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Measles infection of the central nervous system

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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.

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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).

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 autoimmune 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 resistant 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 persistence 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.

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