

Measles virus infection of the CNS: human disease, animal models, and approaches to therapy

Dajana Reuter · Jürgen Schneider-Schaulies

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Abstract Viral infections of the central nervous system (CNS) mostly represent clinically important, often life-threatening complications of systemic viral infections. After acute measles, CNS complications may occur early (acute postinfectious measles encephalitis, APME) or after years of viral persistence (subacute sclerosing panencephalitis, SSPE). In spite of a presumably functional cell-mediated immunity and high antiviral antibody titers, an immunological control of the CNS infection is not achieved in patients suffering from SSPE. There is still no specific therapy for acute complications and persistent MV infections of the CNS. Hamsters, rats, and (genetically unmodified and modified) mice have been used as model systems to study mechanisms of MV-induced CNS infections. Functional CD4⁺ and CD8⁺ T cells together with IFN- γ are required to overcome the infection. With the help of recombinant measles viruses and mice expressing endogenous or transgenic receptors, interesting aspects such as receptor-dependent viral spread and viral determinants of virulence have been investigated. However, many questions concerning the lack of efficient immune control in the CNS are still open. Recent research opened new perspectives using specific antivirals such as short interfering RNA (siRNA) or small molecule inhibitors. In spite of obvious hurdles, these treatments are the most promising approaches to future therapies.

Keywords Measles virus (MV) · CNS complications · Subacute sclerosing panencephalitis (SSPE) · Persistent brain infection · Antiviral siRNA · Antiviral compounds

Introduction

Measles virus (MV) belongs to the genus Morbillivirus of the family *Paramyxoviridae* [1]. After entering the upper respiratory tract, MV exhibits a pronounced tropism for mono- and lymphocytic cells, and soon viral replication is detected in draining lymph nodes [2]. In the course of its spread, MV remains highly cell associated and can be isolated from blood leukocytes early during infection. During measles, patients develop a pronounced leukopenia that may be due to an enhanced adhesion of lymphocytes in secondary lymphoid organs [3]. In immunocompetent patients, the MV infection is usually cleared by the virus-specific immune response, while the general immune response to other antigens is suppressed for several weeks after the rash (for review see: [4]).

Following replication in lymphoid tissues, virus spreads to various organs can be detected in the skin, where viral antigen is concentrated near blood vessels, and in endothelial cells of dermal capillaries, and may also enter the brain (for review see: [5]). Various routes of CNS invasion of MV (or other Morbilliviruses in their respective hosts) may be utilized, such as the blood stream and transmigration of infected leukocytes across the blood brain barrier (BBB), migration through the choroid plexus, infection of microvascular endothelial cells and basolateral virus release, or viral transport in infected nerves of the olfactory bulb [6–9]. We found that enhanced adhesion of infected leukocytes may play a role in the establishment of acute

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D. Reuter · J. Schneider-Schaulies (✉)
Institute for Virology and Immunobiology,
University of Würzburg, Versbacher Str. 7,
97078 Würzburg, Germany
e-mail: jss@vim.uni-wuerzburg.de

and persistent CNS complications, since *in vitro* experiments demonstrated that MV infection of leukocytes not only induced a block in their trans migratory capacity across endothelial barriers, but also enhanced their adhesion to endothelial cells and thus enabled the endothelial cell infection [10]. CNS invasion has also been investigated using canine distemper virus (CDV), another Morbillivirus, in ferrets. Here, after massive infection of the lymphatic system, CDV used both the anterograde and the hematogenous pathway for neuroinvasion [9].

As the most frequent CNS complication APME occurs in approximately 0.1% of cases with a lethality of approximately 20% [11], it is likely that a clinically inapparent cerebral dysfunction is common in uncomplicated measles as documented by abnormalities of the electroencephalogram (EEG) and pleocytosis in the cerebrospinal fluid (CSF) in about 50% of patients. Since MV-specific nucleic acids have been detected only with highly sensitive methods within the CNS of patients suffering from APME [12], the observed clinical signs are thought to result from a virally induced pathogenic immune response in the brain with autoimmune components [13, 14]. This inflammatory immune reaction may be triggered by infected leukocytes adhering to brain microvascular endothelial cells, or by infected endothelial cells in the brain.

In contrast to APME, MV is abundantly present in brain cells of patients with SSPE and measles inclusion body encephalitis (MIBE), both of which develop after clinically silent periods of months to years after acute measles and are inevitably fatal [15]. Whereas MIBE is confined to immunosuppressed or -deficient patients, and may thus be considered as an opportunistic infection of the CNS, SSPE develops with a frequency of 1:10000–20000 approximately 6–12 years after primary infection with wild-type MV in patients with an apparently normal antiviral immune response [11, 16–18]. As revealed by molecular epidemiological studies, the primary MV infection of patients with SSPE takes place predominantly below the age of 2, when the immune system of the host is still immature and residual maternal antibodies may be absent or not sufficient for complete virus neutralization. This immature immune response in conjunction with a transient immunosuppression due to other infections may favor the establishment of a persistent MV infection (see below: animal models). SSPE is characterized by an excessive intrathecal synthesis of MV-specific antibodies. Oligoclonal IgG bands detected by isoelectric focusing with MV-specific immunoblotting are present in the cerebrospinal fluid and the MV-specific IgG index is elevated [19, 20]. Serum titers of MV-specific IgG usually are also substantially elevated.

MV-specific sequences obtained from SSPE autopsy material are, except from mutations accumulated in certain regions of the genome (predominantly the matrix gene),

homologous to the corresponding gene sequences of genotypes circulating at the time of primary exposure of the patients to MV [21–23]. In few cases, infectious viruses could be isolated from SSPE brains that conserved their highly neurovirulent properties after propagation *in vitro* in animal models [24–26]. However, recombinant MV containing the matrix gene from an SSPE isolate grows considerably less efficient in tissue culture and transgenic mice [27]. This strongly supports the notion that there are no circulating MV genotypes, which are particularly neurovirulent, and that persistent brain infections are established initially by ‘normal’ wild-type MV strains. After measles vaccination, SSPE is not observed [28, 29].

Mechanisms contributing to measles virus persistence and pathogenesis

The establishment of a viral CNS infection depends not only on the biological properties of the invading agent but also on the breakdown of the host defence mechanisms that normally protect cells in the CNS from infection. Due to existence of the BBB and absence of lymphatic tissues in the CNS, the immune response in this organ is peculiar. In addition, an unbalanced immune response in the immature host may play a decisive role for the early establishment of a persistent MV infection. As mentioned above, MV spread in brains of patients with SSPE occurs in the presence of extremely high titers of anti-measles antibodies. However, these antibodies fail to control the infection. Interestingly, it has been observed in tissue culture experiments that virus-neutralizing antibodies are capable of interfering with intracellular viral gene expression particularly in neural cells. In the presence of polyclonal anti-MV antibodies, a selective reduction of the viral P and M proteins was found in infected HeLa cells [30, 31]. A complete downregulation of intracellular viral transcription and protein expression following the treatment with neutralizing anti-H monoclonal antibodies was observed in persistently MV-infected rat glioma and mouse neuroblastoma cells, but not in persistently infected Vero and lung fibroblast cells [32, 33]. This so called antibody-induced antigenic modulation (AIAM) has been linked to a so far unidentified transmembrane signal, which leads intracellularly to the downregulation of the viral gene expression, and may support the establishment of a slow persistent viral infection.

The involvement of single nucleotide polymorphisms of immunologically important genes encoding molecules such as IL-2, IL-4, IL-12, MxA, and TLR-3 in the susceptibility to the establishment of SSPE is controversially discussed [34–38]. In the CSF of patients with SSPE, elevated levels of type I IFN have been detected and were suggested to

play a role in the establishment of the slowly progressing persistent brain infection. The IFN- α/β -inducible human MxA protein, which interferes with transcription and/or translation of various viruses, exerts a direct antiviral activity against MV in tissue culture, and has been shown to be expressed in glial cells around active lesions in the brain of patients with SSPE [39–42]. In tissue culture, MV infection of neuroblastoma cells (in contrast to astrocytoma cells) failed to activate NF- κ B, and to induce IFN- α/β and MHC class I expression [43, 44]. This failure may provide a potential mechanism allowing MV to persist preferentially in neurons. In addition, it has been found that wild-type MV-isolates have a considerably lower capacity to induce type I IFN in human peripheral blood lymphocytes than vaccine strains [45]. A different specific antiviral mechanism appears to be exerted by type II interferon (IFN- γ) in patients with SSPE, where an inverse correlation between IFN- γ production by peripheral blood mononuclear cells and disease progression was found [46]. Interestingly, IFN- γ exerts a direct antiviral role in tissue culture mediated to a large extent by indolamine-2,3-dioxygenase [47], an enzyme that has also immunoregulatory properties [48]. The importance of IFN- γ was confirmed in animal models (see below, [49, 50]). Discrepancies between various reports in the literature concerning IFN- γ , IL-6, IL-12, and IL-10 expression in patients with SSPE might be due to different ages of patients, stages of the disease, and treatments of the patients studied [51–54].

CD150 was identified as receptor for both, vaccine and wild-type MV strains [55–57], whereas CD46 acts as cellular receptor only for vaccine strains [58, 59]. In concordance with the lymphotropism of MV, the costimulatory molecule CD150 is expressed on activated T and B lymphocytes, memory cells, activated dendritic, and monocytic cells [60–62], but has not been found on epithelial, endothelial, and various brain cell types [8, 63]. However, in SSPE brains, neurons, oligodendrocytes, astrocytes, and few microvascular endothelial cells are infected [7]. Therefore, it is likely that wild-type MV utilizes additional molecule(s) as receptors on these cells as well as on epithelial cells [64–66], the nature of which is still unknown. Within heavily infected MV-positive brain lesions of patients with SSPE, CD46 was undetectable, independent of whether MV antigens were present in these individual cells, whereas in SSPE brain tissue distant from the lesion, normal levels of CD46 were found suggesting that CD46 expression was reduced by the MV infection [8, 63].

As documented by immunohistochemistry and later by sequence analyses from autopsies, the expression of MV envelope proteins is strongly reduced in brains of patients with SSPE and MIBE. Transcriptional restrictions of the corresponding genes and mutations within the coding sequences interfering with the synthesis of functional gene

products were found [67]. As a consequence, the expression of viral envelope proteins (matrix (M), fusion (F), and haemagglutinin (H) protein) is restricted by various means. In particular the M and the cytoplasmic part of the F protein harbor single or hyper-mutations or deletions, which prevent their proper expression, reduce budding, support cell fusion, and enhance intracellular RNP replication [68–70]. Cell-to-cell spread of virus appears to be an important mechanism supporting persistence in the human and animal models of measles encephalitis [7, 71–73]. MV spreads in differentiated human neuronal cells lacking CD150 and CD46, as well as in CD46-positive human neuroblastoma cells, in astrocytoma, and in oligodendroglioma cells by an intracellular route, most likely involving local microfusion events at cell contact points [74]. Vesicular stomatitis viruses pseudotyped with viral envelope proteins from patients with SSPE infected target cells in a CD150- and CD46-independent manner, confirming that for infection of neural cells, other unknown receptors are used [75].

Taken together, an early infection in life, a genetic predisposition, the IFN-response in glial cells and its possible lack in neurons, the antibody-induced antigenic modulation, and a steep viral expression gradient, the accumulation of point- and hypermutations within envelope genes associated with enhanced intracellular replication of RNPs, and the cell-to-cell spread of RNPs support the persistent brain infection and the failure of the immune response to eliminate the virus.

Animal models of the CNS infection

Resistance and susceptibility to MV-induced encephalitis in rodents correlate with the MHC haplotype of the respective inbred strain [76–78]. In resistant mouse strains, depletion of the CD4+ T-cell subset by monoclonal antibodies led to a breakdown of resistance, whereas depletion of CD8+ T cells had no effect [79]. This may be different in the human, since in vitro experiments demonstrated that CD8+ T lymphocytes control the dissemination of virus [80]. The importance of antigen presentation for the immune defense became evident in TAP-transporter-deficient mice, which cannot present antigen on MHC class I molecules [72]. Under these conditions, MV was found to spread considerably more transneuronally to the next order of neurons. This indicates that infected neurons are indeed target cells of cytotoxic T lymphocytes (CTL), and that brain infections to some extent can be inhibited by CTL activity. A breakdown of resistance is also observed after neutralization of IFN- γ leading to the generation of a TH2 response [49, 81]. Further investigation into this measles encephalitis model revealed that CD4+ T cells are able to protect either alone, through cooperation with CD8+ T

cells, or after immunization as secondary T cells (depending on the mouse strain used), and CD8⁺ T cells are able to protect alone after immunization if they are cytolytic [81, 82]. As found earlier in non-transgenic mice, IFN- γ has also a critical role for the protection of CD46-transgenic mice against MV encephalitis [50]. Interestingly, this protection functions in a non-cytolytic manner without neuronal loss. Hyperthermic pre-conditioning of mice enhanced the efficacy of the cell-mediated immune response and promoted virus clearance from the brains of persistently infected mice [83].

Interestingly, MV lacking the complete matrix protein is functional and spreads even more efficiently in the brain of CD46-transgenic IFN- α/β -receptor-deficient mice [84]. When a matrix gene of an SSPE isolate was introduced in a recombinant MV, this virus replicated at a reduced level, but led to a protracted CNS infection in CD46-transgenic mice [27]. MV spreads also in rat hippocampal neurons by cell-to-cell contact and in a polarized fashion [85].

We investigated importance of the viral H protein for virus spread and neurovirulence using a recombinant MV in which the H gene of MV Edmonston had been replaced by the H gene of the neurovirulent strain CAM/RB. After intracerebral injection into suckling C57BL/6 mice, this recombinant virus-induced neurological disease and MV antigen were found in neurons and neuronal processes of the hippocampus, frontal, and olfactory cortices and neostriatum [86, 87]. Replacement of only two amino acids in

the CAMH-protein at positions 195 G \rightarrow R and 200 S \rightarrow N caused the complete loss of neurovirulence, which points to the usage of unknown neuron-specific receptors by CAMH [88, 89]. The viral H protein plays also an important role for the neurovirulence of CDV in ferrets, in which the disease duration was determined by the viral H protein [90].

In order to investigate aspects of immune control, we established a model of persistent brain infection in fully immunocompetent mice using 2-weeks-old normal C57BL/6 mice, an age at which the mice survived the intracerebral (i.c.) infection, while the immune system is still not fully mature [91]. After i.c. infection with 1000 PFU recombinant MV-CAMH, virus spread is maximal after 1 week (Fig. 1), and later, approximately 80% of mice carry a persistent infection. These mice can be used to study the role of the immune response for the persistent CNS infection and to assess antivirals in the brain. In this mouse model, neither rodent CD46- and CD150-homologues function as MV receptors nor are required, and also transgenic human receptors are dispensable. This allows the use of any genetically modified mouse on C57BL/6 background to study immunologically relevant questions.

Other investigations were performed using mice expressing the human MV-receptors CD46 and/or CD150. Transgenic expression of CD46 in mice has been used to define the role of a cellular receptor for neurovirulence and pathogenicity. A similar susceptibility of newborn mice for

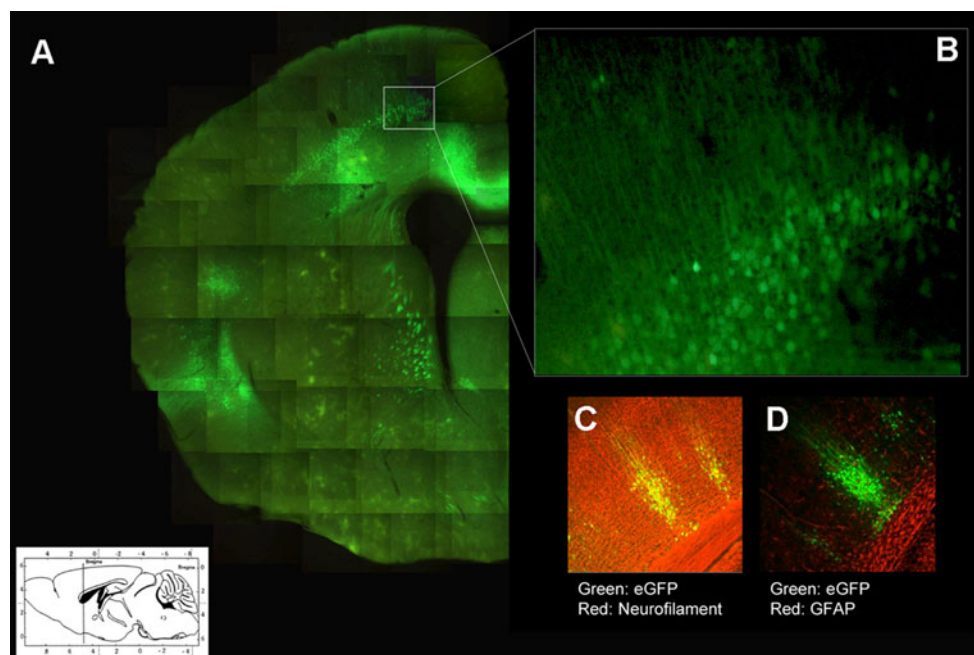


Fig. 1 GFP expression in a brain of a 2-week-old mouse infected with recombinant measles virus MV-eGFP-CAMH [91]. The overview (coronal section) of the left hemisphere (a), enlargement (b),

and GFP/marker co-localizations with neurofilament in neurons (red) (c), and absence of colocalization with GFAP in astrocytes (red) (d) demonstrates the exclusive infection of neurons

infection with MV strain Edmonston as in non-transgenic animals was found in such mice expressing CD46 ubiquitously [92–95]. In the periphery of adult CD46-transgenic mice or rats, the receptor expression did not lead to a significant increase in susceptibility for MV [96, 97], whereas in IFN- α/β -receptor-deficient mice expressing CD46, intracerebral inoculation of adult animals with low doses of MV-Edm caused encephalitis with mostly lethal outcome [98]. Recent findings using CD46-transgenic neurokinin-1-deficient mice suggest that the substance P receptor is involved in trans-synaptic virus spread [99]. The ubiquitous expression of transgenic CD150 rendered suckling mice susceptible to intranasal infection with wildtype MV. Virus spreads to different organs including the brain, and these animals develop a neurologic disease leading to death within 3 weeks [100]. CD4+ CD25+ FoxP3+ regulatory T cells are enriched following infection, both in the periphery and in the brain [101].

Cytokines induced by the infection of neurons (or neural cells in general) are early important mediators of leukocyte recruitment to sites of viral infection. In brains of CD46-transgenic mice expressing CD46 exclusively in neurons, infiltrating leukocytes, the upregulation of MHC class I and II, and increased levels of RANTES, IP-10, IL-6, TNF- α , and IL-1 β have been observed that preceded the infiltration of reactive T lymphocytes [102, 103]. Using CD46-transgenic Rag-deficient mice, adoptive transfer of lymphocytes revealed that the combined activity of CD4+ T lymphocytes with CD8+ T cells or B cells is required to control the intracerebral infection [104]. Furthermore, transgenic expression of CD150 alone or in combination with CD46 can mediate a substantial systemic MV infection only in conjunction with a defect in the innate immune system [105–107]. Thus, both the innate and the adaptive immune system play important roles to overcome MV-induced neuropathogenesis. CD46-transgenic Rag-deficient mice have also been used to test a hypothesis for the establishment of SSPE, which has been set up earlier in a hamster model [108], i.e. the role of a transient immunosuppression by another virus preceding the infection with MV (dual viral hits) [109]. According to these findings, the young immature immune system and transient immunosuppression during the acute MV infection may also in the human favor the establishment of the persistent brain infection and subsequent development of SSPE.

Approaches to a specific therapy

Newborn mice can be protected against MV infection by injection of monoclonal antibodies to the viral envelope proteins, or by vaccination with vaccinia virus recombinants expressing the corresponding antigens [110–112].

However, anti-MV antibodies can also support the establishment of a persistent infection [113]. In weanling Lewis rats, such monoclonal antibodies did not fully protect against encephalitis, but converted an acute into a subacute persistent infection, whereas the untreated control group succumbed invariably to a fatal encephalopathy within few days (for review see: [14]). Intraperitoneal vaccination with MV protected 2-weeks-old mice from intracerebral infection and subsequent persistent infection. However, when already persistently infected mice were vaccinated, this did not alter the extent of persistent CNS infection [91]. These findings and the fact that patients with SSPE have high concentrations of antiviral antibodies in both, serum and cerebrospinal fluid, suggest that antibodies against viral proteins cannot be used for a specific therapy of the human disease SSPE.

An effective treatment of SSPE is still not available and the usual treatment with ribavirin (RBV), inosiplex (isopinosine), and intraventricular interferon- α (IFN- α) may at best prolong the disease course. Inosiplex is a drug that may activate the host immune system by increasing the number of effector lymphocytes, the function of interferons, and the production of IL-1 and IL-2, but its usage is controversial due to conflicting results. A possible treatment regimen for intraventricular IFN- α (with or without inosiplex) consists of 6-week courses started with 10^5 units/m² of body surface area and subsequently increased to 10^6 units/m² per day given for 5 days a week. Courses are repeated up to six times at 2–6 months intervals (for review, see: [114]).

RBV is a water-soluble synthetic nucleoside with broad spectrum of antiviral properties [115]. It has been shown to be active against MV and improved the survival of i.c. infected hamsters in an SSPE model when administered intracranially (10 mg/kg/day for 10 days), but did not improve the survival when administered intraperitoneally suggesting a failure to cross the BBB [116, 117]. Complexation of RBV with cyclodextrin- α leads to a five-fold decrease in the 50% inhibitory concentration (IC₅₀) against MV in vitro [118]. Interestingly, the cyclodextrin complexation enabled the effective intraperitoneal administration of RBV in mice indicating an improved crossing of the BBB and bioavailability [119, 120]. The lethal dose for mice was determined to be 55 mg/kg RBV, and mice could be treated successfully with 40 mg/kg [119]. Although the high concentrations of RBV required have undesired side effects, its complexation with cyclodextrin could possibly improve the treatment of viral CNS infections with RBV-susceptible viruses.

It has been known for quite a while that MV-associated mortality can be decreased in children by treatment with vitamin A, which is recommended by the WHO [121–123]. There are manifold effects of vitamin A on the immune

system [124]; however, retinoids also directly inhibit MV replication in vitro in a number of cell lines and human peripheral blood mononuclear cells through nuclear retinoid receptor signaling [125]. The molecular mechanism has recently been described as a type I IFN-dependent bystander effect [126]. In a CDV infection model of ferrets, the effects of vitamin A could be demonstrated impressively [127]. Interestingly, low levels of serum vitamin A and beta-carotene have been observed in a fraction of patients with SSPE [128] suggesting that vitamin A supplementation may also support the interferon treatment of patients with SSPE.

Neurodegeneration caused by infection of mice with the hamster neurotropic strain of MV (HNT) could be inhibited by the N-methyl-d-aspartate (NMDA)-receptor antagonist MK801 suggesting that the virus may have indirect NMDA-receptor-dependent effects in the brain leading to the neuronal loss [129].

RNA interference has been described to be active against MV infections [70, 130, 131] and is principally applicable against the intracellularly replicating viral RNPs in SSPE brains. In our own studies [70, 133], we found that silencing of the viral RNP-mRNAs was highly efficient in reducing viral messenger and genomic RNA, whereas siRNA-mediated knockdown of the M protein not only enhanced cell–cell fusion, but also increased the levels of both, viral messenger and genomic RNAs by a factor of 2 to 2.5. These findings support older findings that the M protein acts as a negative regulator of the viral polymerase [132], a mechanism that probably contributes to the efficient replication and spread of M-defective RNPs in SSPE brains. Recently, the efficacy of lentiviral vector-constructs, which integrate after transduction into the cellular genome and permanently express antiviral short hairpin RNAs (shRNA), was tested using persistently MV-infected NT2 cells (human teratocarcinoma cells that can be terminally differentiated into neuronal cells by retinoic acid treatment)[133]. ShRNA against N, P and L –mRNAs led to a reduction of viral proteins below detectable levels in a high percentage of transduced cells and complete virus elimination within 2 weeks [133]. This demonstrated in tissue culture that persistently MV-infected neural cells can be cured by transduction of lentiviral vectors mediating long lasting expression of virus-specific shRNA. However, before antiviral siRNA is applicable in vivo in the brain, several problems must be solved, such as the usage of an optimal vector system for neurons and glial cells, the lack of even distribution in the CNS, and the problem that RNA interference requires the knowledge of exact target sequences in spite of the high frequency of mutations in MV genomes of patients with SSPE.

During the last years, new potent small molecules have successfully been selected that inhibit either MV entry, or

the viral RNA-dependent RNA polymerase (RdRp). Virus entry can be inhibited with compounds interacting with the viral fusion protein [134, 135]. Five substituted anilides showed effective blockade of MV entry, one of which (AS-48) exhibited a 50% inhibitor concentration (IC₅₀) of 0.6–3.0 μM against a panel of wild-type MV strains [136]. However, with respect to a persistent infection, it remains to be investigated if such entry inhibitors can control viral cell-to-cell spread in the brain under conditions, when only small amounts of envelope proteins are expressed. In contrast, inhibitors of the viral polymerase, the activity of which is required for the replication of intracellular viral RNPs, may be more promising therapeutics. A high-throughput screening led to an active compound, which was further chemically improved to achieve the lead compound AS-136A that blocked viral RNA synthesis with IC₅₀ values of as low as 12 nM, and no detectable cytotoxicity at concentrations below 300 μM [137–139]. Adaptation of different MV strains to growth in the presence of this compound identified three candidate hot spots for interaction with AS-136A that are located in conserved domains of the viral L-protein [140]. Recombinant MVs harboring individual resistance mutations showed some delay in the onset of viral growth in vitro suggesting that mutations in these L-protein domains may reduce viral fitness [140]. However, these findings also demonstrated that resistance mutations that enable viral escape may well be present or emerge in vivo.

Taken together, intracellular virus replication by the viral polymerase appears to be the optimal target for specific inhibitors that should be able to eliminate the infectivity from the infected brain. In spite of obvious hurdles, such as the escape of mutant viruses or the bioavailability, treatments with siRNA and small compounds are the most promising approaches to a successful therapy.

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