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Review

Measles virus in the CNS: the role of viral and host factors for the establishment and maintenance of a persistent infection

Jürgen Schneider-Schaulies*[,1], Stefan Niewiesk[1], Sibylle Schneider-Schaulies[1] and Volker ter Meulen[1]

[1]*Institute for Virology and Immunobiology, University of Würzburg, Versbacher Strasse 7, D-97078 Würzburg, Germany*

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Introduction

Acute measles (for review see: Griffin and Bellini, 1996) can be accompanied by early or late central nervous system (CNS) complications. These include the acute postinfectious measles encephalitis (APME), which develops 2–4 weeks after infection, or as late complications, the measles inclusion body encephalitis (MIBE) in immunocompromised patients, and the subacute sclerosing panencephalitis (SSPE) months to years after the initial infection (Table 1). With an incidence of approximately 0.1%, APME is the most frequent, however also the least well understood disease measles associated neurological complication. Since myelin basic protein-specific T cells can be isolated from patients, APME is thought to have an autoimmune etiology (Johnson *et al*, 1984). The two late complications, MIBE and SSPE, are based on persistent measles virus (MV) infections in the brain. In this review we will give a brief overview on a number of virological and immunological findings obtained from MV infected patients, from animal models with MV-induced encephalitis (MVE), and from MV infected primary and permanent neural tissue cultures (for review see Schneider-Schaulies *et al*, 1997).

CNS complications associated with persistent measles virus infections

MIBE and SSPE are invariably fatal progressive inflammatory diseases of the brain. Since MIBE is a rare complication in immunocompromised patients, most data were obtained from SSPE patients. Due to underlying diseases in MIBE, it is evident that this disorder differs from SSPE in the extent of inflammatory reactions and of the humoral immune responses to MV. In contrast, the findings on viral gene expression in brain material of patients with SSPE and MIBE are similar. The route of MV CNS invasion has not been clearly defined as yet. The infection of cerebral endothelial cells may initially provide the opportunity for MV to cross the blood brain barrier (Cosby and Brankin, 1995; Kirk *et al*, 1991). The induction of adhesion molecules by cerebral endothelial cells and the synthesis of cytokines may regulate subsequent lymphocyte homing to the CNS (Brankin *et al*, 1995). A second pathway for the CNS-infection may be given by infiltrating macrophages carrying MV (Mesquita *et al*, 1998). In late stages of the diseases, massive amounts of MV-antigen can be detected in inclusion bodies in various neural cell types (Allen *et al*, 1996; Esiri *et al*, 1981; for review see Norrby and Kristensson, 1997). Apparently, replication-competent measles ribonucleocapsid protein (RNP) complex spreads from cell to cell in the absence of infectious viral particles. The mechanism of this unusual type of viral spread is not known.

A pathognomonic finding for SSPE are the very high levels of antibodies against MV in serum and cerebrospinal fluid (CSF). In the CSF oligoclonal immunoglobulin bands are detectable by isoelectrical focusing indicative for an intrathecal antibody synthesis (Dörries and ter Meulen, 1984; Metha *et al*, 1982; Vandvik and Norrby, 1973). However, these antibodies fail to control the infection. Examination of SSPE brain sections by immunohistological techniques demonstrated the presence of

*Correspondence: J Schneider-Schaulies
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Table 1 CNS complications following measles virus infections in humans

Complication	*Time after infection*	*Incidence*	*Pathogenesis*
Acute postinfectious measles encephalitis (APME)	2–4 weeks	approx. 0.1% after natural infection*	autoimmune (?) (none or very little MV in the brain)
Measles inclusion body encephalitis (MIBE)	months	exclusively in immunosuppressed patients	persistent infection, spread of defective nucleocapsids
Subacute sclerosing panencephalitis (SSPE)	2–10 years	approx. $1/10^5$ after natural infection*	persistent infection, spread of defective nucleocapsids

*The incidence of APME and SSPE is significantly reduced after measles vaccination (Duclos and Ward, 1998).

MV nucleocapsid (N) and phospho (P) proteins in lesions surrounded by infiltrations of activated B, T cells and macrophages. Yet, this cell mediated immune response cannot eliminate infected cells despite the fact that SSPE patients do not reveal any major immunological deficits (Metha *et al*, 1994). Obviously, other factors are involved in the pathogenesis of this progressive CNS disease. Apoptosis has been detected in infected and uninfected cells in SSPE brains in neurons, oligodendrocytes, microglia and infiltrated lymphocytes (McQaid *et al*, 1997b). The role of altered viral gene functions encountered in persistent MV infections of brain cells has been extensively studied in relation to cellular factors and the immune response. Factors intrinsic or induced in neural cells have been proposed to attenuate viral gene expression and to favour non-cytolytic long-lasting persistence of MV (for review see: Schneider-Schaulies *et al*, 1999). As animal models for the MV-induced brain disorders, predominantly rats have been investigated. Using the rodent-adapted MV-strain CAM, 2–14-day-old Lewis rats develop a lethal acute measles encephalitis, whereas older animals develop a subacute measles encephalitis. In contrast, the mortality after MV-infection in Brown Norway (BN) rats decreases faster with age and in adult animals a clinically silent encephalitis is induced (Liebert and ter Meulen, 1987).

Alterations of the MV-genome and defective expression of viral genes during persistence

Expression gradient of viral transcripts

Alterations of the viral gene expression in persistent infections as compared to acute infections have been characterized by using brain material obtained from patients, experimentally infected animals, and tissue cultures of neural cells. The expression of the viral envelope proteins, matrix (M), fusion (F) and hemagglutinin (H), has been found to be generally low or even absent in persistent brain infections, whereas the integrity of the replicative complex as indicated by the expression of N and P proteins is apparently maintained (Figure 1; Baczko *et al*, 1986; Cattaneo *et al*, 1987a,b; Liebert *et al*, 1986). The downregulated expression of the envelope proteins has been ascribed to a variety of independent mechanisms including a transcription gradient from the N to the L gene of MV, and mutations of the coding sequences that may lead to the truncation or complete abolishment of intact reading frames. The progressive decrease of transcriptional efficiency along the viral genome could be observed in brain tissue of experimentally infected rats as well as in tissue culture systems with primary and permanent neural cells (Schneider-Schaulies *et al*, 1989, 1990, 1993a). In analysing potential host factors it became obvious that the MV transcription in cells of neural origin is generally reduced compared to cell systems of non-neural origin. In addition, the differentiation state of the cells may interfere with the viral transcription as seen in brain

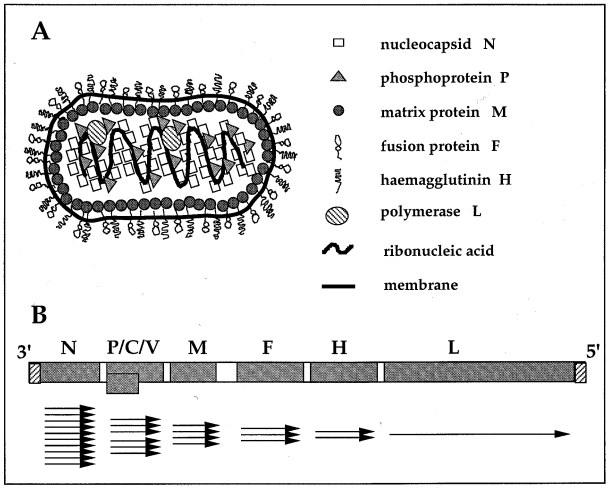

Figure 1 (**A**) Schematic representation of the measles virus (MV) particle with its structural proteins. The envelope proteins M, F, and H are not required for the intracelluar multiplication of ribonucleocpsid protein (RNP) complexes consisting of the viral RNA, and N, P, and L (polymerase) proteins. In SSPE brains, RNP complexes are found in various cell types, mainly in endothelial cells, neurons, and astrocytes (Esiri *et al*, 1981; Kirk *et al*, 1991). (**B**) The single stranded MV-RNA genome of negative polarity is transcribed with decreasing efficiency from its 3′ to the 5′ end with highest relative frequencies of the N-transcripts. The resulting steep expression gradient in neural cells leads to a restriction of the viral envelope mRNAs and corresponding proteins (Cattaneo *et al*, 1987b; Schneider-Schaulies *et al*, 1993a).

material of experimentally infected animals (Liebert *et al*, 1990) and in tissue culture upon *in vitro* differentiation of neuronal cells (Yoshikawa and Yamanouchi, 1984).

Functional alterations of MV-specific transcripts
Based on the comparison with MV vaccine strains, initially very high frequencies of mutations were defined for viral sequences isolated from SSPE brains suggesting that such sequences may characterize neurotropic variants of MV. However, after sequencing of many wild-type isolates during the last years it became clear that SSPE sequences are closly related to 'normal' wild-type strains of MV and that 'SSPE-viruses' do not exist (Rima *et al*, 1995, 1997; Rota *et al*, 1998; Tamin *et al*, 1994). In a lytic infection, natural selection eliminates virus variants loaded with mutations which lead to functional impairments. However, during longlasting persistent infections, mutations may accumulate without these constraints (Baczko *et al*, 1993).

Point mutations are introduced in the viral mRNAs and genomes by the viral RNA-dependent RNA polymerase. In contrast, the hypermutation of the M gene, in which up to 50% of the uridine (U) residues can be replaced by cytidine (C), was not attributed to the action of the viral polymerase, but rather to a cellular enzyme referred to as duplex RNA-dependent adenosine deaminase (DRADA) (Cattaneo *et al*, 1988, 1989; Bass *et al*, 1989). *In vitro*, nuclear extracts of human neuroblastoma cells are highly active in modifying a synthetic MV M-specific dsRNA (Rataul *et al*, 1992). The presence of the hypermutating activity could be demonstrated in cytoplasmic extracts of several neural cell lines upon *in vitro* differentiation (Ecker *et al*, 1995). Due to its specificity for dsRNA templates and its obvious independence of particular sequence requirements, the activity may contribute substantially to the intracellular antiviral response. In support of this hypothesis, several different hypermutated M gene sequences have been encountered in a single SSPE brain (Baczko *et al*, 1993), and F genes truncated in their cytoplasmic domains were found in several SSPE brains (Schmid *et al*, 1992).

Besides changing the frequency of mRNAs, an important site of controlling viral gene expression is undoubtedly translation. Translation may depend on elements intrinsic to the RNA, as 5′ and 3′ noncoding sequences, and/or mutations leading to premature termination of the corresponding protein. For the M mRNA transcript isolated from the brain of experimentally infected Lewis rats with subacute measles encephalitis, translation was restricted *in vivo* and *in vitro*, independent of sequence alterations (Schneider-Schaulies *et al*, 1989). In contrast, a temperature shift of persistently infected rat glioma cells leads to a selective and reversible translation inhibition of MV M and F-specific mRNAs, arguing strongly for the involvement of cellular determinants in controlling viral translation (Ogura *et al*, 1987, 1988). Similar observations of a translational inhibition affecting MV protein synthesis either partially or completely have been described as a consequence of *in vitro* differentiation of tissue culture cells of neural origin (Miller and Carrigan, 1982; Yoshikawa and Yamanouchi, 1984; Schneider-Schaulies *et al*, 1993a). The obviously specific inhibition of viral rather than cellular gene expression is reminiscent to that described for the antiviral activity of certain IFN-induced proteins.

Immune responses to MV-infections of the CNS

Interferon-dependent antiviral mechanisms
Type I interferon (IFN) is amongst the most important line of host defence against viral infections. In the CSF of SSPE patients, elevated levels of type I IFN has been detected (Joncas *et al*, 1976), and was suggested to play a role in the establishment of persistent viral infections of neural cells. The type I IFN inducible Mx proteins have been directly linked to an antiviral action against a variety of RNA viruses interfering with transcription and/or translation of viral genes (Horisberger, 1992; Pavlovic *et al*, 1990; Pitossi *et al*, 1993; Staeheli, 1990; Staeheli and Pavlovic, 1992). MV-infection of human and rat glial cell cultures is accompanied by a rapid induction of the Mx protein expression (Kraus *et al*, 1992; Schneider-Schaulies *et al*, 1994). Stably MxA-transfected human glioblastoma cells (MxA is one of the human Mx proteins) released 50–100-fold less infectious MV and reduced the overall viral transcription by up to 90% (Schneider-Schaulies *et al*, 1994). The marked downregulation of MV-specific mRNA synthesis in brain cell cultures constitutively expressing human MxA suggests indeed an important role of that particular anti-viral protein in contributing to the establishment of a persistent infection. Recently, the MxA expression was investigated histologically in SSPE brains (Ogata *et al*, 1999). In these brains, MxA was found mainly in astrocytes in and around MV-antigen positive lesions, where it surrounds infected cells. The mode of antiviral action of Mx proteins depends on the host cell and the virus. Interestingly, against MV the action of MxA is cell type specific: it affects the viral transcription in brain cells, and the translation of the viral envelope glycoproteins in mononuclear cells (Schnorr *et al*, 1993).

Induction of cytokines in brain cells
For the signalling to brain cells as well as for the chemotaxis and activation of effector cells of the immune system, cytokines play an essential role. Analysis of cytokines in SSPE brains revealed the presence of TNF-α, IFN-γ, interleukin (IL)-1β and

IL-2 positive cells. The TNF-α positive cells had the morphological appearance of astrocytes, while the IFN-γ positive cells appeared to be macrophages/microglial cells (Hofman *et al*, 1991). Induction of IFN-γ has been found outside of the focus of viral replication in the brain, also in the spleen of infected rats (Gogate *et al*, 1991). As further cytokines IL-6, lymphotoxin, and leukemia inhibing factor (LIF) were found in lesions of MV-infected brains (McQuaid *et al*, 1997a; Nagano *et al*, 1994). These data indicate that microglial cells and astrocytes appear to be activated by infiltrating T lymphocytes in SSPE brains and are induced to express MHC class II molecules and certain cytokines. To investigate the actual set of cytokines induced by MV brain-infection, *in vitro* studies with different neural cell types were performed. Infection of human astrocytoma cells with MV resulted in a transient expression of a characteristic set of cytokines, namely IL-1, IFN-β, IL-6 and TNF-α, at the level of mRNA and protein in cell supernatants (Schneider-Schaulies *et al*, 1993b).

Recently, the necessity of viral replication for the induction of cytokines was investigated in astrocytoma cells (Ghali and Schneider-Schaulies, 1998). With the help of a recombinant MV expressing the VSV-G surface protein as envelope protein it was found that the interaction of MV with its receptor already induces low amounts of IL-6, whereas for full induction of the IL-6 synthesis functional transcription of the virus is required. In contrast to newly infected cells, MV persistently infected human astrocytoma cells continually produced IL-6 and IFN-β, whereas TNF-α and IL-1β in most clones were hardly detectable (Schneider-Schaulies *et al*, 1993b). A similar phenomenon was observed in MV infected human monocytes (Leopardi *et al*, 1992). However, the pathways for the induction of TNF-α and IL-1β in astrocytoma cells were not suppressed by the persistent MV infection, since TNF-α and IL-1β could still be induced by external stimuli like diacylglycerole analogue plus calcium ionophore. After additional external stimuli, persistently infected astrocytoma cells synthesized considerably higher levels of TNF-α and IL-1β than uninfected cells (Schneider-Schaulies *et al*, 1993b). These results suggested that in MV infections of the CNS a percentage of persistently infected astrocytes may continually synthesize IL-6 and IFN-β, and in the presence of additional stimuli, as possibly provided by activated lymphocytes, overexpress the inflammatory cytokines TNF-α and IL-1β.

In contrast to astrocytoma cells, MV-infection of the neuroblastoma cells IMR32 fails to activate NF-κB, IFN-β, and MHC class I (Dhib-Jalbut *et al*, 1999). This failure may provide a potential mechanism for the ability of MV to persist in neurons and to escape immune surveillance.

Expression of MHC and costimulatory molecules in MV infected brains

In contrast to uninfected brains, numerous major histocompatibility complex (MHC) class I and II positive cells can be detected imunohistochemically particularly around blood vessels in SSPE brains. Antigen presenting HLA-DR positive cells have been identified by morphological criteria to be mainly macrophages/microglial cells and reactive astrocytes (Hofman *et al*, 1991). In primary cultures of astrocytes from newborn Lewis rats, MV-infection leads to the induction of MHC class II and increase of MHC class I expression (Massa *et al*, 1987). The increase in expression of MHC class I and the costimulatory intercellular adhesion molecule (ICAM-1) on primary rat astrocytes was found to be mediated by type I interferons and is enhanced by TNF-α (Dhib-Jalbut and Cowan, 1993; Kraus *et al*, 1992).

MHC class I molecules, which are essential for the elimination of infected cells by cytotoxic T cells (CTL), are normally absent on uninfected neurons, and the lack of MHC expression has been discussed as a possible factor supporting the viral persistence in neurons. However, MHC class I expression was found to be inducible on neurons by cytokines or infectious agents (Gogate *et al*, 1991; Wong *et al*, 1985). Also on neurons of SSPE patients MHC class I molecules have been detected (Gogate *et al*, 1996). The importance of the antigen presentation by MHC class I molecules for the immune defence became evident in TAP-transporter deficient mice, which cannot present antigen on MHC class I molecules (Urbanska *et al*, 1997). In this study, MV was found to spread impressively more transneuronally to the next order of neurons. This indicates that infected neurons are indeed target cells of CTL, and that brain infections to some extent can be inhibited by CTL activity. However, in spite of the presence of MHC class I on neurons in SSPE brains, the immune system in these patients fails to control the infection. The reason for this is unknown. It is conceivable that the MHC class I expression and viral clearance was induced too late, when viral RNP's had spread already to multiple areas in the brain. Experiments with the neurotropic coronavirus mouse hepatitis virus (MHV-JHM) in Lewis and BN rats support the view that the kinetics of the induction of the immune response is decisive for the outcome of the CNS infection (Dörries *et al*, 1991; Imrich *et al*, 1994). On the other hand, the occurrence of genomic mutations of MV during SSPE could lead to the disappearance of dominant viral CTL epitopes and the failure to clear MV from the brain.

Role of the humoral immune response

Antibodies are certainly important in combatting viral invasion to, or spread of virus in the CNS. Newborn mice can be protected against infection with the MV-strain CAM by the injection of monoclonal antibodies against the viral hemagglu-

tinin (H) and the fusion (F) proteins. These findings are consistent with the resistance to encephalitis observed in BN rats that mount early a high level of MV-specific antibodies (Liebert and ter Meulen, 1987). However, in weanling Lewis rats which are susceptible to the infection with MV-strain CAM, such monoclonal antibodies do not fully protect against encephalitis, but convert an acute into a subacute persistent infection, whereas the untreated control group succumbs invariably to a fatal encephalopathy within few days (Liebert *et al*, 1990).

In tissue culture experiments it has been observed that virus neutralizing antibodies are capable to interfere 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 (Joseph and Oldstone, 1975; Fujinami and Oldstone, 1980). 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 (Barrett *et al*, 1985; Schneider-Schaulies *et al*, 1992). This phenomenon has been referred to as antibody induced antigenic modulation (AIAM) and has been linked to a so far unidentified transmembrane signal which leads to the downregulation of the intracellular viral gene expression.

Molecular biological studies of AIAM of MV infected Lewis rats treated with monoclonal antibodies revealed that the expression of the MV envelope proteins in brain tissue was shown to be reduced as a consequence of a significantly restricted expression of viral transcripts. Data obtained by *in situ* hybridization indicated that the reduced efficiency of viral transcription was due to a restriction at the single cell level rather than reflecting an inhibition of virus spread in the brain. Similar findings were obtained in the presence of high titers of virus-neutralizing antibodies naturally produced in response to the experimental infection in weanling BN rats (Liebert *et al*, 1990; Dörries *et al*, 1988). MV escape variants to these neutralizing antibodies were isolated *in vitro* which had differential neurovirulent properties in rats and could not be neutralized by the corresponding mAbs administered i.p. (Liebert *et al*, 1994). Thus, the neurovirulence of MV is at least partially governed by B cell epitopes of the MV-H protein. From these data it has to be concluded that only rapid and effective elimination of virus-infected CNS cells will prevent long-lasting antibody controlled persistence of the virus. Since the early stage of MV infection in SSPE cannot be studied, it is unknown which role the antiviral hyperimmune response plays in this disease and why it does not prevent the infection to spread to the CNS.

Role of the cell-mediated immune response

Attempts to characterize the cell mediated immune response in SSPE patients have not revealed a specific defect which could be linked to the pathogenesis of this disease or to the establishment of viral persistence. Infiltrates of inflammatory cells consist of CD4+ and CD8+ T cells, as well as monocytes and B cells (Hofman *et al*, 1991; Nagano *et al*, 1991). As found in many inflammatory CNS disorders, levels of beta-2-microglobulin, soluble IL-2 receptor and soluble CD8 are increased in the cerebrospinal fluid (Metha *et al*, 1994).

In mice (Niewiesk *et al*, 1993) and rats (Liebert and ter Meulen, 1987), resistance and susceptibility to MV-induced encephalitis correlates with the MHC haplotype of the respective inbred strain. In resistant mouse (Finke and Liebert, 1994) and rat (Bankamp *et al*, 1991) strains depletion of the CD4+ T cell subset by mAb leads to breakdown of resistance whereas depletion of CD8+ T cells is of no effect in mice (and technically not feasible in rats). In susceptible rats CD4+ T cells evidently cannot protect against MVE. However, transfer of secondary CD4+ T cells confers protection against encephalitis (Bankamp *et al*, 1991; Reich *et al*, 1992). These data have been interpreted in that only CD4+ T cells are important for viral clearance of the CNS. However, recent data suggest that CD8+ T cells require CD4+ T cell help to protect against CNS infection (Zimmermann *et al*, 1997; Stohlman *et al*, 1998). It is interesting to note that the MHC class I molecule K^k binds MV derived peptides with low affinity and in consequence susceptible C3H mice generate a weak CTL reponse whereas the L^d molecule binds epitope peptides efficiently and produces highly lytic CTL (Niewiesk *et al*, 1993; Neumeister *et al*, 1998). Undoubtedly, CD4+ T cells are the main effectors in overcoming MV-induced encephalitis. The mechanism of the antiviral activity of CD4+ T cells in vivo is not at all resolved. Neutralization of IFN-γ leads to the generation of a TH2 response in resistant mice and a breakdown of resistance (Finke *et al*, 1995). As also susceptible C3H mice produce a TH2 response it has been suggested that this shift in the TH response is responsible for susceptibility. However, IFN-γ has been shown to have pleiotropic effects (amongst others antiviral activity, migration, induction of adhesion molecules, antigen processing) which might also contribute to resistance against MV-induced encephalitis.

Neurotropism and neurovirulence of MV-strains

The role of virus receptors

CD46 (membrane cofactor protein, MCP) was identified as a receptor for MV-vaccine strains (Naniche *et al*, 1993; Dörig *et al*, 1993). CD46 is a

member of the 'regulators of complement activation' (RCA) protein family, that serves critical functions in protecting cells from unspecific complement mediated lysis by inactivating complement factors. CD46 is expressed by most human cells, except erythrocytes (Liszweski *et al*, 1991). A receptor modulation following the MV infection renders cells susceptible to lysis by human complement (Schneider-Schaulies *et al*, 1996; Schnorr *et al*, 1995). However, in contrast to vaccine-like strains, a number of wild-type MV-strains do not use CD46 as cellular receptor (Bartz *et al*, 1998; Hsu *et al*, 1998; Tanaka *et al*, 1998). The nature of this MV wild-type receptor is not known.

CD46 is expressed at relatively low levels by neurons and astrocytes in normal brains. Within heavily infected MV-positive brain lesions of SSPE patients, CD46 was not detectable, irrespective of whether MV antigens were present in these individual cells or not. In contrast, normal levels of CD46 were found in SSPE brain tissue distant from the lesion (Ogata *et al*, 1997). These observations suggest that the CD46 expression was reduced by the MV infection.

However, since only a little CD46 is expressed by a proportion of neural cells, it is questionable whether MV in SSPE uses this receptor for its spread in the human brain. Two further facts mentioned above argue against a role of CD46 as MV-receptor in the human brain: (1) Measles sequences of SSPE patients are related to wild-type strains which may not interact with CD46, and (2) the viral RNP complex is spreading in the brain in the virtual absence of the viral envelope proteins. Alternative mechanisms of cell to cell spread in neural tissue of MV have been demonstrated (Allen *et al*, 1996; Meissner and Korschel, 1995; Urbanska *et al*, 1997). This is supported by the finding that MV spreads in differentiated human neuronal cells lacking CD46 from cell to cell by an intracellular route most likely involving localized fusion events at cell contact points (McQuaid *et al*, 1998).

In transgenic mice, the expression of CD46 has been used to define the role of CD46 in relation to neurovirulence and pathogenicity. In these animals, the apathogenic Edmonston strain is able to cause widespread neuronal infection and death in neonates, and also infects scattered neurons in adult mice as shown by histological examination (Rall *et al*., 1997). These findings support the view that expression of a suitable receptor in neurons can enhance the neurovirulence of a corresponding virus. The effect, however, was predominantly observed in neonatal animals, the CNS of which is still developing, and to a lower extent in adult animals. In the periphery of adult CD46-transgenic mice or rats, the receptor expression did not lead to a significant increase of susceptibility for MV (Blixenkrone-Møller *et al*, 1998; Horvat *et al*, 1996; Niewiesk *et al*, 1997), whereas in IFN-α/β-receptor-deficient knockout mice additionally expressing CD46, intracerebral inoculation of adult animals with low doses of MV-Edm caused encephalitis with mostly lethal outcome (Mrkic *et al*, 1998). These results support to the undoubted importance of the IFN-system in viral brain infections.

Recombinant measles viruses in brain research
A few years ago, the group of Martin Billeter in Zürich succeeded in generating recombinant MV (Radecke *et al*., 1995). This technology now opened the way for new approaches to investigate the brain pathogenesis and virulence of viruses carrying mutations introduced experimentally into the viral genomes. Using this technology, the role of the matrix protein and the cytoplasmic domain of the fusion protein, the expression of both of which is disturbed by mutations in SSPE brains (Baczko *et al*, 1993; Schmid *et al*, 1992), was now investigated using mutated viruses in mouse brains. An infectious matrix protein (M)-less MV exhibited a higher fusogenic capacity than standard virus and penetrated more deeply into the brain parenchyma (Cathomen *et al*, 1998a). Similar results concerning the spread of virus were found with recombinant viruses lacking the cytoplasmic tail of the fusion (F) or hemagglutinin (H) protein suggesting the interaction of the M protein with the cytoplasmic parts of these proteins is involved in the regulation of virus-induced cell fusion (Cathomen *et al*, 1998b).

The influence of the viral attachment protein H on neurovirulence was investigated using a recombinant MV in which the H of the Edmonston strain had been replaced by the H of the neurovirulent CAM strain (Duprex *et al*, 1999). After intracerebral injection into suckling C57/BL/6 mice this recombinant virus (EdtagCAMH) induced neurological disease, and MV antigen was found in neurons and neuronal processes of the hippocampus, frontal and olfactory cortices and neostriatum. However, the neurovirulence of EdtagCAMH was reduced compared to the neurovirulent wild type strain CAM indicating that other viral genes contribute also to the CAM-induced CNS disease.

Conclusions

The molecular biological studies of MV interaction with brain cells have contributed greatly to elucidate virological aspects of the persistent MV infection in SSPE and MIBE (Figure 2). It is now possible to understand why the persistent infection in brain cells is not productive, why hypermutations of MV RNA occur, and why so little viral envelope proteins appear on the surface of infected brain cells. However, major questions concerning epidemiology and pathogenetic mechanisms are

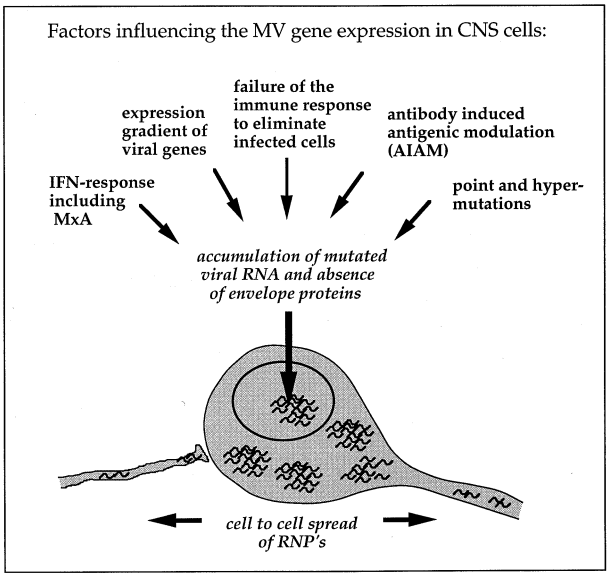

Figure 2 Several factors influence the establishment of a persistent MV-infection in the brain: the IFN response, the neural cell type specific steep expression gradient, antibody induced antigenic modulation, and hypermutations lead to the restriction of the MV replication. The virus spreads from cell to cell as RNP, while the cell mediated immune response cannot eliminate the intracellular pathogen from the CNS.

still unanswered. There is no explanation why CNS diseases are so rare in contrast to acute measles, why more boys than girls develop SSPE and why SSPE is more prevalent in rural areas than in large cities. Moreover, the factors determining the long incubation periods of months to years after onset of acute measles and the factors which trigger the disease process are unknown. It would be important to determine how and when measles virus enters the CNS in the course of acute measles, and why the immune response fails to control the infection or destroy infected brain cells. Does measles virus reach the CNS during viremia or by infected lymphocytes or monocytes as observed in canine distemper virus infection in dogs (ter Meulen and Carter, 1982)? Therefore, the characterization of MV infection in lymphocytes and monocytes will be important not only in view of MV induced immune regulatory changes and life-long immunity, but also to find out whether latently infected lymphocytes exist *in vivo* which could, after antigenic stimulation, reach the CNS and carry the virus to brain tissue.

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