Journal of NeuroVirology, 9: 247–252, 2003
 ISSN 1355–0284/03 $12.00+.00
DOI: 10.1080/13550280390193993

Taylor & Francis
Taylor & Francis Group

Measles infection of the central nervous system

Jürgen Schneider-Schaulies, Volker ter Meulen, and Sibylle Schneider-Schaulies

Institute for Virology and Immunobiology, University of Würzburg, Würzburg, Germany

Central nervous system (CNS) complications occuring early and late after acute measles are serious and often fatal. In spite of functional cell-mediated immunity and high antiviral antibody titers, an immunological control of the CNS infection is not achieved in patients suffering from subacute sclerosing panencephalitis (SSPE). The known cellular receptors for measle virus (MV) in humans, CD46 and CD150 (signaling lymphocyte activation molecule, SLAM), are important components of the viral tropism by mediating binding and entry to peripheral cells. Because neural cells do not express SLAM and only sporadically CD46, virus entry to neural cells, and spread within the CNS, remain mechanistically unclear. Mice, hamsters, and rats have been used as model systems to study MV-induced CNS infections, and revealed interesting aspects of virulence, persistence, the immune response, and prerequisites of protection. With the help of recombinant MV and mice expressing transgenic receptors, questions such as receptor-dependent viral spread, or viral determinants of virulence, have been investigated. However, many questions concerning the human MV-induced CNS diseases are still open. *Journal of NeuroVirology* (2003) **9,** 247–252.

Keywords: CD46; cell-to-cell spread of virus; measles encephalitis; measles virus; SLAM

Acute measles, early and late central nervous system complications

After entering the upper respiratory tract, measles virus (MV) exhibits a pronounced tropism for mono- and lymphocytic cells, and soon viral replication is detected in draining lymph nodes. In the course of its spread, MV remains highly cell associated and can be isolated from blood leukocytes early during infection. Following replication in lymphoid tissues, virus spreads to various organs, and replication continues in the epithelia of the lung and buccal cavity. Viral antigens can be detected in the skin, where they are concentrated near blood vessels and in endothelial cells of dermal capillaries. In immunocompetent patients, MV is usually cleared by the virus-specific immune response, whereas the general immune response to other antigens is suppressed for several weeks after the rash (for review, see Griffin and Bellini, 1996; Katz, 1995).

Address correspondence to Jürgen Schneider-Schaulies, Institute for Virology and Immunobiology, University of Würzburg, Versbacher Str. 7, D-97078 Würzburg, Germany. E-mail: jss@vim.uni-wuerzburg.de

Received 24 September 2002; revised 22 October 2002; accepted 13 November 2002.

As most common central nervous system (CNS) complications, the acute postinfectious measles encephalitis (APME) occurs in approximately 0.1% of cases, with a lethality of approximately 20%. 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. Because MV-specific nucleic acids have been detected only with highly sensitive methods within the CNS of patients suffering from APME (Nakayama *et al*, 1995), the observed clinical signs are considered to result from a virally induced pathogenic immune response with autoimune components (Liebert, 1997).

In contrast to APME, MV is abundantly present in brain cells of patients with subacute sclerosing panencephalitis (SSPE) and measle inclusion body encephalitis (MIBE), both of which develop after clinically silent periods of months to years after acute measles and are inevitably fatal (ter Meulen *et al*, 1983). Whereas SSPE develops in fully immunocompetent individuals, MIBE is confined to immunosuppressed or -deficient patients, and may thus be considered as opportunistic infection of the CNS due to inappropriate immunological control. Virus spread in the brain during SSPE occurs in the presence of

high titers of antimeasle antibodies in serum and CSF. It is not clear which role elevated levels of antibodies with other specificities, e.g., anti-CD9 (Shimizu *et al*, 2002), may have. An effective treatment of SSPE is still not available and conflicting results have been reported about the use of amantadine, inosiplex (isoprinosine), and intraventricular interferon-α (IFN-α).

As revealed by molecular epidemiological studies, SSPE patients had been infected at very young age, when the immune system of the host is still immature and residual maternal antibodies may be absent or not sufficient for complete virus neutralization. MV gene sequences obtained from SSPE autopsy material are, except from mutations accumulated in certain regions of the genome, homologous to the corresponding gene sequences of genotypes circulating at the time of primary exposure of the patients to MV (Jin *et al*, 2002; Rima *et al*, 1997). In few cases, viruses could be isolated from SSPE brains, and have conserved their highly neurovirulent properties after propagation *in vitro* (Ito *et al*, 2002). However, *in vivo*, natural selection eliminates virus variants loaded with mutations that lead to functional impairments. Supporting this view, a recombinant MV containing the matrix gene from an SSPE isolate grows considerably less efficient in tissue culture and transgenic mice (Patterson *et al*, 2001). This strongly supports the notion that there are no circulating MV genotypes that are particularly neurovirulent and that persistent brain infections are established initially by 'normal' wild-type MV strains. After vaccination, SSPE is not observed (Duclos and Ward, 1998).

Mechanisms contributing to the measles virus persistence and pathogenesis

In SSPE brains, neurons, oligodendrocytes, astrocytes, and microvascular endothelial cells have been found to be infected (Allen *et al*, 1996). Numerous major histocompatibility complex (MHC) classes I and II–positive cells can be detected imunohistochemically in SSPE brains, particularly around blood vessels. 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). MHC class I molecules have also been detected on neurons of SSPE patients (Gogate *et al*, 1996). No specific defect in the immune system of SSPE patients could be detected.

SSPE has been observed in a patient in whom natural measle infection was anteceded by immunization with anti-MV immune serum (Rammohan *et al*, 1982). Confirming this finding, it has been demonstrated experimentally that after intracranial (IC) infection of newborn hamsters and mice with rodent-adapted MV, the presence of maternal or aquired anti-MV immunoglobulins supports the development of a persistent CNS infection (Rammohan *et al*, 1981, 1983). Thus, an unbalanced immune response in the immature host may play a decesive role for the early establishment of a persistent MV infection. 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 (Urbanska *et al*, 1997). Under these conditions, MV was found to spread impressively more transneuronally to the next order of neurons. This indicates that infected neurons are indeed target cells of cytotoxic T lymphocytes (CTLs), and that brain infections to some extent can be inhibited by CTL activity. However, in spite of the presence of MHC class I molecules and CTLs, the immune system in SSPE patients fails to control the infection.

In the CSF of SSPE patients, 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 interfering with transcription and/or translation of various viruses exerts a direct antiviral action against MV (for review, see Schneider-Schaulies *et al*, 1999). In tissue culture, MV infection of neuroblastoma cells (in contrast to astrocytoma cells) failed to activate nuclear factor kappa B (NF-κB), IFN-α/β, and MHC class I (Dhib-Jalbut *et al*, 1999; Fang *et al*, 2001). This failure may provide a potential mechanism allowing MV to persist especially 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 (Naniche *et al*, 2000).

A different specific antiviral mechanism appears to be exerted by type II interferon (IFN-γ) in SSPE patients, where an inverse correlation between IFN-γ production by peripheral blood mononuclear cells and disease progression was found (Hara *et al*, 2000). The important role of IFN-γ was confirmed in animal models (see below; Finke *et al*, 1995; Patterson *et al*, 2002).

As documented by immunohistochemistry and later by sequence analyses with autopsies, the expression of MV envelope proteins is strongly reduced in brains of SSPE and MIBE patients. Transcriptional restrictions of the corresponding genes and mutations within the coding sequences interfering with the synthesis of functional gene products were found (Cattaneo *et al*, 1988). As a consequence, expression of the viral envelope proteins is generally low or even absent in persistent brain infections, whereas the integrity of the replicative complex as indicated by the presence of ribonucleoprotein particles (RNPs) is apparently maintained. Sequence analyses revealed that a single initially infecting virus is replicated, accumulating numerous mutations during the time of spread (clonal expansion) (Baczko *et al*, 1993). Interestingly, MV lacking the complete matrix protein is viable and spreads even more efficiently in the brain of CD46-transgenic, IFN-α/β–receptor-deficient mice (Cathomen *et al*, 1998). When a matrix gene of an

SSPE isolate was introduced in a recombinant MV, this virus replicated at a reduced level and led to a protracted CNS infection in CD46-transgenic mice (Patterson *et al*, 2001).

Cell-to-cell spread of virus appears to be an important mechanism supporting persistence in the human and animal models of measles encephalitis (Allen *et al*, 1996; Lawrence *et al*, 2000; Meissner and Koschel, 1995; Urbanska *et al*, 1997). MV spreads in differentiated human neuronal cells lacking 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 (Duprex *et al*, 1999b). Taken together, the IFN response and its possible lack in neurons, a steep viral expression gradient, the accumulation of point and hypermutations within envelope genes, the antibody-induced antigenic modulation, and the observed cell-to-cell spread of nucleocapsids support the persistent brain infection, with failure of the immune response to eliminate the virus (for review, see Schneider-Schaulies *et al*, 1995). Given these constraints, it is not surprising that giant cell formation is not seen in SSPE and MIBE *in situ*, and that reisolation of infectious virus from SSPE autopsy material is only rarely successful and requires localization of active lesions in diseased brains (Ogura *et al*, 1997).

MV tropism and receptor usage

The cellular receptor for MV vaccine strains has been found to be CD46 (Dörig *et al*, 1993; Naniche *et al*, 1993). Recently, CD150 (signaling lymphocyte activation molecule, SLAM) was identified as a cellular receptor for both vaccine and wild-type MV strains (Erlenhoefer *et al*, 2001; Hsu *et al*, 2001; Tatsuo *et al*, 2000). The costimulatory molecule SLAM is expressed on activated T and B lymphocytes, memory cells, and activated dendritic and monocytic cells (Cocks *et al*, 1995; Minagawa *et al*, 2001; Ohgimoto *et al*, 2001; Polacino *et al*, 1996; Punnonen *et al*, 1997). As found for CD46, SLAM is efficiently downregulated from the cell surface after infection or contact with MV, which might contribute to the immunosuppressive capacity of the virus (Erlenhoefer *et al*, 2001).

It is not clear yet whether MV wild-types do interact with CD46 at all, or may use it as a low-affinity receptor on the surface of certain cells (Manchester *et al*, 2000; Ono *et al*, 2001). CD46 has been found to be expressed also, albeit at relatively low levels, by a fraction of neurons, oligodendrocytes, and astrocytes in normal brains (McQuaid and Cosby, 2002; Ogata *et al*, 1997). Within heavily infected MV-positive brain lesions of SSPE patients, 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 (McQuaid and Cosby, 2002; Ogata *et al*, 1997). SLAM is expressed on subsets of lymphoid cells, but has not been found on epithelial, endothelial, and various brain cell types (McQuaid and Cosby, 2002). Therefore, wild-type MV might use additional molecule(s) as receptors on these cells, or spread in a receptor-independent mechanism from cell to cell.

Neurovirulence and immune control in animal models

In newborn rodents, the rat brain–adapted MV strain CAM/RB spreads efficiently, causing a lethal acute encephalitis. Newborn mice can be protected against the infection by injection of monoclonal antibodies against the viral hemagglutinin (H) or fusion (F) proteins (Fournier *et al*, 1997; Partidos *et al*, 1997). These findings are consistent with the resistance to encephalitis observed in BN rats, which rapidly mount a high level of MV-specific antibodies. However, in newborn rodents, anti-MV antibodies can also support the establishment of a persistent infection (Rammohan *et al*, 1981). In weanling Lewis rats, which are susceptible to the infection with CAM/RB, 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 Liebert, 1997).

In rodents, resistance and susceptibility to MV-induced encephalitis correlates with the MHC haplotype of the respective inbred strain (Neumeister and Niewiesk, 1998; Niewiesk *et al*, 1993). In resistent mouse strains, depletion of the CD4+ T-cell subset by monoclonal antibody (mAb) led to breakdown of resistance, whereas depletion of CD8+ T cells had no effect (Finke and Liebert, 1994). A breakdown of resistance is also observed after neutralization of IFN-γ leading to the generation of a TH2 response (Finke *et al*, 1995). Further investigation of this measles encephalitis model revealed that CD4+ T cells are able to protect either alone (resistant mice), through cooperation with CD8+ T cells (intermediate susceptible), or after immunization as secondary T cells (susceptible mice), and CD8+ T cells are able to protect alone after immunization if they are cytolytic (Weidinger *et al*, 2000). As found earlier in nontransgenic mice, IFN-γ has also a critical role for the protection of CD46-transgenic mice against MV encephalitis (Patterson *et al*, 2002). Interestingly, this protection functions in a noncytolytic manner without neuronal loss.

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 (Andersson *et al*, 1991). The importance of the viral H protein for neurovirulence was investigated 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 was found in neurons and neuronal processes of the hippocampus, frontal and olfactory cortices, and neostriatum (Duprex *et al*, 1999a). To investigate the molecular basis of the CAM-H protein–mediated neurovirulence, a panel of recombinant MVs expressing mutant H proteins was generated. Replacement of only two amino acids in the H protein at positions 195 G → R and 200 S → N, caused the complete loss of neurovirulence (Moeller *et al*, 2001). However, because neither mouse nor rat CD46 and SLAM homologues function as MV receptors, it remains undefined which receptor(s) or mechanisms determine virulence in this animal model.

Neuron-specific expression of CD46 in transgenic mice has been used to define the role of a cellular receptor for 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). Infiltrating leukocytes, up-regulation of MHC classes I and II, and increased levels of RANTES (regulated on activation normal T cell expressed and secreted), IP-10 (IFN-gamma-inducible protein-10), interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β have been observed in brains of these mice (Manchester *et al*, 1999). A similar susceptibility of newborn mice for infection with MV strain Edmonston was found in transgenic mice expressing CD46 ubiquitously (Evlashev *et al*, 2000; Oldstone *et al*, 1999). These findings indicate that expression of a suitable receptor in neurons can mediate neurovirulence. Neurovirulence was predominantly observed in neonatal animals, where the CNS is not fully developed, and is reduced with increasing age of the animal. In the periphery of adult CD46-transgenic mice or rats, the receptor expression did not lead to a significant increase of susceptibility for MV (Horvat *et al*, 1996; Niewiesk *et al*, 1997), whereas in IFN-α/β receptor–deficient mice expressing CD46, intracerebral inoculation of adult animals with low doses of MV Edmonston caused encephalitis with mostly lethal outcome (Mrkic *et al*, 1998). Thus, besides the adaptive immune system, the innate immune system and unknown intracellular factors play an important role for the MV-induced neuropathogenesis.

Conclusions

Although many details about MV infection of the CNS in human and experimental animals are available, there are still some unanswered questions: (1) In which cells can MV persist for years? (2) How and when is MV getting into the CNS in cases of SSPE, i.e., during acute measles or at a later time? (3) Which factors determine the long incubation period between acute measles and onset of SSPE? (4) Which host factors control MV persistance before the onset of SSPE and prevent the development of an acute encephalitis after infectious MV has entered the brain, like observed in animals? (5) Which factors trigger the activation of MV replication in SSPE? (6) How can the infectious process during SSPE be stopped to successfully treat the patient? Certainly more research is needed based on a collaboration between different research fields and the application of new methods such as the microarray technology, which hopefully will lead to a better understanding of this fatal disease.

References

Allen IV, McQuaid S, McMahon J, Kirk J, McConnell, R (1996). The significance of measles virus antigen and genome distribution in the CNS in SSPE for mechanisms of viral spread and demyelination. *J Neuropathol Exp Neurol* **55:** 471–480.

Andersson T, Schultzberg M, Schwarz R, Löve A, Wickman C, Kristensson K (1991). NMDA-receptor antagonist prevents measles virus-induced neurodegeneration. *Eur J Neurosci* **3:** 66–71.

Baczko K, Lampe J, Liebert UG, Brinckmann U, ter Meulen V, Pardowitz I, Budka H, Cosby SL, Isserte S, Rima BK (1993). Clonal expansion of hypermutated measles virus in a SSPE brain. *Virology* **197:** 188–195.

Cathomen T, Mrkic B, Spehner D, Drillien R, Naef R, Pavlovic J, Aguzzi A, Billeter MA, Cattaneo R (1998). A matrix-less measles virus is infectious and elicits extensive cell fusion: consequences for propagation in the brain. *EMBO J* **17:** 3899–3908.

Cattaneo R, Schmid A, Eschle D, Baczko K, ter Meulen V, Billeter MA (1988). Biased hypermutation and other genetic changes in defective measles viruses in human brain infections. *Cell* **55:** 255–265.

Cocks BG, Chang C-CJ, Carballido JM, Yssel H, de Vries JE, Aversa G (1995). A novel receptor involved in T-cell activation. *Nature* **376:** 260–263.

Dhib-Jalbut S, Xia J, Rangaviggula H, Fang Y-Y, Lee T (1999). Failure of measles virus to activate nuclear factor-κB in neuronal cells: implications on the immune response to viral infections in the central nervous system. *J Immunol* **162:** 4024–4029.

Dörig RE, Marcil A, Chopra A, Richardson CD (1993). The human CD46 molecule is a receptor for measles virus (Edmonston strain). *Cell* **75:** 295–305.

Duclos P, Ward BJ (1998). Measles vaccines. A review of adverse events. *Drug Experience* **6:** 435–454.

Duprex WP, Duffy I, McQuaid S, Hamill L, Schneider-Schaulies J, Cosby L, Billeter M, ter Meulen V, Rima B (1999a). The H gene of rodent brain-adapted measles virus confers neurovirulence to the Edmonston vaccine strain. *J Virol* **73:** 6916–6922.

Duprex WP, McQuaid S, Hangartner L, Billeter MA, Rima BK (1999b). Observation of measles virus cell-to-cell spread in astrocytoma cells by using a green fluorescent protein-expressing recombinant virus. *J Virol* **73:** 9568–9575.

Erlenhoefer C, Wurzer WJ, Löffler S, Schneider-Schaulies S, ter Meulen V, Schneider-Schaulies J (2001). CD150 (SLAM) is a receptor for measles virus, but is not involved in viral contact-mediated proliferation inhibition. *J Virol* **75:** 4499–4505.

Evlashev A, Moyse E, Valentin H, Azocar O, Trescol-Biemont M-C, Marie JC, Rabourdin-Combe C, Horvat B (2000). Productive measles virus brain infection and apoptosis in CD46 transgenic mice. *J Virol* **74:** 1373–1382.

Fang Y-Y, Song Z-M, Dhib-Jalbut S (2001). Mechanism of measles virus failure to activate NFκ-B in neuronal cells. *J NeuroVirol* **7:** 25–34.

Finke D, Brinckmann UG, ter Meulen V, Liebert UG (1995). Gamma interferon is a major mediator of the antiviral defense in experimental measles virus-induced encephalitis. *J Virol* **69:** 5469–5474.

Finke D, Liebert UG (1994). CD4+ T cells are essential in overcoming experimental murine measles encephalitis. *Immunology* **83:** 184–189.

Fournier P, Brons NH, Berbers GA, Wiesmuller KH, Fleckenstein BT, Schneider F, Jung G, Muller CP (1997). Antibodies to a new linear site at the topographical or functional interface between the haemagglutinin and fusion proteins protect against measles encephalitis. *J Gen Virol* **78:** 1295–1302.

Gogate N, Swoveland P, Yamabe T, Verma L, Woyciechowska J, Tarnowska-Dziduszko E, Dymecki J, Dhib-Jalbut S (1996). Major histocompatibility complex class I expression on neurons in subacute sclerosing panencephalitis and experimental subacute measles encephalitis. *J Neuropathol Exp Neurol* **55:** 435–443.

Griffin DE, Bellini WJ (1996). Measles virus. In: *Fields Virology.* Fields BN, Knipe DM , Howley PM, et al (eds). Philadelphia: Lippincott-Raven Publishers, pp 1267–1312.

Hara T, Yamashita S, Aiba H, Nihei K, Koide N, Good RA, Takeshita K (2000). Measles virus-specific T helper 1/T helper 2-cytokine production in subacute sclerosing panencephalitis. *J NeuroVirol* **6:** 121–126.

Hofman FM, Hinton DR, Baemayr J, Weil M, Merrill JE (1991). Lymphokines and immunoregulatory molecules in subacute sclerosing panencephalitis. *Clin Immunol Immunopathol* **58:** 331–342.

Horvat B, Rivailler P, Varior-Krishnan G, Cardoso A, Gerlier D, Rarourdin-Combe C (1996). Transgenic mice expressing human measles virus (MV) receptor CD46 provide cells exhibiting different permissivities to MV infections. *J Virol* **70:** 6673–6681.

Hsu EC, Iorio C, Sarangi F, Khine AA, Richardson CD (2001). CDw150(SLAM) is a receptor for a lymphotropic strain of measles virus and may account for the immunosuppressive properties of this virus. *Virology* **279:** 9–21.

Ito N, Ayata M, Shingai M, Furukawa K, Seto T, Matsunaga I, Muraoka M, Ogura H (2002). Comparison of the neuropathogenicity of two SSPE sibling viruses of the Osaka-2 strain isolated with Vero and B95a cells. *J NeuroVirol* **8:** 6–13.

Jin L, Beard S, Hunjan R, Brown D, Miller E (2002). Characterization of measles virus strains causing SSPE: a study of 11 cases. *J NeuroVirol* **8:** 335–344.

Katz M (1995). Clinical spectrum of measles. *Curr Top Microbiol Immunol* **191:** 1–12.

Lawrence DMP, Patterson CE, Gales TL, D'Orazio JL, Vaughn MM, Rall GF (2000). Measles virus spread between neurons requires cell contact but not CD46 expression, syncytium formation, or extracellular virus production. *J Virol* **74:** 1908–1918.

Liebert UG (1997). Measles virus infections of the central nervous system. *Intervirology* **40:** 176–184.

Manchester M, Eto DS, Oldstone MBA (1999). Characterization of the inflammatory response during acute measles encephalitis in NSE-CD46 transgenic mice. *J Neuroimmunol* **96:** 207–217.

Manchester M, Eto DS, Valsamakis A, Liton PB, Fernandez-Munoz R, Rota PA, Bellini WJ, Forthal DN, Oldstone MBA (2000). Clinical isolates of measles virus use CD46 as a cellular receptor. *J Virol* **74:** 3967–3974.

McQuaid S, Cosby SL (2002). An immunohistochemical study of the distribution of the measles virus receptors CD46 and SLAM, in normal human tissues and subacute sclerosing panencephalitis. *Lab Invest* **82:** 1–7.

Meissner NN, Koschel K (1995). Downregulation of endothelin receptor mRNA synthesis in C6 rat astrocytoma cells by persistent measles virus and canine distemper virus infections. *J Virol* **69:** 5191–5194.

Minagawa H, Tanaka K, Ono N, Tatsuo H, Yanagi Y (2001). Induction of the measles virus receptor SLAM (CD150) on monocytes. *J Gen Virol* **82:** 2913–2917.

Moeller K, Duffy I, Duprex P, Rima B, Beschorner R, Fauser S, Meyermann R, Niewiesk S, ter Meulen V, Schneider-Schaulies J (2001). Recombinant measles viruses expressing altered hemagglutinin (H) genes: functional separation of mutations determining H antibody escape from neurovirulence. *J Virol* **75:** 7612–7620.

Mrkic B, Pavlovic J, Rulicke T, Volpe P, Buchholz CJ, Hourcade D, Atkinson JP, Aguzzi A, Cattaneo R (1998). Measles virus spread and pathogenesis in genetically modified mice. *J Virol* **72:** 7420–7427.

Nakayama T, Mori T, Yamaguchi S, Sonoda S, Asamura S, Yamashity R, Takeuchi Y, Urano T (1995). Detection of measles virus genome directly from clinical samples by reverse transcriptase-polymerase chain reaction and genetic variability. *Virus Res* **35:** 1–16.

Naniche D, Varior-Krishnan G, Cervoni F, Wild TF, Rossi B, Rabourdin-Combe C, Gerlier D (1993). Human membrane cofactor protein (CD46) acts as a cellular receptor for measles virus. *J Virol* **67:** 6025–6032.

Naniche D, Yeh A, Eto D, Manchester M, Friedman RM, Oldstone MBA (2000). Evasion of host defenses by measles virus: wild-type measles virus infection interferes with induction of alpha/beta interferon production. *J Virol* **74:** 7478–7484.

Neumeister C, Niewiesk S (1998). Recognition of measles virus-infected cells by CD8+ T cells depends on the H-2 molecule. *J Gen Virol* **79:** 2583–2591.

Niewiesk S, Brinckmann U, Bankamp B, Sirak S, Liebert UG, ter Meulen V (1993). Susceptibility to measles virus-induced encephalitis in mice correlates with impaired

antigen presentation to cytotoxic T lymphocytes. *J Virol* **67:** 75–81.

Niewiesk S, Schneider-Schaulies J, Ohnimus H, Jassoy C, Schneider-Schaulies S, Diamond L, Logan JS, ter Meulen V (1997). CD46 expression does not overcome the intracellular block of measles virus replication in transgenic rats. *J Virol* **71:** 7969–7973.

Ogata A, Czub S, Ogata S, Cosby SL, McQuaid S, Budka H, ter Meulen V, Schneider-Schaulies J (1997). Absence of measles virus receptor (CD46) in lesions of subacute sclerosing panencephalitis brains. *Acta Neuropathol* **94:** 444–449.

Ogura H, Ayata M, Hayashi K, Seto T, Matsuoka O, Hattori H, Tanaka K, Tanaka K, Takano Y, Murata R (1997). Efficient isolation of subacute sclerosing panencephalitis virus from patient brains by reference to magnetic resonance and computed tomographic images. *J NeuroVirol* **3:** 304–309.

Ohgimoto S, Ohgimoto K, Niewiesk S, Klagge IM, Pfeuffer J, Johnston ICD, Schneider-Schaulies J, Weidmann A, ter Meulen V, Schneider-Schaulies S (2001). The hemagglutinin protein is an important determinant for measles virus tropism for dendritic cells in vitro and immunosuppression in vivo. *J Gen Virol* **82:** 1835–1844.

Oldstone MBA, Lewicki H, Thomas D, Tishon A, Dales S, Patterson J, Manchester M, Homann D, Naniche D, Holz A (1999). Measles virus infection in a transgenic model: virus-induced immunosuppresion and central nervous system disease. *Cell* **98:** 629–640.

Ono N, Tatsuo H, Hidaka Y, Aoki T, Minagawa H, Yanagi Y (2001). Measles virus on throat swabs from measles patients use signalling lymphocytic activation molecule (CDw150) but not CD46 as a cellular receptor. *J Virol* **75:** 4399–4401.

Partidos CD, Ripley J, Delmas A, Obeid OE, Denbury A, Steward MW (1997). Fine specificity of the antibody response to a synthetic peptide from the fusion protein and protection against measles virus-induced encephalitis in a mouse model. *J Gen Virol* **78:** 3227–3232.

Patterson CE, Lawrence DMP, Echols LA, Rall GF (2002). Immune-mediated protectionfrom measles virus-induced central nervous system disease is non-cytolytic and gamma interferon dependent. *J Virol* **76:** 4497–4506.

Patterson JB, Cornu TI, Redwine J, Dales S, Lewicki H, Holz A, Thomas D, Billeter MA, Oldstone MBA (2001). Evidence that hypermutated M protein of a subacute sclerosing panencephalitis measles virus actively contributes to the chronic progressive CNS disease. *Virology* **291:** 215–225.

Polacino PS, Pinchuk LM, Sidorenko SP, Clark EA (1996). Immunodeficiency virus cDNA synthesis in resting T lymphocytes is regulated by T cell activation signals and dendritic cells. *J Med Primatol* **25:** 201–209.

Punnonen J, Cocks BG, Carballido JM, Bennett B, Peterson D, Aversa G, de Vries J (1997). Soluble and membrane-bound forms of signalling lymphocytic activation molecule (SLAM) induce proliferation and Ig synthesis by activated human B lymphocytes. *J Exp Med* **185:** 993–1004.

Rall GF, Manchester M, Daniels LR, Callahan EM, Belman AR, Oldstone MB (1997). A transgenic mouse model for measles virus infection of the brain. *Proc Natl Acad Sci USA* **94:** 4659–4663.

Rammohan KW, McFarland HF, Bellini WJ, Gheuens J, McFarlin DE (1983). Antibody-mediated modification of encephalitis induced by hamster neurotropic measles virus. *J Infect Dis* **147:** 546–550.

Rammohan KW, McFarland HF, McFarlin DE (1981). Induction of subacute murine measles encephalitis by monoclonal antibody to virus haemagglutinin. *Nature* **290:** 588–589.

Rammohan KW, McFarland HF, McFarlin DE (1982). Suacute sclerosing panencephalitis after passive immunization and natural measles infection: role of antibody in persistence of measles virus. *Neurology* **32:** 390–394.

Rima BK, Earle JAP, Baczko K, ter Meulen V, Carabana J, Caballero M, Celma ML, Fernandez-Munoz R (1997). Sequence divergence of measles virus haemagglutinin during natural evolution and adaptation to cell culture. *J Gen Virol* **78:** 97–106.

Schneider-Schaulies J, Niewiesk S, Schneider-Schaulies S, ter Meulen V (1999). Measles virus in the CNS: the role of viral and host factors for the establishment and maintenance of a persistent infection. *J NeuroVirol* **5:** 613–622.

Schneider-Schaulies S, Schneider-Schaulies J, Dunster LM, ter Meulen V (1995). Measles virus gene expression in neural cells. *Curr Top Microbiol Immunol* **191:** 101–116.

Shimizu T, Matsuishi T, Iwamoto R, Handa K, Yoshioka H, Kato H, Ueda S, Hara H, Tabira T, Mekada E (2002). Elevated levels of anti-CD9 antibodies in the cerebrospinal fluid of patients with subacute sclerosing panencephalitis. *J Infect Dis* **185:** 1346–1350.

Tatsuo H, Ono N, Tanaka K, Yanagi Y (2000). SLAM (CDw150) is a cellular receptor for measles virus. *Nature* **406:** 893–897.

ter Meulen V, Stephenson JR, Kreth HW (1983). Subacute sclerosing panencephalitis. In: *Comprehensive virology*, Vol. 18. Fraenkel-Conrat H, Wagner RR (eds), New York: Plenum Press, pp 105–159.

Urbanska EM, Chambers BJ, Ljunggren HG, Norrby E, Kristensson K (1997). Spread of measles virus through axonal pathways into limbic structures in the brain of Tab −/− mice. *J Med Virol* **52:** 362–369.

Weidinger G, Czub S, Neumeister C, Harriott P, ter Meulen V, Niewiesk S (2000). Role of CD4+ and CD8+ T cells in the prevention of measles virus-induced encephalitis in mice. *J Gen Virol* **81:** 2707–2713.