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Review

Molecular mechanisms of measles virus persistence

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Abstract

As measles virus causes subacute sclerosing panencephalitis and measles inclusion body encephalitis due to its ability to establish human persistent infection, without symptoms for the time between the acute infection and the onset of clinical symptoms, it has been the paradigm for a long term persistent as opposed to chronic infection by an RNA virus. We have reviewed the mechanisms of persistence of the virus and discuss specific mutations associated with CNS infection affecting the matrix and fusion protein genes. These are placed in the context of our current understanding of the viral replication cycle. We also consider the proposed mechanisms of persistence of the virus in replicating cell cultures and conclude that no general mechanistic model can be derived from our current state of knowledge. Finally, we indicate how reverse genetics approaches and the use of mouse models with specific knock-out and knock-in modifications can further our understanding of measles virus persistence.

Keywords: Measles virus; Persistent infection; Subacute sclerosing panencephalitis; Brain receptor; Mechanisms of persistence; Pathogenesis

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1. The scope of the review

Measles virus (MV) still provides one of the main paradigms of a long-term persistent infection by an RNA virus due to its involvement in the disease subacute sclerosing panencephalitis (SSPE), a progressive fatal neurological disease caused by high levels of neuronal infection by MV in the central nervous system (CNS). Hence, there has always been an interest in studying the underlying mechanisms of MV persistence. Initially, in the late 1960s and the 1970s, this was studied using cell cultures. However, with the advent in the 1980s and early 1990s of cDNA cloning and sequencing technology it became possible to examine virus genomes present in autopsy material obtained from the CNS of patients. This review will briefly recapitulate the main findings of the earlier studies and will then concentrate on setting out what has been found since the early 1990s. It will illustrate the utility of reverse genetic approaches and transgenic mouse studies and show how these, in the future, may further our understanding of viral persistence in a mechanistic sense. To date no study has been able to explain why the virus is able to persist. As such we use this review to highlight the most pertinent questions which remain to be addressed.

2. Subacute sclerosing panencephalitis and measles inclusion body encephalitis

The main impetus for the study of MV persistence has come from the discovery that MV was the cause of SSPE, a human CNS disease that manifests itself long after the acute infection with the virus. MV infection is associated with neurological complications in a small minority of cases. About 1:1000 cases will suffer post-infection encephalitis, which involves mainly perivascular demyelination (Litvak et al., 1943). This often fatal complication appears to be autoimmune in nature as no virus can be demonstrated in the brain of such patients. SSPE has been reported to occur in 1:300,000 cases. However, more recent data suggests that it is much more prevalent and can follow acute MV infection in 1:10,000 cases (Takasu et al., 2003). On average, symptoms present 8 years after the acute infection, but this ranges from 9 months to 30 years. Acute infection below the age of two is a risk factor in this disease, which, as yet inexplicably predominates in males at a 2.5:1 ratio (Halsey et al., 1980). The disease manifests itself in severe demyelination and profound infection of neurones. In the latter stages of SSPE small numbers of oligodendrocytes, astrocytes and endothelial cells have been shown to be affected (Kirk et al., 1991). This inevitably leads to severe neurological deficits and death of the patient. One of the longest recorded patients carried the persistent infection over three decades before the onset of symptoms. In terms of the duration of the symptomatic period, there is a report of a 52 years old who died 4 years after diagnosis (Tanaka et al., 1987). There is no evidence for a reduction in the cell-mediated immune responses to MV in SSPE patients. Furthermore, antibody responses lead to hyperimmunity with extremely high titres of neutralising antibody in both the serum and cerebrospinal fluid (CSF) of patients. The CSF contains oligoclonal bands specific to MV and it has been demonstrated that the antibodies present in these have undergone affinity maturation (Smith-Jensen et al., 2000).

In immuno-compromised patients, measles can give rise to an additional CNS infection, measles inclusion body encephalitis (MIBE) (ter Meulen et al., 1983). In contrast to SSPE, MIBE is not associated with a hyperimmune antibody response to measles proteins or oligoclonal bands in the CNS. Recently MIBE caused the death of a 13-year-old boy who had been treated for chronic granulomatous disease by stem cell therapy. Neither the patient nor the stem cell donor had apparent recent measles exposure or vaccination and neither had visited a region of the world where MV was endemic (Freeman et al., 2004). The simplest explanation may be persistence of the virus in either the donor or the recipient. Nevertheless repeat exposure cannot be ruled out in this case as the virus is highly infectious.

Other suggested sequelae of MV infection are multiple sclerosis, chronically active autoimmune hepatitis, Paget's disease, otosclerosis, Crohn's disease and autism among many other diseases (e.g. Reddy et al., 1999). However, no confirmed evidence has been presented to substantiate these associations, let alone prove a causative relationship and as such discussion of these falls outside the scope of this review.

3. MV: the virus and its replication

In order to understand what is known of the molecular mechanisms of MV persistence it is first necessary to describe the molecular biology and pathology of MV.

3.1. Virion

MV is an enveloped RNA virus classified in the family *Paramyxoviridae* (Griffin, 2001) in the genus *Morbillivirus*