Measles virus, immune control, and persistence

Diane E. Griffin, Wen-Hsuan Lin & Chien-Hsiung Pan

W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Correspondence: Diane E. Griffin, W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St. Rm E5132, Baltimore, MD 21205, USA. Tel.: +1 410 955 3459; fax: +1 410 955 0105; e-mail: dgriffin@jhsph.edu

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Abstract

Measles remains one of the most important causes of child morbidity and mortality worldwide with the greatest burden in the youngest children. Most acute measles deaths are owing to secondary infections that result from a poorly understood measles-induced suppression of immune responses. Young children are also vulnerable to late development of subacute sclerosing panencephalitis, a progressive, uniformly fatal neurologic disease caused by persistent measles virus (MeV) infection. During acute infection, the rash marks the appearance of the adaptive immune response and CD8⁺ T cell-mediated clearance of infectious virus. However, after clearance of infectious virus, MeV RNA persists and can be detected in blood, respiratory secretions, urine, and lymphoid tissue for many weeks to months. This prolonged period of virus clearance may help to explain measles immunosuppression and the development of lifelong immunity to re-infection, as well as occasional infection of the nervous system. Once MeV infects neurons, the virus can spread trans-synaptically and the envelope proteins needed to form infectious virus are unnecessary, accumulate mutations, and can establish persistent infection. Identification of the immune mechanisms required for the clearance of MeV RNA from multiple sites will enlighten our understanding of the development of disease owing to persistent infection.

Introduction

Measles remains one of the most important causes of child morbidity and mortality worldwide with the greatest burden in the youngest children (Moss & Griffin, 2006; Nandy et al., 2006; Wolfson et al., 2009). Measles is unique for childhood rash diseases, in that it is associated with substantial mortality with a case fatality rate of 5–10% in Africa (Nandy et al., 2006; Grais et al., 2007) and up to 25% in refugee camps and virgin populations (Moss, 2007; Shanks et al., 2011). Mortality is highest in girls, and most acute measles deaths are owing to secondary infections that result from a poorly understood measles-induced suppression of immune responses (Beckford et al., 1985; Tamashiro et al., 1987; Garenne, 1994; Shanks et al., 2011). In addition to the risks of acute infection, children, particularly boys, under the age of 2 years are also vulnerable to the development of subacute sclerosing panencephalitis (SSPE), a progressive, uniformly fatal neurologic disease associated with persistent measles virus (MeV) infection of the nervous system. SSPE has a long latent period and presents many years after the original MeV infection (Freeman et al., 1967; Cattaneo et al., 1986; Bellini et al., 2005).

A safe and efficacious live-attenuated virus vaccine is available, and recent strides have been made toward global measles control. However, logistical and financial difficulties in sustaining the current vaccination strategies in developing countries have led the World Health Organization to forecast an increase in the number of measles cases and deaths (Centers for Disease Control, 2009). Furthermore, complacency and concerns about safety, along with philosophical and religious objections to vaccination, have resulted in failure to control measles in many industrialized nations (Muscat et al., 2009; Richard & Masserey Spicher, 2009).
MeV and virus replication

MeV is a negative-sense RNA virus with a nonsegmented genome (Fig. 1b) and a lipid envelope that belongs to the morbillivirus genus of the family Paramyxoviridae. The 16 kb genome encodes eight proteins and most likely evolved from rinderpest virus, a recently eradicated disease of cattle (Barrett, 1999; Furuse et al., 2010; Horzinek, 2011). Six proteins are found in the virion (Fig. 1a). The envelope has surface projections composed of the viral hemagglutinin (H) and fusion (F) glycoproteins with the matrix (M) protein lining the interior. The helical nucleocapsid is formed from the genomic RNA wrapped with the nucleocapsid (N) protein and is packed within the envelope in the form of a symmetrical coil with the phosphoprotein (P) and large polymerase (L) proteins attached. There are two nonstructural proteins, C and V, encoded within the P gene that regulates the cellular response to infection and modulates interferon (IFN) signaling (Bellini et al., 1985; Cattaneo et al., 1989a). C is translated from an alternative start site by leaky scanning to produce a basic protein of 186 amino acids. V has the same N-terminus (231 amino acids) as P, but insertion of an additional guanine by RNA editing alters the reading frame to produce a unique 68 amino acid cysteine-rich C-terminal domain that is highly conserved among paramyxoviruses (Cattaneo et al., 1989a, b; Liston & Briedis, 1994).

H interacts with the virus receptor for attachment and F interacts with H and with the same or an additional cellular protein for fusion and entry (Fig. 1c).

Three receptors have been identified: membrane cofactor protein or CD46 (Dorig et al., 1993; Naniche et al., 1993), signaling lymphocyte activation molecule (SLAM) or CD150 (Tatsuo et al., 2000), and poliovirus receptor-related 4 (PVRL4) or nectin 4 (Muhlebach et al., 2011; Noyce et al., 2011). CD46 is a widely distributed human complement regulatory protein expressed on all nucleated cells (Riley-Vargas et al., 2004). It acts as a cofactor for the proteolytic inactivation of C3b/C4b by factor I (Riley-Vargas et al., 2004), but also induces proliferation and differentiation of regulatory T cells (Kemper et al., 2003). SLAM is a costimulator molecule expressed on activated cells of the immune system (Sidorenko & Clark, 2003). The cytoplasmic domain has an immunoreceptor tyrosine-based switch motif that binds small SH-2 domain adaptor proteins important for cell signaling (Yanagi et al., 2002; Ohno et al., 2003). Nectin-4 is an adherens junction protein of the immunoglobulin superfamily expressed on epithelial cells (Sinn et al., 2002, 2010). The receptor-binding regions on H are all found on the lateral surface of the head structure and are contiguous or overlapping (Santiago et al., 2002, 2010; Schneider et al., 2002; Masse et al., 2004; Vongprunawat et al., 2004; Colf et al., 2007; Hashiguchi et al., 2007, 2011). Both vaccine and wild-type strains of MeV can use SLAM as a receptor, but wild-type strains do not use CD46 efficiently (Ono et al., 2001; Erlenhofer et al., 2002; Yanagi et al., 2002). Differences in receptor usage may involve interactions with F as well as H (Kouomou & Wild, 2002; Takeuchi et al., 2002).

Fig. 1. Schematic diagrams of the measles virion (a), genome (b), and intracellular replication cycle (c). (a) The enveloped virion has six proteins: two surface glycoproteins, hemagglutinin (H), and fusion (F); a matrix (M) protein; a nucleocapsid (N) protein that surrounds the negative-sense RNA and two replicase proteins, the phosphoprotein (P) and large (L) polymerase protein. (b) The P gene also encodes two host cell response regulatory proteins, V and C. (c) The H protein interacts with one of several MeV receptors resulting in F-mediated fusion with the plasma membrane. Replication occurs in the cytoplasm and assembled virions bud from the plasma membrane (Moss & Griffin, 2006).
MeV probably uses additional receptors. In acute infections, endothelial cells, as well as epithelial and immune system cells, are infected (Esolen et al., 1995; Oldstone et al., 2002; Andres et al., 2003; Takeuchi et al., 2003), and in persistent infections, neurons and glial cells are important targets for infection (McQuaid & Cosby, 2002; Shingai et al., 2003). The vaccine virus was attenuated by growth in chicken cells.

H and F cooperate to induce fusion of the viral envelope and cellular plasma membrane for entry. Infected cells expressing the viral glycoproteins at the cell surface can also fuse with uninfected cells to produce multinucleated giant cells followed by cell death. However, not all types of infected cells fuse to form syncytia. In vivo, giant cells are observed in the lung, skin, and lymphatic tissue, but not the central nervous system (CNS). Cellular protein synthesis is relatively unaffected by MeV infection, but specific cellular proteins (e.g. cell surface receptors) and functional responses (e.g. signal transduction and expression of transcription factors) may be altered in a cell-type-specific manner (Bazarsky et al., 1997; Fishman et al., 1997; Indoh et al., 2007).

MeV replication is interferon (IFN)-sensitive (Leopardi et al., 1992; Naniche et al., 2000) and some IFN-stimulated proteins (e.g. MxA, ADAR1) inhibit MeV replication in a cell-type-specific manner (Schnorr et al., 1993; Schneider-Schaulies et al., 1994; Ward et al., 2011). However, MeV effectively inhibits both the induction of IFN synthesis and IFN signaling in infected cells, and this property may play an important role in the ability of MeV to establish persistent infection. The C-terminal domain of the protein prevents the induction of type I IFN synthesis both through the toll-like receptor (TLR)/MyD88 and RNA helicase pathways (He et al., 2002). V binds IKKα and inhibits TLR7/9-mediated phosphorylation of IRF7 in plasmacytoid dendritic cells (DCs) (Schlender et al., 2005; Pfäffer & Conzelmann, 2008). V also binds MDA5, but not RIG-I, to prevent activation and induction of IFNβ synthesis through the RNA helicase pathway (Andrejeva et al., 2004; Childs et al., 2009). Strains of MeV differ in V sequence, and transient transcription studies indicate strain-dependent differences in function (Takaki et al., 2011).

If IFN is produced by infected cells, the common N-terminal domains of the P and V proteins inhibit IFN-induced STAT1 activation (Palosaari et al., 2003; Caignard et al., 2007, 2009) and the C-terminal domain of V inhibits STAT2 activation (Ramachandran et al., 2008; Ramachandran & Horvath, 2010). However, the role of type I IFN in natural MeV infection is unclear. There is little evidence that IFNα/β is induced in vivo, and studies of IFN induction by MeV in vitro have been confounded by the frequent presence of defective interfering (DI) RNAs in virus stocks. DI RNAs are potent inducers of IFN, and one mechanism used to establish cell lines persistently infected with MeV (Rima et al., 1977; Yount et al., 2008).

### Acute disease and tissue sites of replication

MeV is efficiently spread by the respiratory route and is highly infectious. Knowledge of measles pathogenesis comes from the study of naturally infected humans and experimentally infected macaques, animals that develop measles very similar to that of humans. Infection is initiated in the respiratory tract followed by rapid spread of virus to local lymphoid tissue and then to multiple other organs (Moench et al., 1988). Wild-type virus replicates efficiently in activated cells of the immune system that express SLAM (Yanagi et al., 2006; Condack et al., 2007; de Swart et al., 2007) and it is likely that immature pulmonary DCs or alveolar macrophages capture and transport MeV to regional lymph nodes where the immune response is initiated and the spread of infection is facilitated (Kaiserlian & Dubois, 2001; Schneider-Schaulies et al., 2002; Lemon et al., 2011).

There is a latent period of 10–14 days and a 2–3 day prodrome of fever, coryza, cough, and conjunctivitis followed by the appearance of a characteristic maculopapular rash (Lessler et al., 2009). Multiple organs (e.g. liver, lung, thymus, spleen, and skin) are infected, and target cells include epithelial cells, endothelial cells, B lymphocytes, T lymphocytes, monocyte/macrophages, and DCs (Moench et al., 1988; Plaza & Nuovo, 2005; de Swart et al., 2007), all cells that can be replaced if eliminated by the immune response during the process of virus clearance. Neurons and glial cells are not usually the targets of acute infection (Moench et al., 1988; McQuaid et al., 1998), but infected CNS endothelial cells have been observed in autopsy specimens (Esolen et al., 1995).

The onset of the rash coincides with the appearance of the adaptive immune response and initiation of clearance of infectious virus (Auwaerter et al., 1999). After the rash has faded, infectious virus can rarely be recovered and this correlates with decreased transmission of infection (Permar et al., 2001; Van Binnendijk et al., 2003; Pan et al., 2005). However, viral RNA persists for many weeks (Fig. 2). Mechanisms of immune-mediated clearance of infectious virus and viral RNA from different types of cells may be distinct and occur at different rates.

### Immune response and clearance

Replication of MeV usually causes death of cells in culture, but this is not necessarily the case in vivo. Persistent
noncytopathic infection can be established in vitro, and this is most easily accomplished in neuronal cells, but persistent infections in lymphoid, epithelial, and glial cells have also been established (Miller & Carrigan, 1982; Rima & Duprex, 2005). Cellular factors that affect the ability of MeV to establish and maintain persistent infection include increased expression of heat-shock proteins, IFN-inducible proteins, and altered regulation of lipid metabolism (Miller & Carrigan, 1982; Schnorr et al., 1993; Rima & Duprex, 2005; Takahashi et al., 2007; Robinzon et al., 2009). Antisense RNA can be used to cure persistently infected cells (Koschel et al., 1995).

If the cell survives infection, virus clearance will require immune-mediated elimination of the cell or of intracellular virus. For many virus infections, factors produced by the innate immune response directly in response to virus infection (e.g. IFN-α/β, TNF, IL-1, IL-6, and IL-8) inhibit virus spread and set the stage for the adaptive immune response. However, the innate response to normal measles has not been well characterized. In vitro studies have shown that innate responses triggered by the interaction of MeV RNA or proteins with pathogen recognition receptors at the cell surface or in the cytoplasm to activate signaling pathways involving transcription factors NFkB and IRF 3 differ with the strain of virus, are cell-type-specific and are highly regulated by the viral P, C, and V proteins (Katayama et al., 2000; Helin et al., 2001; Bieback et al., 2002; Teneover et al., 2002; Sato et al., 2008; Duhen et al., 2010; Schuhmann et al., 2011). MeV replication in vitro is sensitive to the inhibitory effects of IFNα/β. There is little evidence that type I IFN is produced in vivo during the acute phase of disease (Griffin et al., 1990; Leopardi et al., 1992; Schnorr et al., 1993; Tanabe et al., 2003; Yu et al., 2008), and this may be important for virulence as mutation of the V gene leads to virus attenuation (Devaux et al., 2011). IL-1 and IL-8 can be detected in plasma (Zilliox et al., 2007), but roles for these factors in control of MeV infection have not been identified.

Adaptive cellular immune responses are generally regarded as most important for the clearance of MeV. Children with agammaglobulinemia recover from infection, while those with defects in cellular immunity (e.g. HIV infection, congenital immune deficiency, transplant immunosuppression, and chemotherapy) are prone to develop progressive infections of the lung (giant cell pneumonia) or CNS (inclusion body encephalitis) (Good & Zak, 1956; Enders et al., 1959; McAulay et al., 1998; Albertyn et al., 2011). MeV-specific antibody and T cell responses appear coincident with the onset of the rash, and rash biopsies show infiltration of CD4+ and CD8+ T lymphocytes in regions of epithelial cell infection (Fig. 3).

Several lines of evidence suggest that CD8+ T lymphocytes are particularly important for control and clearance of infectious virus. MeV-specific cytotoxic T lymphocytes are found in the blood during the rash and CD4+ and CD8+ T cells infiltrate sites of virus replication (Myou et al., 1993; Jaye et al., 1998; Mongkolsapaya et al., 1999; Polack et al., 1999) (Fig. 3). In monkeys, depletion of CD8+ T cells, but not B cells, at the time of infection results in a higher and more prolonged viremia (Permar et al., 2003, 2004). In vitro, addition of CD8+, but not CD4+, T cells to MeV-infected B cells prevents spread to uninfected B cells (de Vries et al., 2010), and depletion of CD4+ T cells does not affect virus titers in the lungs of infected cotton rats (Pueschel et al., 2007). Both cytotoxicity and IFN-γ production have been implicated as effector mechanisms important for CD8+ T cell-mediated MeV clearance. The relative importance of each is likely to differ depending on the target cell and tissue (Finke et al., 1995; Patterson et al., 2002; Tishon et al., 2006; Stubblefield et al., 2011). For instance, IFN-γ-induced indoleamine 2,3-dioxygenase is important for the control of MeV replication in epithelial, endothelial, and astroglial cells, but not in lymphoid or neuronal cells (Obojes et al., 2005).

In immunologically normal individuals, infectious virus cannot be recovered shortly after the rash fades (Fig. 2). Clearance of infectious virus and resolution of the accompanying rash are associated with clinical recovery in most children. However, clearance of infectious virus is only part of the story. Our studies of Zambian children with natural measles and of rhesus macaques experimentally infected with a wild-type strain of MeV have shown that viral RNA persists in multiple locations long after infectious virus is no longer detectable (Fig. 2) (Permar et al., 2001; Pan et al., 2005; Riddell et al., 2007). In prospective studies of children hospitalized with measles, MeV RNA was detected in 62% of children from at least one site (peripheral blood mononuclear cells [PBMCs], urine, or...
nasopharyngeal aspirates) at 1–2 months after discharge from the hospital and in 37% at 3–4 months after discharge (Permar et al., 2001; Riddell et al., 2007). These data indicate that clearance of MeV RNA after infection is a prolonged process.

Rhesus macaques infected with wild-type MeV have provided additional information on clearance because they can be followed closely from the time of infection. Infectious virus appears in the blood 4–7 days after infection and is cleared by 14–18 days. However, MeV RNA can be detected in PBMCs for 4–6 months (Pan et al., 2005). Clearance of virus and viral RNA from PBMCs occurs in phases. After an initial peak of RNA coinciding with recovery of infectious virus, there is a period of rapid decline in viral RNA, followed by a rebound and then a slow decline to undetectable levels. In animals studied for longer periods of time, viral RNA may reappear in PBMCs after apparent elimination suggesting persistence in other tissues (Pan et al., 2005). The length of time required for clearance from lymphoid and other tissues is not known.

Sequencing of RNA from late samples has identified no mutations in the variable regions of either the N or H genes (Riddell et al., 2007). These data suggest slow clearance as an explanation for the prolonged presence of MeV RNA after apparent recovery rather than mutation and escape from the immune response. A switch in the type of T cell response from type 1 to type 2 with the production of regulatory T cells and cytokines may play a role in slowing clearance of viral RNA (Ward et al., 1991; Moss et al., 2002b; Yu et al., 2008). Prolonged presence of viral RNA is highly relevant to the development of persistent infection and could explain the immunologic abnormalities that persist after the rash fades as well as the development of lifelong immunity that characterizes the recovery from measles.

**Persistent infection**

The frequency of failure of virus clearance from various tissues is not known, but clinically significant disease in immunologically normal individuals has only been convincingly linked to persistent infection of the CNS. Approximately 1 in 10 000 children (boys > girls) will develop SSPE as a late complication of measles (Takasu et al., 2003; Bellini et al., 2005). Both host and virus factors are likely to play a role in establishing persistence. SSPE is most likely to develop if the primary MeV infection occurs before the age of 2 years when the immune system is immature and residual maternal antibody may still be present (Jabbour et al., 1972; Detels et al., 1973; Modlin et al., 1977; Halsey et al., 1980; Miller et al., 1992; Bellini et al., 2005). In developing countries with high birth rates, measles often occurs in young infants.
cytes and antibody-secreting B cells (Dawson, 1934; Hern-

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(Halsey et al., 1980; Moss et al., 2002a, 2008; Grais et al., 2007) and these countries appear to have a higher burden of SSPE (Saha et al., 1990; Takasu et al., 2003). This high burden is likely further exacerbated when there is a high prevalence of HIV infection because children of HIV-infected mothers are at increased risk to acquire measles at an early age (Embree et al., 1992; Moss et al., 2002a), and animal models suggest that prior infection with an immunosuppressive virus increases the likelihood of persistent CNS infection (Oldstone et al., 2005).

Antibody to MeV may play a role in establishing persistent CNS infection either through the alteration of the induction of the primary immune response at the time of initial infection or through the modulation of infection once virus is in the nervous system (Fujinami & Old-

stone, 1979; Rammohan et al., 1982; Endo et al., 2001). Passage of infected cells in the presence of antiviral antibody has been used to establish persistent infection in vitro (Rustigian, 1966). In small animals, treatment with antibody after intracerebral infection with MeV decreases acute disease, but increases the likelihood of persistent virus infection and subacute or chronic encephalitis (Wear & Rapp, 1971; Rammohan et al., 1981; Liebert et al., 1990). Cases of SSPE have been associated with passive transfer of immune globulin (Rammohan et al., 1982).

The average time to onset of SSPE after measles is 6–10 years, but ranges from 1 to 24 years (Modlin et al., 1977; Campbell et al., 2007). At the time that neurologic symptoms occur, neurons and glial cells contain nuclear and cytoplasmic MeV inclusion bodies and there is an extensive mononuclear inflammatory reaction in the CNS that includes CD4+ and CD8+ T cells, as well as monocytes and antibody-secreting B cells (Dawson, 1934; Herndon & Rubinstein, 1968; Brody et al., 1972; Esiri et al., 1982; Anlar et al., 2001). The antibody response to MeV is accentuated with significant production of MeV-specific antibody by plasma cells residing in the CNS (Burgoon et al., 2005). Thus, there is no evidence for a global defect in immune responses, but these immune responses are ineffective in clearing virus from the CNS.

Strains of MeV differ in ability to establish persistent infection in the same host cell in vitro (Fernandez-Munoz & Celma, 1992), but there is no clustering of SSPE cases to suggest that the wild-type virus causing the initial infection is different from the virus causing uncomplicated disease. Sequence analysis of viral RNA from various parts of the brain shows that the virus is clonal (Baczko et al., 1993), implying that virus may have entered the brain during the original acute infection, perhaps by infecting endothelial cells (Kirk et al., 1991; Eso-

len et al., 1995; Dittmar et al., 2008; Ludlow et al., 2009), was not cleared and gradually spread throughout the nervous system. Once within neurons, virus can spread from neuron-to-neuron without the release of infectious particles (Ehrengruber et al., 2002) and it has been suggested that the MeV F protein interacts at the synapse with the substance P receptor neurokinin-1 to mediate trans-synaptic spread (Makhortova et al., 2007).

However, the virus that is present in cell lines persistently infected with MeV and in the CNS at the time of the onset of clinically apparent SSPE differs substantially from the original wild-type virus. Although viral antigen and RNA are abundant in both inclusion body encephali-
tis of immune-compromised individuals and in SSPE, the virus is difficult, if not impossible, to culture from CNS tissue. In fact, some viruses thought to be SSPE viruses have been discovered to be laboratory contaminants (Rima et al., 1995). Variants associated with persistent infection in vitro often display properties indicative of impaired replication such as temperature-sensitivity (Ragger-Zisman et al., 1984; Takahashi et al., 2007), accumulation of intranuclear and intracytoplasmic nucleocapsids, and decreased release of infectious virus (Robinson et al., 2009). Some cell lines produce no infectious virus, and persistent infection is maintained by the passage of encapsidated viral RNA to daughter cells during cell division (Burnstein et al., 1974).

In SSPE, no virus is seen budding from the surface of infected cells. Nuclear inclusions are filled with 'smooth' nucleocapsids that lack associated RNA and P protein (Herndon & Rubinstein, 1968; Dubois-Dalcq et al., 1974). The cytoplasm contains 'fuzzy' nucleocapsids of N-encapsidated RNA decorated with P that extend into neuronal processes. Thus, virus can spread within the CNS by synaptic transmission of the ribonucleoprotein from cell to cell, a process that has been observed both in vivo and in vitro (Sawaishi et al., 1999; Duprex et al., 2000; Lawrence et al., 2000; Ehrengruber et al., 2002). Limited expression of viral proteins on the surface of persistently infected cells has led to the suggestion that defects in synthesis of viral envelope proteins or processing of F may be an important determinant of persistent infection (Menna et al., 1975; Young et al., 1985). Defects in glycoprotein expression may be due in part to limited production of mRNAs for these proteins associated with steep transcriptional gradients and an increase in bicistronic messages (Cattaneo et al., 1987). However, mutations in these genes are frequent and often lead to the synthesis of proteins with altered expression or function.

Frequent U to C changes suggest that mutation of viral RNA by adenosine deaminase (biased or A/I hypermuta-

tion) is occurring in persistently infected cells (Cattaneo et al., 1988b; Wong et al., 1991; Kuhne et al., 2006). Failure to recover infectious virus is likely due to the
mutations that accumulate in the genes for the M, F, and H envelope proteins that interfere with assembly and budding of infectious virus (Roos et al., 1981; Baczkó et al., 1986; Cattaneo et al., 1988a, 1989b; Jin et al., 2002). In general, expression of M protein is low (Liebert et al., 1986) because of either the lack of synthesis of M or to the instability of the synthesized protein (Stephenson et al., 1981; Sheppard et al., 1986) and this is accompanied by low levels of antibody to M (Hall et al., 1979). In addition, defects in the M protein hinder the association of N with the viral glycoproteins and facilitate persistence (Patterson et al., 2001). Studies in transgenic mice have shown that a functional M protein is not needed for virus replication and spread in the CNS (Cathomen et al., 1998; Patterson et al., 2001). Truncations, mutations, and deletions in the cytoplasmic domain of F that interfere with virus budding are almost universal (Schmid et al., 1992; Cattaneo & Rose, 1993). H proteins are often defective in intracellular transport and protein–protein interactions important for cell–cell fusion (Cattaneo & Rose, 1993). It is not known whether these mutations facilitate spread within the CNS and are necessary to establish or perpetuate CNS infection or accumulate because of the lack of selective pressure to maintain envelope functions during replication in the CNS because virus spread can occur trans-synaptically without production of infectious virus.

Concluding remarks

The frequency of MeV RNA persistence in the absence of disease is unknown. MeV has been identified by RT-PCR or morphologic analysis in tissues from normal individuals (Haase et al., 1984; Schneider-Schaulies et al., 1991; Katayama et al., 1995, 1998). In addition to SSPE, MeV antigen or RNA has been described as present and postulated to be playing an etiologic role in a large number of chronic diseases of unknown etiology (e.g. multiple sclerosis, Paget’s disease, otosclerosis, chronic active hepatitis, achalasia, and Crohn’s disease) (Haase et al., 1981; Wakefield et al., 1993; Kawashima et al., 1996; Friedrichs et al., 2002; Niedermeyer et al., 2007). None of these diseases has been convincingly linked to persistent MeV infection, but a better understanding of the immune mechanisms and their regulation necessary for the clearance of virus and viral RNA and of how and where the virus or viral RNA persists could help to determine if a causative role is plausible.

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References


