
Pathogenesis of Encephalitis Caused by Persistent Measles Virus Infection

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1. Introduction

Demyelinating encephalitis is a type of encephalitis in which the insulating myelin sheath surrounding nerve fibers is damaged. Most types of demyelinating encephalitis are known to be caused by viral infection, and therefore the nature of viral persistence in the central nervous system (CNS) has become crucial to understanding the pathogenesis of associated diseases. Subacute sclerosing panencephalitis (SSPE) is a progressive fatal demyelinating disease caused by infection with high levels of neuronal measles virus (MV) in the CNS. Thus, MV infection provides one of the main paradigms of persistent viral infection that causes encephalitis. Many reviews have been published explaining how MV establishes a persistent infection in the CNS [1, 2, 3]. A number of studies on SSPE using cDNA cloning and sequencing techniques have revealed that MV genomes are present in samples obtained from SSPE patients. This demonstrates the presence of mutations that may lead to MV persistence in the CNS. However, no study has been able to explain how persistent MV is reactivated and results in subsequent pathogenesis of the CNS. In this review, we describe a brief overview of MV and SSPE. We will attempt to focus on host cell modifications related to MV persistence, and on reactivation mechanisms of MV during persistent infections. We will then discuss the pathogenesis of persistent MV infections in patients to highlight molecular events that lead to the manifestation of SSPE symptoms. These key advances in the understanding of MV persistence will provide novel insights into the elucidation of SSPE pathogenesis.

2. Measles and the CNS sequelae

Measles. Measles is a highly contagious respiratory disease caused by MV. More than 10 million people worldwide are affected by MV each year, resulting in several hundred thou-

sand deaths [4]. Clinical symptoms of infection are fever, cough, conjunctivitis, rash, and Koplik spots. Immunosuppression for many weeks after apparent recovery is also a characteristic of MV infection. CNS involvement in measles is a common feature, although most patients do not present with clinical evidence of encephalitis. However, transient electroencephalography abnormalities are observed in approximately 50% of patients [5]. Measles can induce encephalitis in at least four different paradigms: primary measles encephalitis (PME); acute post-infectious measles encephalomyelitis (APME); measles inclusion-body encephalitis (MIBE) and SSPE. PME and MIBE are caused by an active or ongoing MV infection, but SSPE and APME are not. APME, which occurs in approximately 0.1% of MV cases (with a lethality of approximately 20%), develops shortly after infection, but active virus is not observed in the CNS. In APME and SSPE, neuropathological demyelination has been observed to develop.

SSPE. SSPE is a progressive fatal neurological disease that causes widespread demyelination of the CNS and infection of neurons. This is followed by infection of oligodendrocytes, astrocytes and endothelial cells [6]. It takes approximately 6–8 years after an acute MV infection for the first symptoms of SSPE to appear [7, 8]. In the early stages, affected children present with poor school performance. Motor regression is eventually seen in 100% of affected individuals, and then the disease progresses to a vegetative state [9]. Serum and cerebrospinal fluid (CSF) contain high, or very high, titers of antibodies against MV [10, 11]. Intranuclear and/or intracytoplasmic inclusion bodies are often present [12, 13]. Infiltrating mononuclear cells are first apparent in the meninges, and perivascular cuffs and infiltrates can become extensive. Some infected neurons and oligodendrocytes contain fibrillary tangles similar to those seen in other neurodegenerative diseases [14, 15].

MV. MV is a negative-sense, single-stranded RNA virus that belongs to the genus *Morbillivirus*, family *Paramyxoviridae*. The virus is composed of six structural proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), hemagglutinin (H), and large protein (L). Among these structural proteins, the N, P, and L proteins are essential for viral replication and transcription. MV genomic RNA is packaged into ribonucleoprotein (RNP) complexes, consisting of the N protein and a viral RNA-dependent RNA polymerase (RdRp). The RdRp is composed of the P and L proteins, both of which are responsible for replication and transcription of the MV genome. In addition to these structural proteins, the P gene of MV encodes accessory proteins, C and V.

MV persistence. MV produces not only an acute lytic infection, but also an occasional persistent infection. A growing body of evidence supports the persistence of MV in the infected host. As an example, a boy who had been treated for granulomatous disease using stem cell therapy died owing to MV complications [16]. Because neither the patient nor the stem cell donor had recently been exposed to MV or been vaccinated, it is most likely that MV persisted in either the donor or the patient and was reactivated. It is possible that a MV infection can persist throughout a patient's lifetime without triggering overt disease [17]. It is also possible that reactivation of a persistent MV infection can sometimes cause SSPE long after the acute infection [18].

SSPE virus strains. The sequences of viral genomes from SSPE cases are typically not related to current circulating wild-type viruses, but instead to those in circulation when patients developed an acute MV infection. This is confirmation that SSPE is caused by a persistent MV infection [19, 20]. Genetic analyses have also revealed that persistent MVs derived from SSPE cases (SSPE virus strains, SSPEVs) contain numerous mutations. The existence of characteristic mutations common to SSPEVs has been suggested [21, 22]. The M gene of SSPEVs appears to be particularly vulnerable to mutation, and its expression is restricted. In many SSPEVs, an A-to-G hypermutation occurs in the genome and destroys the M protein-coding frames. Although hypermutation of the M gene results in the defective expression of the M protein, replacement of the M gene did not confer a neurovirulent phenotype in hamsters [23]. Hypermutations in the M gene likely slow down the migration of the virus and thereby prolong infection. A mutated M protein interacts at low affinity, or not at all, with RNP complexes and is associated with the accumulation of nucleocapsids inside infected cells [24]. Other changes in SSPEV structural proteins have been found in the F and H proteins. The F proteins of some SSPEVs have been demonstrated to contribute to neurovirulence in animals by showing hyperfusion activity [23, 25]. The H protein also contributed to neurovirulence to some extent [23, 25], although it is not required for trans-synaptic transmission [26].

3. Host cell modifications in MV persistence

Modifications in MV-infected cells. The growth of RNA viruses depends on the mRNA translation machinery of the cells. Many viruses modify the host cell machinery to favor translation of their own mRNA. During the acute phase of MV infection, the virus induces suppression of protein synthesis (designated “shut-off”) in host cells and viral mRNAs are preferentially translated [27]. The phosphorylation of eukaryotic initiation factor (eIF) 2 α and the binding of the N protein to eIF3-p40, which are cellular initiation factors required for cap dependent translation, are involved in the induction of shut-off [27, 28]. The La protein is involved in the preferential translation of viral mRNAs [29]. All these modifications are found in the acute MV infection (Figure 1A). A persistent MV infection becomes clinically apparent many years after the acute infection. There are no apparent symptoms in the time between acute infection, and the onset of SSPE clinical symptoms; this would indicate that replication of the persistently infecting MV is in equilibrium with replication of the host cells. Some as yet unidentified modifications might be involved in disease progression during MV persistence (Figure 1B). These need to be investigated to understand the mechanisms of persistence and pathogenicity.

Modulation of gene expression patterns in MV-infected cells. Several studies examining gene expression in MV-infected cells have been reported [30-32]. MV infection of dendritic cells up-regulates a broad array of interferon (IFN)- α s, but fails to up-regulate double-stranded RNA-dependent protein kinases [31]. MV infection of human peripheral blood mononuclear cells (PBMCs) modulates the activity of NF- κ B transcription factors [30]. MV infection also induces expression of molecules involved in defense against en-

doplasmic reticulum (ER) stress and apoptosis in PBMCs and human lung epithelial cells [30, 32]. All these molecules affected in MV-infected cells might be involved in SSPE pathogenesis. As an example, long-term administration of IFNs is one type of SSPE therapy [33]. NF- κ B may be a determinant of multiple sclerosis (MS) susceptibility, a chronic demyelinating disease of the CNS in humans [34]. As glial cells appear to be vulnerable to ER stress, altered expression of the molecules involved in ER stress can perturb myelination by oligodendrocytes [35]. Apoptotic processes have also been suggested to contribute to MS, where local tissue damage involves apoptosis of oligodendrocytes and neurons [36].

Lipid metabolism in cells persistently infected with MV. Most studies examining gene expression in MV-infected cells have been performed in non-neuronal cells. Because modulation in gene expression is cell-type dependent [37], studies using neuronal cells are more informative. The molecules affected during persistent infection might be different from those in the acute infection. Two studies using neuronal cells persistently infected with MV revealed alterations in lipid metabolism, such as decreased cholesterol synthesis and impaired β -oxidation, that were associated with MV persistence [38, 39]. Myelination is a complex process that requires a precise stoichiometry for gene dosage, along with protein and lipid synthesis. An alteration in lipid metabolism during persistent MV infection would affect the maintenance of myelin in the CNS.

4. Reactivation mechanisms of persistent MV

It is known that persistent MV infection is asymptomatic but can eventually result in SSPE [2]. The latent MV should be reactivated at the onset of disease, resulting in clinical signs of SSPE (Figure 1C). However, the molecular mechanisms of MV persistence and reactivation are yet to be elucidated.

Heat shock protein 72 (hsp72). One potential molecule involved in MV reactivation is hsp72. Hsp72 binds to two conserved motifs in the variable tail of the N protein, known as box 2 (amino acids 489–506) and box 3 (amino acids 517–525) [40]. The tail of the N protein is within the same area where the XD domain of the P protein (amino acids 459–507) binds to the N protein [41]. *In vivo* models using mice expressing hsp72, or hyperthermal preconditioned mice, have revealed that hsp72 levels can serve as a host determinant of viral neurovirulence in mice. This indicates the direct influence of hsp72 on viral gene expression [42, 43]. Hsp72 induction by some type of reactivation event might enhance the replication of persistent MV in the CNS, resulting in the onset of clinical symptoms. Accumulation of the H protein inside the cell during persistent MV infection might be such a reactivation event, as antibodies against the MV can decrease cell surface expression of viral glycoproteins, which has been suggested to contribute to the establishment of MV persistence [44, 45]. Indeed, overexpression of the H protein leads to induction of hsp72 (Figure 2).

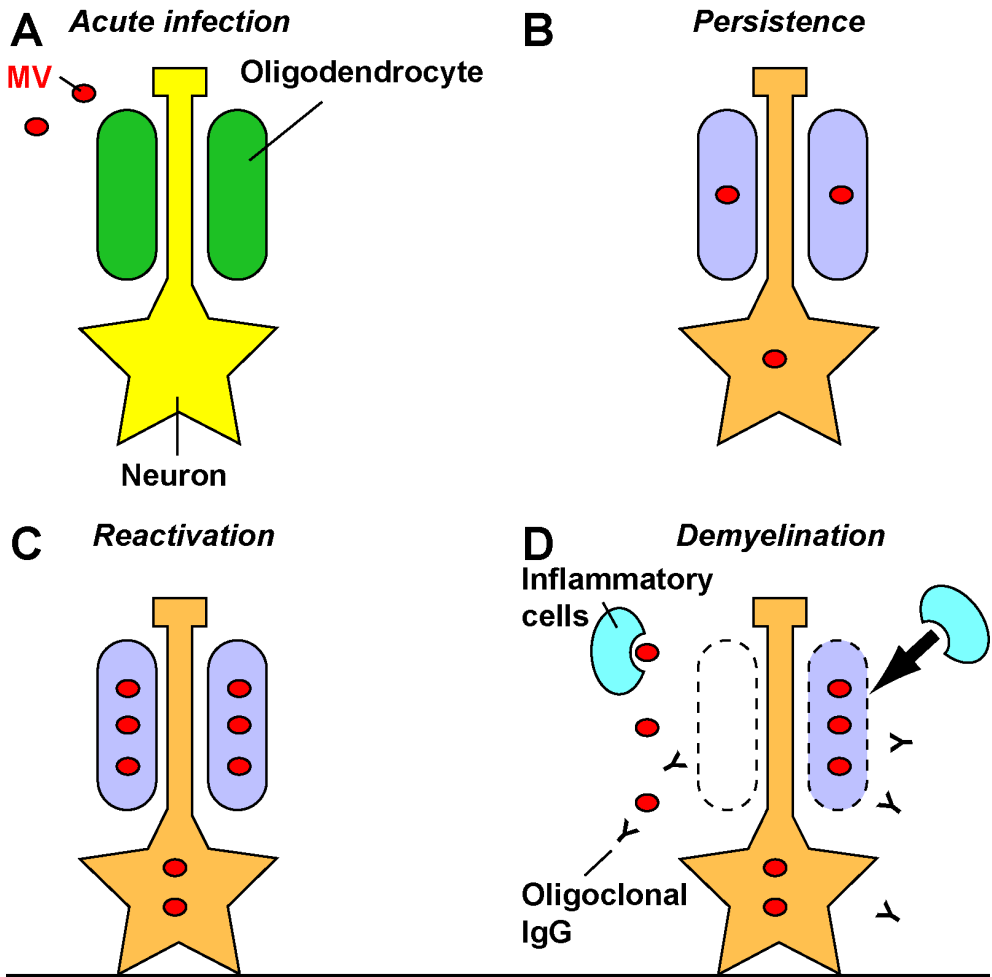


Figure 1. A model for the pathogenesis of persistent MV infection. (A) Acute infection. MV enters the CNS and infects neurons and oligodendrocytes. (B) Persistent infection. MV establishes a persistent infection in the CNS. MV replication is attuned to the host cells, with minor or reversible modifications of the cells. Minor or reversible modifications, such as alterations in lipid metabolism, in MV-infected cells might be involved in a progressive infection. (C) Reactivation. Some reactivation events stimulate the latent MV, leading to rapid replication in the CNS. (D) Demyelination. Reactivated MV destroys host cells, including oligodendrocytes, and drives damaging inflammatory responses, resulting in demyelination. Damaging resulting from MV infection can lead to a spreading of epitopes that generate autoimmune responses. The oligoclonal IgG found in the SSPE brain and the CSF, which is directed against MV, possibly cross-reacts with myelin proteins. Activated autoreactive T cells, or T cells activated by viral antigens can cross the blood-brain barrier and enter the brain parenchyma. These infiltrating inflammatory cells induce extensive lesions in the CNS.

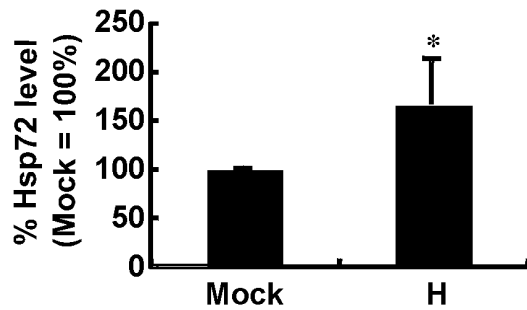


Figure 2. Hsp72 induction by the H protein. 293T cells were mock-transfected, or transfected with the H protein. At 24 h post-transfection, cells were harvested, and quantitative analysis of hsp72 was performed using quantitative real-time RT-PCR. Values are expressed as mean plus S.E. and compared with those from mock-transfected cells. * $p < 0.05$.

Peroxioredoxin 1 (Prdx1). Prdx1, another potential molecule involved in SSPE, has recently been identified as a critical component during MV replication and transcription [46]. It was shown to bind to the same area of the N protein as the P protein (box 2), and competes with binding of the P protein. A reduction in Prdx1 expression appears to result in a steeper MV transcription gradient, as it has less of an effect on the N protein expression compared with the L protein expression. The binding affinity of Prdx1 to the N protein is approximately 40-fold lower than that for the P protein. This would suggest that Prdx1 may only play a role in MV RNA synthesis during the early stages of infection, when the amount of cellular Prdx1 is much greater than that of the viral P protein [46]. Likewise, Prdx1 might play a role in the reactivation of latent MVs that are attuned to host cells. Recent studies have implicated Prdx as a target of age-related modifications [47]. Age-related modifications, such as hyperoxidation, likely affect Prdx1 thereby influencing MV transcription, and may explain why it takes several years after an acute MV infection for the first symptoms of SSPE to appear.

Post-translational modifications. Generally, infectious virus cannot be recovered from the CNS at autopsy, or from a biopsy of SSPE cases. In SSPE, MV-specific inclusions are present in the cytoplasm and nuclei of infected cells, and the incidence of certain types of inclusion bodies decline with prolonged duration of the disease [12, 13]. The N protein is most abundantly expressed in infected cells, and a major component of MV-specific inclusions. The N protein has been shown to be modified post-translationally by phosphorylation [48, 49]. The phosphorylation at serine residues 479 and 510 in the tail of the N protein has been shown to play an important role in viral replication and transcription [48]. Some reactivation events might stimulate host cell kinases responsible for these phosphorylations. Other post-translational modifications could possibly be involved in the reactivation of latent MV.

5. Pathogenesis of persistent MV infection

MV infection induces clinically significant immunosuppression, which can continue for many weeks after an apparent recovery from measles [50, 51]. Long-lived cytokine imbalan-

ces and direct effects on the proliferation of lymphocytes are reportedly implicated with the immunosuppression. In contrast, a persistent brain infection leads to a hyperimmune antibody response, a pathogenic feature of SSPE [10, 11]. For example, there are extremely high titers of neutralizing antibodies in the serum and CSF against viral structural proteins. The immune system would appear to be involved in SSPE pathogenesis (Figure 1D).

Direct cytopathic effects. Persistent MV infection might destroy infected cells, including oligodendrocytes, and damage inflammatory responses, thereby resulting in demyelination. Consistent with this idea, there is a strong correlation among the extent of viral fusion activity, cytopathic effects of MV, and severity of neurovirulence in a hamster model [23]. More commonly, T and B cells may directly attack viral antigens expressed on persistently infected glial cells and destroy these cells. Damage resulting from MV infection can lead to a spreading of epitopes that may result in the generation of autoimmune responses [52]. In SSPE patients, brain-antigen-reactive T cells are found in the periphery [53].

Autoantigen. Autoimmune responses to myelin proteins are considered to be possible causes of some demyelinating diseases including SSPE. The level of antibodies against CD9, a glycoprotein that is abundant at the surface of myelin, is elevated and reaches a peak that coincides with the appearance of brain atrophy in SSPE patients [54]. It has also been suggested that autoimmunity could arise as a result of cross-reactivity between viral and myelin antigens [55, 56]. Myelin basic protein (MBP)-homologous sequences in the N and C proteins may account not only for encephalomyelitis in humans, but also for cross-reactions as detected by delayed skin tests with MBP in measles-sensitized guinea pigs [57].

Superantigen. Another mechanism has been proposed that implicates superantigens in the etiology of autoimmune demyelinating diseases [58]. Superantigens activate T cells through the variable domain of the T cell receptor β chain. This distinctive mode of T cell activation, together with the ability of superantigens to bind to a wide variety of major histocompatibility complex molecules outside the antigen groove, leads to one superantigen activating a whole class of T cells irrespective of antigen specificity. Activated T cells can cross the blood-brain barrier and enter the brain parenchyma. A few cells homing to the brain have been shown to be enough to induce extensive lesions in the CNS [58]. Once activated, autoreactive T cells enter the brain and initiate inflammatory lesions. The permeability of the blood-brain barrier increases, leading to an influx of soluble factors, such as tumor necrosis factor, into the CNS. All these events will result in extensive CNS lesions. Exogenous superantigens can be produced by bacteria, mycoplasma or viruses [59], and therefore the existence of superantigens during persistent MV infection should be investigated in future studies.

6. Conclusion

Many previous studies have demonstrated that changes in host cell homeostasis contribute to the pathogenesis of persistent MV infections. Rapid replication of MV that has been quiescent for years is triggered by some reactivation event(s) and results in hyper-

reactive immune responses. Demyelination in persistent MV infections is due to a complex combination of viral cytopathic effects on neuronal cells and immune-mediated mechanisms. Although the pathogenesis of persistent MV infection remains to be fully elucidated, some of the key advances outlined in this review will provide novel insights into the understanding of human demyelinating encephalitis, and other encephalitis types induced by viruses.

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References

- [1] Rima BK & Duprex WP. Molecular mechanisms of measles virus persistence. *Virus Res* 2005;111(2):132-147.
- [2] Reuter D & Schneider-Schaulies J. Measles virus infection of the CNS: human disease, animal models, and approaches to therapy. *Med Microbiol Immunol* 2010;199(3):261-271.
- [3] Schneider-Schaulies J, et al. Measles infection of the central nervous system. *J Neuro-Virol* 2003;9:247-252.
- [4] Moss WJ & Griffin DE. Global measles elimination. *Nat Rev Microbiol* 2006;4(12):900-908.

- [5] Gibbs FA., et al. Electroencephalographic abnormality in “uncomplicated” childhood diseases. *JAMA* 1959;171(8):1050-1055.
- [6] Kirk J, Zhou AL, McQuaid S, Cosby SL, & Allen IV. Cerebral endothelial cell infection by measles virus in subacute sclerosing panencephalitis: ultrastructural and in situ hybridization evidence. *Neuropathol Appl Neurobiol* 1991;17(4):289-297.
- [7] Modlin JF, Jabbour JT, Witte JJ, & Halsey NA. Epidemiologic studies of measles, measles vaccine, and subacute sclerosing panencephalitis. *Pediatrics* 1977;59(4):505-512.
- [8] Tuncay R, et al. MRI in subacute sclerosing panencephalitis. *Neuroradiology* 1996;38(7):636-640.
- [9] Akram M, Naz F, Malik A, & Hamid H. Clinical profile of subacute sclerosing panencephalitis. *J Coll Physicians Surg Pak* 2008;18(8):485-488.
- [10] Connolly JH, Allen IV, Hurwitz LJ, & Millar JH. Measles-virus antibody and antigen in subacute sclerosing panencephalitis. *Lancet* 1967;1(7489):542-544.
- [11] Tourtellotte WW, Parker JA, Herndon RM, & Cuadros CV. Subacute sclerosing panencephalitis: brain immunoglobulin-G, measles antibody and albumin. *Neurology* 1968;18(1 Pt 2):117-121.
- [12] Tomoda A, Müike T, Miyagawa S, Negi A, & Takeshima H. Subacute sclerosing panencephalitis and chorioretinitis. *Brain Dev* 1997;19(1):55-57.
- [13] Lewandowska E, Lechowicz W, Szpak GM, & Sobczyk W. Quantitative evaluation of intranuclear inclusions in SSPE: correlation with disease duration. *Folia Neuropathol* 2001;39(4):237-241.
- [14] McQuaid S, Allen IV, McMahon J, & Kirk J. Association of measles virus with neurofibrillary tangles in subacute sclerosing panencephalitis: a combined in situ hybridization and immunocytochemical investigation. *Neuropathol Appl Neurobiol* 1994;20(2):103-110.
- [15] Ikeda K, et al. Numerous glial fibrillary tangles in oligodendroglia in cases of subacute sclerosing panencephalitis with neurofibrillary tangles. *Neurosci Lett* 1995; 194(1-2):133-135.
- [16] Freeman AF, et al. A new complication of stem cell transplantation: measles inclusion body encephalitis. *Pediatrics* 2004;114(5):e657-660.
- [17] Katayama Y, Hotta H, Nishimura A, Tatsuno Y, & Homma M. Detection of measles virus nucleoprotein mRNA in autopsied brain tissues. *J Gen Virol* 1995;76 (Pt 12): 3201-3204.
- [18] Haase AT, Ventura P, Gibbs CJ, & Tourtellotte WW. Measles virus nucleotide sequences: detection by hybridization in situ. *Science* 1981;212(4495):672-675.

- [19] Jin L, Beard S, Hunjan R, Brown DW, & Miller E. Characterization of measles virus strains causing SSPE: a study of 11 cases. *J Neurovirol* 2002;8(4):335-344.
- [20] Rima BK, et al. Temporal and geographical distribution of measles virus genotypes. *J Gen Virol* 1995;76 (Pt 5):1173-1180.
- [21] Ayata M, Hirano A, & Wong TC. Structural defect linked to nonrandom mutations in the matrix gene of biken strain subacute sclerosing panencephalitis virus defined by cDNA cloning and expression of chimeric genes. *J Virol* 1989;63(3):1162-1173.
- [22] Cattaneo R, Schmid A, Billeter MA, Sheppard RD, & Udem SA. Multiple viral mutations rather than host factors cause defective measles virus gene expression in a subacute sclerosing panencephalitis cell line. *J Virol* 1988;62(4):1388-1397.
- [23] Ayata M, et al. The F gene of the Osaka-2 strain of measles virus derived from a case of subacute sclerosing panencephalitis is a major determinant of neurovirulence. *J Virol* 2010;84(21):11189-11199.
- [24] Patterson JB, et al. Evidence that the hypermutated M protein of a subacute sclerosing panencephalitis measles virus actively contributes to the chronic progressive CNS disease. *Virology* 2001;291(2):215-225.
- [25] Cattaneo R & Rose JK. Cell fusion by the envelope glycoproteins of persistent measles viruses which caused lethal human brain disease. *J Virol* 1993;67(3):1493-1502.
- [26] Young VA & Rall GF. Making it to the synapse: measles virus spread in and among neurons. *Curr Top Microbiol Immunol* 2009;330:3-30.
- [27] Inoue Y, Tsukiyama-Kohara K, Yoneda M, Sato H, & Kai C. Inhibition of host protein synthesis in B95a cells infected with the HL strain of measles virus. *Comp Immunol Microbiol Infect Dis* 2009;32(1):29-41.
- [28] Sato H, et al. Measles virus N protein inhibits host translation by binding to eIF3-p40. *J Virol* 2007;81(21):11569-11576.
- [29] Inoue Y, et al. Selective translation of the measles virus nucleocapsid mRNA by la protein. *Front Microbiol* 2011;2:173.
- [30] Bolt G, Berg K, & Blixenkrone-Møller M. Measles virus-induced modulation of host-cell gene expression. *J Gen Virol* 2002;83(Pt 5):1157-1165.
- [31] Zilliox MJ, Parmigiani G, & Griffin DE. Gene expression patterns in dendritic cells infected with measles virus compared with other pathogens. *Proc Natl Acad Sci U S A* 2006;103(9):3363-3368.
- [32] van Diepen A, et al. Quantitative proteome profiling of respiratory virus-infected lung epithelial cells. *J Proteomics* 2010;73(9):1680-1693.
- [33] Gutierrez J, Issacson RS, & Koppel BS. Subacute sclerosing panencephalitis: an update. *Dev Med Child Neurol* 2010;52(10):901-907.

- [34] Yan J & Greer JM. NF-kappa B, a potential therapeutic target for the treatment of multiple sclerosis. *CNS Neurol Disord Drug Targets* 2008;7(6):536-557.
- [35] D'Antonio M, Feltri ML, & Wrabetz L. Myelin under stress. *J Neurosci Res* 2009;87(15):3241-3249.
- [36] Mc Guire C, Beyaert R, & van Loo G. Death receptor signalling in central nervous system inflammation and demyelination. *Trends Neurosci.* 2011;34(12):619-628
- [37] Sato H, et al. Measles virus induces cell-type specific changes in gene expression. *Virology* 2008;375(2):321-330.
- [38] Takahashi M, Watari E, Shinya E, Shimizu T, & Takahashi H. Suppression of virus replication via down-modulation of mitochondrial short chain enoyl-CoA hydratase in human glioblastoma cells. *Antiviral Res* 2007;75(2):152-158.
- [39] Robinzon S, et al. Impaired cholesterol biosynthesis in a neuronal cell line persistently infected with measles virus. *J Virol* 2009;83(11):5495-5504.
- [40] Taylor MJ, et al. Identification of several different lineages of measles virus. *J Gen Virol* 1991;72 (Pt 1):83-88.
- [41] Bourhis JM, et al. The intrinsically disordered C-terminal domain of the measles virus nucleoprotein interacts with the C-terminal domain of the phosphoprotein via two distinct sites and remains predominantly unfolded. *Protein Sci* 2005;14(8):1975-1992.
- [42] Carsillo T, Carsillo M, Niewiesk S, Vasconcelos D, & Oglesbee M. Hyperthermic preconditioning promotes measles virus clearance from brain in a mouse model of persistent infection. *Brain Res* 2004;1004(1-2):73-82.
- [43] Carsillo T, Traylor Z, Choi C, Niewiesk S, & Oglesbee M. hsp72, a host determinant of measles virus neurovirulence. *J Virol* 2006;80(22):11031-11039.
- [44] Joseph BS & Oldstone MB. Immunologic injury in measles virus infection. II. Suppression of immune injury through antigenic modulation. *J Exp Med* 1975;142(4):864-876.
- [45] Fujinami RS & Oldstone MB. Alterations in expression of measles virus polypeptides by antibody: molecular events in antibody-induced antigenic modulation. *J Immunol* 1980;125(1):78-85.
- [46] Watanabe A, et al. Peroxiredoxin 1 is required for efficient transcription and replication of measles virus. *J Virol* 2011;85(5):2247-2253.
- [47] Wang Q, et al. Differential proteomics analysis of specific carbonylated proteins in the temporal cortex of aged rats: the deterioration of antioxidant system. *Neurochem Res* 2010;35(1):13-21.
- [48] Hagiwara K, et al. Phosphorylation of measles virus nucleoprotein upregulates the transcriptional activity of minigenomic RNA. *Proteomics* 2008;8(9):1871-1879.

- [49] Prodhomme EJ, et al. Extensive phosphorylation flanking the C-terminal functional domains of the measles virus nucleoprotein. *J Proteome Res* 2010;9(11):5598-5609.
- [50] Moss WJ, Ota MO, & Griffin DE. Measles: immune suppression and immune responses. *Int J Biochem Cell Biol* 2004;36(8):1380-1385.
- [51] Schneider-Schaulies S & ter Meulen V. Measles virus and immunomodulation: molecular bases and perspectives. *Expert Rev Mol Med* 2002;4(13):1-18.
- [52] Miller SD, et al. Persistent infection with Theiler's virus leads to CNS autoimmunity via epitope spreading. *Nat Med* 1997;3(10):1133-1136.
- [53] Johnson RT, et al. Measles encephalomyelitis--clinical and immunologic studies. *N Engl J Med* 1984;310(3):137-141.
- [54] Shimizu T, et al. Elevated levels of anti-CD9 antibodies in the cerebrospinal fluid of patients with subacute sclerosing panencephalitis. *J Infect Dis* 2002;185(9):1346-1350.
- [55] Oldstone MB. Molecular mimicry and autoimmune disease. *Cell* 1987;50(6):819-820.
- [56] Wucherpfennig KW & Strominger JL. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. *Cell* 1995;80(5):695-705.
- [57] Jahnke U, Fischer EH, & Alvord EC. Sequence homology between certain viral proteins and proteins related to encephalomyelitis and neuritis. *Science* 1985;229(4710):282-284.
- [58] Brocke S, Veromaa T, Weissman IL, Gijbels K, & Steinman L. Infection and multiple sclerosis: a possible role for superantigens? *Trends Microbiol* 1994;2(7):250-254.
- [59] Kotzin BL, Leung DY, Kappler J, & Marrack P. Superantigens and their potential role in human disease. *Adv Immunol* 1993;54:99-166.

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