated protein kinase (68). Additionally, dsRNA is known to affect the expression of other virus-induced tran-

FIG. 9. TMEV titer in vitro. Glial cultures of either me/me or normal littermate mice (+/- Control) were inoculated with TMEV. Virus was harvested in both supernatants (released) and cell lysates (cell associated) at 3 and 6 days after infection (P.I.) and quantified by plaque assays. Histograms indicate the mean PFU per milliliter in supernatants and PFU per cell based on protein content in cell lysates. Statistical differences between specimens were measured by Student's t test (one tailed). Each experiment was performed in triplicate. Error bars indicate standard errors of the means. Differences in the means between normal littermate (+/- Control) and moth-eaten (me/me) glial cultures were significant at each time after infection for both released and cell-associated viruses (P < 0.001).
scription factors and genes (13, 23) that may also be modulated by SHP-1 activity in virus-infected cells. Finally, it was recently shown that SHP-1 is required for the induction of neuronal nitric oxide synthetase (NOS1) activity in nonhematopoietic cells (31), and NOS1 activity has been shown to be a critical antiviral activity for controlling CNS virus infections (21, 46). Future studies will be aimed at determining the role of SHP-1 in regulating these multiple antiviral pathways in the CNS.

In a number of models of virus-induced demyelinating disease, infection often involves astrocytes and oligodendrocytes in the white matter in the vicinity of demyelinating lesions (1, 2, 18, 24, 44, 47, 49, 69). Demyelination caused by virus infection in CNS white matter can result from at least two mechanisms that are relevant to the present study. One is direct cytotoxic effects of the virus on oligodendrocytes, and the second is an indirect immunopathologic response to the virus or autoantigens involving inflammation and oligodendrocyte pathology. Of particular note, the latter is often promoted by proinflammatory cytokine secretion and major histocompatibility complex expression induced by viruses in astrocytes (10, 26, 33, 35, 57, 58). The relative contributions of these mechanisms to the demyelinating process in TMEV-infected moth-eaten cells are presently unknown. Nonetheless, increased virus replication in oligodendrocytes and astrocytes is likely to promote both pathways to myelin degeneration. With respect to possible immunopathology in the demyelinating process, extensive demyelinating lesions in spinal cords showed increased levels of cellular infiltrates indicative of an inflammatory component. However, inflammation may occur as a secondary event in the removal of myelin debris by phagocytic cells following demyelination, such as is seen in toxin-induced models (15). Therefore, the mechanism of virus-induced demyelination in mice lacking SHP-1 remains to be determined but is most likely controlled by both direct and indirect consequences of increased virus replication in astrocytes and oligodendrocytes in the white matter of these mice.

The present and previous studies on virus-induced demyelination indicate that mechanisms of demyelination are complex and are controlled by multiple genes that regulate innate, adaptive, and autoimmune responses (11, 41, 56, 64). In the present report, we have focused on a genetic alteration that may act at the level of the CNS glia for controlling TMEV replication. We have found that, compared to normal littermates, mice lacking SHP-1 produce more virus in brains and spinal cords after TMEV infection, succumb to a rapid-onset demyelinating disease, and display early spastic limb paralysis. We believe that disease in mice with a genetic deficiency in SHP-1 activity is caused by a specific defect in innate antiviral responses against TMEV in the CNS glia. Our current studies are directed at discovering virus-glia interactions that are altered in the absence of SHP-1 and that lead to increased virus replication, oligodendrocyte pathology, and demyelination.

ACKNOWLEDGMENTS

This work was supported by grants from the National Institutes of Health (NS41593-01) and from the National Multiple Sclerosis Society (RG 2569B4/5).

REFERENCES

5. Bedecs, K., N. Elbaz, M. Sutren, M. Nossal, C. Susini, A. D. Strohberg, and J. E. Love. 1999. The role of SHP-1 and SHP-2 in the suppression of CD4+ and CD8+ T cells responses against TMEV in the CNS glia. Our current studies indicate that mechanisms of demyelination are complex and are controlled by multiple genes that regulate innate, adaptive, and autoimmune responses (11, 41, 56, 64). In the present report, we have focused on a genetic alteration that may act at the level of the CNS glia for controlling TMEV replication. We have found that, compared to normal littermates, mice lacking SHP-1 produce more virus in brains and spinal cords after TMEV infection, succumb to a rapid-onset demyelinating disease, and display early spastic limb paralysis. We believe that disease in mice with a genetic deficiency in SHP-1 activity is caused by a specific defect in innate antiviral responses against TMEV in the CNS glia. Our current studies are directed at discovering virus-glia interactions that are altered in the absence of SHP-1 and that lead to increased virus replication, oligodendrocyte pathology, and demyelination.

SHP-1 CONTROLS TMEV-INDUCED CNS DISEASE 8345


Downloaded from http://jvi.asm.org/ on September 27, 2016 by guest