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Measles Virus Infection: Mechanisms of Immune Suppression

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1. Introduction

Measles virus (MV) is a highly contagious respiratory pathogen that causes systemic disease; most individuals recover with lifelong immunity to MV. Enormous progress toward measles elimination has been made worldwide, in large part due to the availability of a safe and effective vaccine (CDC, 2000; WHO, 2005; 2009; 2010). However, measles infections still cause 500,000 deaths annually, mostly due to subsequent opportunistic infections associated with MV induced immune-suppression (Wild, 1999). Prior to the introduction of vaccines and a global eradication programme coordinated by the World Health Organisation (WHO) (Wild, 1999), global death rates were as high as 7–8 million children annually. The introduction of a live measles vaccine has significantly reduced the incidence of acute measles in industrialized countries. In developing countries however, measles is still an important health problem and the major viral killer of children.

2. The disease

General symptoms of an acute MV infection consist of a maculopapular rash, dry cough, coryza, fever, conjunctivitis and photophobia, usually preceded by characteristic spots on the mucosal surface of the mouth, called Koplik spots. Complications consist of diarrroea, pneumonia, laryngotracheobronchitis, otitis media and stomatitis. In developing countries, increased case fatality is associated with age at infection and nutritional status. Around 0.1% of measles cases develop acute measles encephalitis during or shortly after acute measles with a mortality rate of 10-30%; maybe as a consequence of MV induced autoimmune reaction against brain antigens (Moench *et al.*, 1988). The most serious complications of MV infection occur within the central nervous system (CNS); three most common are acute disseminated encephalomyelitis (ADEM) (Liebert, 1997; Rima & Duprex, 2006), subacute sclerosing panencephalitis (SSPE) and, in immunocompromised individuals, measles inclusion body encephalitis (MIBE) (Chadwick *et al.*, 1982; Moench *et al.*, 1988).
ADEM occurs 5–6 days after the initial rash in about 1/1000 infected children (Leake *et al.*, 2004; Menge *et al.*, 2005). It is less common in vaccinees and children under 2 years of age

(Menge *et al.*, 2005; Nasr *et al.*, 2000; Rima & Duprex, 2006). Symptoms occur once the initial rash has disappeared and consist of a sudden recurrence of fever, decreased consciousness, seizures and multifocal neurological signs.
SSPE and MIBE are rare late complications of measles (Chadwick *et al.*, 1982; Moench *et al.*, 1988) and can occur months or even years after acute infection and are invariably fatal (Liebert, 1997; Rima & Duprex, 2006; Sips *et al.*, 2007). These fatal diseases exhibit virological and immunological features quite different from those seen in acute measles or measles encephalitis. Both diseases have their basis in a persistent MV infection in brain cells, where neurons, glial cells and endothelial cells can be infected. However, giant cell formation and budding virus particles as typically found in measles infection are virtually absent in SSPE and MIBE, indicating defective MV replication in CNS tissue. This is supported by the observation that MV cannot be isolated by standard procedures from diseased CNS tissue, and only occasionally by co-cultivation methods.

2.1 Clinical epidemiology

Immunization has altered the epidemiology of measles by reducing the susceptible individuals in the population, causing an increase in the average age at infection and resulting in a lengthening of the inter-epidemic period (Cutts & Markowitz, 1994). Very young infants are protected from measles by maternal antibody. In countries with poor immunization, the majority of measles patients are children because the older populations have gained immunity by natural infection. However, in countries with high rates of immunization, as elevated herd immunity reduces transmission and indirectly protects children from infection, the average age for measles patients has increased (Black, 1982). Therefore, when outbreaks occur in areas of sustained high vaccine coverage, an increasingly large portion of the cases may be in older individuals who are susceptible because of primary or secondary vaccine failure. For example in 1973, persons 20 years of age and older accounted for only 3% of cases. In 1994, adults accounted for 24%, and in 2001, for 48% of all reported cases.

2.1.1 Countries with no endemic measles virus

Measles is very rare in countries and regions of the world that are able to sustain high vaccination coverage. In North and South America, Finland, among others, endemic measles transmission has been interrupted through vaccination (see Figure 1A). In Europe, Australia, Mongolia, New Zealand, Philippines, the Pacific Island Nations and the Arab Gulf States, measles transmission has been interrupted or is at very low levels (WHO, 1995).
The importance of maintaining high vaccine coverage even after eradication has been achieved, is exemplified by the United States (USA) experience. During the 1980s, measles was very rare in USA, but from 1989 through 1991 a dramatic increase in cases occurred. A total of 27,786 cases were reported in 1990, of whom 64 died, the largest annual number of deaths from measles since 1971. The most important cause of the measles resurgence of 1989–1991 was low vaccine coverage (Lee *et al.*, 2004). After intensive efforts to vaccinate preschool-aged children, reported cases of measles declined rapidly. Since 1993, fewer than 500 cases have been reported annually, falling to <200 cases per year since 1997 (Papania *et al.*, 2004). A record low annual total of 37 cases were reported in 2004. There are still sporadic cases of measles in USA due to importation by visitors from other countries or US citizens travelling abroad becoming infected during travel and spreading the infection to unvaccinated or unprotected individuals (CDC, 2005).

2.1.2 Countries with endemic transmission of measles virus

Despite significant progress in Africa and Asia in reduction of measles-related mortality, countries like the Democratic Republic of Congo, Ethiopia, Niger, Nigeria (CDC, 2009), India and Pakistan (CDC, 2007) continue to sustain large numbers of measles-related deaths. In 2003 India reported more than 47,000 measles cases; the reported 115 measles-related deaths are likely to be an underestimate (Singh *et al.*, 1994; Sivasankaran *et al.*, 2006; WHO, 2008) (see Figure 1A). Reported vaccine coverage has been consistently high (>80%), but the estimated coverage is much lower (40–70%), and varies between states (WHO, 2008). Similarly Niger still reports large outbreaks (CDC, 2009); from November 2003 to June 2004,

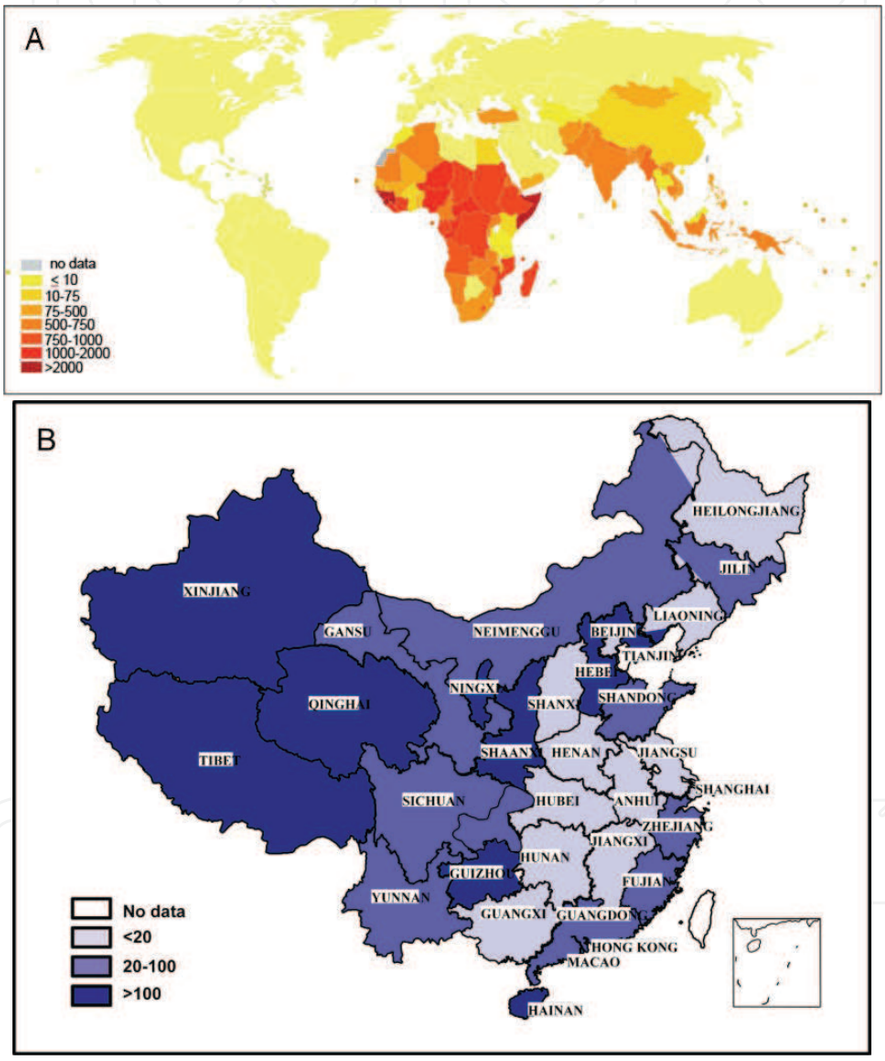

Fig. 1. Incidence of measles virus infection in the world and in China.
A. Regional map of the world, colour coded to show the incidence of measles per 100,000 population in any one year. Guide to the various colours used is shown on the left.
B. Average incidence of measles infection in China (2004-2007) Map of China showing various states, with colour coding to highlight areas of high (>100 cases per 100,000 population), mid (20-100) and low (<20) incidence. Guide to the colours used is shown on the left

11,073 cases were reported with 75% of cases and 86% of deaths being in children under five (WHO, 2008). Unacceptably high mortality related to measles epidemics in Niger, Nigeria, and Chad were reported during 2003-2005, with the overall case fatality ratios (CFRs) of 3.9%, 7.0% and 2.8%, respectively; CFR among under-fives were 4.6%, 10.8% and 4.0% (Grais *et al.*, 2007). The continuing high burden of preventable measles mortality during these epidemics results from poor access to appropriate treatment and the incomplete implementation of the WHO/UNICEF measles mortality–reduction strategy (Grais *et al.*, 2007).

3. Global vaccine initiative

In 2001, WHO and United Nations Children's Fund (UNICEF) developed a 5-year strategic plan to reduce global measles mortality by 50% in the year 2005, compared to 1999 levels (WHO/UNICEF, 2001). In regions with established measles elimination goals, the objective was to achieve and maintain interruption of indigenous measles transmission.

WHO estimates that measles is responsible for 4% of the 6 million annual deaths in children <5 years of age. Ninety-eight percent of these deaths occur in developing countries (Organization, 2005). In 2004, WHO reported an estimated 76% coverage of measles containing vaccines (MCV) world-wide (WHO, 2006). With 30 million estimated annual cases (WHO-UNICEF, 2001), most of them in unvaccinated individuals, MCV is still under-utilized. Of 23.3 million infants in 2007 who missed receiving their first dose of measles vaccine by the age of 12 months, 15.3 million (65%) reside in 8 highly populated countries (WHO, 2008).

3.1 Current status of measles eradication in the WHO Western Pacific region

In the WHO Western Pacific region (excluding China), reported confirmed measles cases decreased by 86% between 2000 and 2008 and measles mortality dropped by 92% (WHO/UNICEF, 2009). Progress has been made, and 24 of the 37 countries in this region have either achieved or nearly achieved elimination (WHO/UNICEF, 2009). However, China reported 109,023 measles cases in 2007 and 131,441 cases in 2008. A large measles outbreak in Japan resulted in >18,000 reported cases in 2007 and 11,015 cases in 2008. Intensified efforts to eliminate measles by Member States, particularly in China and Japan, are needed to achieve the WHO goal of measles elimination in the Western Pacific by 2012. China and Japan account for 82% of the region's population and >97% of its confirmed measles cases (WHO, 2009).

3.1.1 Current challenges in China

Prior to widespread use of measles vaccine, 2000 to 15000 cases per million population were reported each year in China (Wu, 2000). Monovalent measles vaccine was first used in China in 1965 and came into widespread use in 1978 when the China Expanded Program on Immunization (EPI) was established, covering all provinces in 1983 (Wang *et al.*, 2003; Ze, 2002). In 1986, the national 2-dose regimen was implemented (Wang *et al.*, 2003). To support continued progress in measles control, the Ministry of Health issued the *Plan for Acceleration of Measles Control in China* (CMOH, 1997b) and *National Strategic Plan for Measles Surveillance* in 1997 (CMOH, 1997a). These efforts enabled significant progress in measles control.

Measles prevalence varies significantly across the 31 provinces of China. The developed provinces of Eastern China have lower disease incidence with higher number of adult patients and more cases who have a history of immunisation but are susceptible because of primary or secondary vaccine failure. The resource-limited provinces located in Western China have a high measles prevalence with majority of patients being under 14 years of age with no measles vaccination history (CMOH, 1997a) (Figure 1B).

Although the developed Eastern provinces have moved ved from outbreak prevention to measles elimination, measles outbreaks still occur. A dramatic increase in measles cases in Zhejiang (see Figure 1B) was observed in 2005, with an incidence rate higher than 350 per million population (Zuo *et al.*, 2006). 51.4% of the total reported patients were migrant workers from other regions of China, of whom only 21.4% reported a vaccination history, in contrast to 33.5% of all patients who were permanent residents (Zuo *et al.*, 2006). In Shanghai, 2,838 measles cases were reported in 2005 (He *et al.*, 2006) compared with 415 in the previous year (Hu *et al.*, 2005). Migrant workers accounted for 68.1% of the total reported measles cases from 2000 to 2004 of whom, only 6.5% had a vaccination history (He *et al.*, 2006). Additional to the high measles incidence among hard to reach migrant workers, the Eastern provinces also face increased adult measles incidence. About 53.3% of measles patients were older than 20 years of age in Shanghai from 2000 to 2004 (He *et al.*, 2006), while 49.1% of the reported patients were older than 15 years in Zhejiang (Zuo *et al.*, 2006).

Different disease patterns were found in the less developed Western provinces including Qinghai, Tibet, Guizhou, and Xinjiang (Figure 1B). Measles epidemics occur every 3-4 years in these provinces. A dramatic increase in measles incidence was reported in 2004 in Xinjiang (301 cases per million population); 85% cases were younger than 14 years, and 32% of the patients had a vaccination history (Yu *et al.*, 2007b). Later in the same year, an effective measles mass vaccination campaign was implemented covering all children between 8 months and 14 years of age; only 259 measles cases (0.14 cases per million population) were reported in 2005 (Yu *et al.*, 2006). Similarly, in Guizhou, the measles incidence was 500 cases per million population in 2004; following a mass vaccination campaign, it decreased to 14.3 and 20.6 per million population respectively in 2005 and 2006 (Zhu *et al.*, 2008). In contrast to the Eastern provinces, the majority of the cases were children (Du *et al.*, 2010). Furthermore, in contrast to the developed provinces, fewer measles cases reported a vaccination history, e.g., only 18.1% and 32% of measles cases had measles vaccination history in Guizhou in 2008 (Du *et al.*, 2010) and in Xinjiang in 2004 (Yu *et al.*, 2007b), respectively. Clearly, region specific strategies are needed for control of measles in China.

In recent years, the percentage of pre-vaccination infants with measles has increased in all provinces (Zuo *et al.*, 2006). Multiple studies addressing this issue (Li, 2001; Lu *et al.*, 2008; Zhou *et al.*, 2003) suggest that the low antibody levels in child-bearing-women are insufficient to protect their babies from measles infection. Therefore, child-bearing-women should be included in the target population during measles mass vaccination campaigns.

Recent studies have found that liver dysfunction and pneumonia are very common in hospitalized adult measles patients as seen in outbreaks in Zhejiang and Shanghai (Jiang *et al.*, 2007; Kong & Zhang, 2009; Liang *et al.*, 2005; Ma & Song, 2009; Yu *et al.*, 2007a). Interestingly, the clinical manifestation of measles infection in hospitalized children is quite different, with almost no liver dysfunction being reported, while pneumonia is the most

common complication (Kong & Zhang, 2009; Wang *et al.*, 2010; Yu *et al.*, 2009). The difference in the disease symptoms is not due to differing vaccination histories; most adult patients did not know their vaccination history (Liang *et al.*, 2005; Yu *et al.*, 2007a) and the majority of hospitalized children were infants <2 years of age without previous measles vaccination (Wang *et al.*, 2010; Yu *et al.*, 2009).

4. Infectious cycle of MV and clinical progression

MV has an incubation period of around 14 days and the infected person is contagious for around 2 to 4 days before the rash appears and then 2 to 5 days after the rash appears. So, in total the infected person can spread the disease to others for 4 to 9 days.

Initial infection is established in the respiratory tract with virus replication in tracheal and bronchial epithelial cells and pulmonary macrophages (Sakaguchi *et al.*, 1986). From the respiratory tract, spread extends to local lymphatic tissues. The MV infection runs its course for around 2 weeks usually without causing any complications (Griffin, 2006). Amplification of virus in regional lymph nodes results in viremia and spread of virus through the blood to infect a variety of organs including the skin, conjunctivae, kidney, lung, gastrointestinal tract, respiratory mucosa, genital mucosa, and liver (Esolen *et al.*, 1995; Esolen *et al.*, 1993; Forthal *et al.*, 1992; Peebles, 1967; Takahashi *et al.*, 1996). Viremia and systemic infection inevitably occur before host defence mechanisms control viral replication and clear infected cells (McChesney *et al.*, 1997). Lymphoid organs and tissues (e.g., thymus, spleen, lymph nodes, appendix, and tonsils) are prominent sites of virus replication (Sakaguchi *et al.*, 1986).

4.1 Clinical symptoms of measles

After an incubation period of 8–12 days, measles begins with increasing fever (to 39–40.5 °C) cough, coryza, and conjunctivitis (Robbins, 1962). Symptoms intensify over the next 2–4 days before the onset of rash and peak on the first day of rash. The rash is usually first noted on the face and neck, appearing as discrete erythematous lesions. The lesions increase in number for 2 or 3 days, especially on the trunk and the face, where they frequently become confluent. Discrete lesions are usually seen on the distal extremities, and with careful observation, small numbers of lesions can be found on the palms of 25%–50% of those infected (Robbins, 1962). The rash lasts for 3–7 days and then fades in the same manner as it appeared. An exaggerated desquamation is commonly seen in malnourished children (Morley, 1974; Robbins, 1962; Scheifele & Forbes, 1972). Fever usually persists for 2 or 3 days after the onset of the rash, and the cough may persist for as many as 10 days (Robbins, 1962). Koplik's spots appearing as discrete, tiny, gray-white papules on a dull-red base on the buccal mucosa, usually appear 1 day before the onset of rash and persist for 2 or 3 days (Suringa *et al.*, 1970). Koplik's spots have been reported in 60%–70% of patients with measles but are probably present in most persons who develop measles (Babbott & Gordon, 1954). Photophobia from iridocyclitis, sore throat, headache, abdominal pain, and generalized mild lymphadenopathy are also common.

Milder forms of measles occur in children and adults with pre-existing partial immunity. Infants who have low levels of passively acquired maternal antibody and persons who receive blood products that contain antibody often have subclinical infections or minimal symptoms that may not be diagnosed as measles (Cherry *et al.*, 1972; Edmonson *et al.*, 1990). Vaccination protects 90% of recipients against disease, but after exposure to natural

measles, some vaccinees develop enhanced antibody response associated with mild symptoms and may have rash with little or no fever (Chen *et al.*, 1990; Smith *et al.*, 1982; Whittle *et al.*, 1999).

Atypical measles has been reported in children who received formalin inactivated (killed) measles vaccine that was in use in the USA from 1963 to 1968 (Fulginiti *et al.*, 1967). These children developed high fever, a rash that was most prominent on the extremities, often included petechiae and a high rate of pneumonitis (Fulginiti *et al.*, 1967; Rauh & Schmidt, 1965). Recent studies in monkeys indicate that this illness was caused by antigen-antibody immune complexes resulting from incomplete maturation of the antibody response to the vaccine (Polack *et al.*, 1999).

4.2 Disease progression

MV initially infects epithelial cells of the respiratory tract as well as pulmonary macrophages. MV subsequently infects regional lymph nodes, maybe disseminated via infected macrophages, and eventually establishes a systemic infection. The primary immune cell infected in blood is the monocyte, but T cells and B cells can be infected in vitro and probably *in vivo* as well (Grivel *et al.*, 2005; McChesney *et al.*, 1989). As MV infects immune cells, host innate immune response is inevitably activated to control viral replication and clear infected cells evidenced by up-regulated proinflammatory cytokines such as Interferon (IFN)-γ, Interleukin (IL)-2, etc. MV then spreads to the skin and conjunctivae leading to inflammation of the upper respiratory tract and conjunctivitis.

The lower respiratory tract and lungs are infected when MV spreads to lungs and leads to pneumonia. The infection of dermal endothelial cells can be accompanied by vascular dilatation, increased vascular permeability, mononuclear cell infiltration, and infection of surrounding tissue (Kimura *et al.*, 1975); infection of keratinocytes in the stratum granulosum of the overlying epidermis leads to focal keratosis and edema (Takahashi *et al.*, 1996) which displays as skin rash. Koplik's spots found on the oral mucosa are pathologically similar and involve the submucous glands. The rash and Koplik's spots occur about 2 weeks after infection marking the onset of a strong immune response which is effective in clearing virus and establishing long-term immunity (Roscic-Mrkic *et al.*, 2001). However, at this time numerous abnormalities of immune responses, such as MV-induced suppression of the immune system are also detected, which result in a greatly increased susceptibility to opportunistic bacterial infections that are largely responsible for the morbidity and mortality associated with measles (Borrow & Oldstone, 1995).

4.2.1 MV infection of CNS

Around 0.1% of measles cases develop acute measles encephalitis during or shortly after acute measles, with a mortality rate of 10-30%, maybe as a consequence of MV induced autoimmune reaction against brain antigens (Moench *et al.*, 1988).

4.2.1.1 Acute disseminated encephalomyelitis

ADEM occurs about 5–6 days after the initial rash in about 1/1000 infected children (Menge, et al., 2005; Leake et al., 2004; Nasr et al., 2000; Sips et al., 2007). Symptoms occur once the initial rash has disappeared and consist of a sudden recurrence of fever, decreased consciousness, seizures and multifocal neurological signs. The disease has an abrupt onset, often reaching its peak within the first 24 h with 20% mortality (Johnson, 1994). The

cerebrospinal fluid usually shows a mild elevation of protein and mononuclear cells, but is normal in about one-third of patients (Menge, et al., 2005; Leake et al., 2004). The pathology of ADEM consists of a pattern of widespread perivascular demyelination and infiltration of mononuclear cells. Histologically, the pattern of demyelination resembles that observed in experimental allergic encephalomyelitis (EAE), an animal model of multiple sclerosis (Wegner, 2005). The exact pathological mechanism of this demyelination remains unclear. An autoimmune reaction has been suggested, but at present there is no consensus about the exact aetio-pathology of ADEM.

4.2.1.2 Measles inclusion body encephalitis

MIBE usually occurs between 2 and 6 months after MV infection in immunocompromised patients (Menge *et al.*, 2005; Nasr *et al.*, 2000; Rima & Duprex, 2006) and can follow both wild-type virus infection and vaccination (Aicardi *et al.*, 1977; Bitnun *et al.*, 1999; Mustafa *et al.*, 1993; Rima & Duprex, 2006; Valmari *et al.*, 1987). Prognosis is poor with a 76% mortality rate and all survivors retain a persistent neurological disorder (Mustafa *et al.*, 1993). Characteristic neuropathologic changes are glial cell proliferation and focal necrosis, with varying degrees of perivascular inflammation. Intranuclear and/or intracytoplasmic inclusion bodies are often present (Mustafa *et al.*, 1993). The diagnosis of MIBE can only be confirmed post mortem, by RT-PCR for MV RNA or by immunohistochemistry. A few cases have been described in which MIBE followed vaccination and here dysgammaglobulinaemia or a pre-existing undiagnosed immune abnormality was suggested to be a predisposing factor (Bitnun *et al.*, 1999; Valmari *et al.*, 1987). The mechanism of viral spread and persistence in the brain in MIBE patients is not well understood.

4.2.1.3 Subacute sclerosing panencephalitis

SSPE is thought to complicate about 1/1,000,000 cases of MV infection (Johnson, 1994; Rima & Duprex, 2006). SSPE occurs approximately 5 - 10 years after initial MV infection, with infection under the age of 2 being a risk factor (Jabbour *et al.*, 1972; Modlin *et al.*, 1979). In the early stage, children present with loss of attention span and neurological symptoms, typically stereotyped myoclonic jerks. As the disease progresses, they gradually slide into a vegetative state and eventually die from the infection (Ishikawa *et al.*, 1981). SSPE is an example of a chronic defective CNS infection (Connolly *et al.*, 1967). The factors that turn an acute MV infection into a chronic one are as yet unknown, although various mechanisms have been postulated over the years. Geographic clustering of SSPE occurs in several countries, and there is an increased incidence in children residing in rural areas (Halsey *et al.*, 1980). These data suggest that as-yet-undefined environmental factors, most likely another infectious agent, contribute to this disease.

4.2.2 Molecular basis of CNS disease

MV is an enveloped virus with a negative sense, single stranded RNA genome and belongs to the genus Paramyxovirus, within the *Paramyxoviridae* family, order *Mononegavirales*. Its genome is composed of six genes encoding the structural proteins, three of which form the viral envelope and three the ribonucleoprotein core (Figure 2A). The nucleoprotein (N) is the major component of the ribonucleoprotein core, the other two being the large (L) polymerase and the polymerase cofactor, phosphoprotein (P). The L polymerase catalyses

the transcription and replication of the viral genome. The envelope is made up of the matrix protein (M), haemagglutinin protein (H), and fusion protein (F) (Griffin, 2006) (Figure 2A). The P gene also codes for two non-structural proteins, the C protein via an internal initiation site for translation and V via the insertion of a non-templated G nucleotide during transcription that results in a frameshift (see Figure 2B); C and V are implicated in inhibition of the host response.

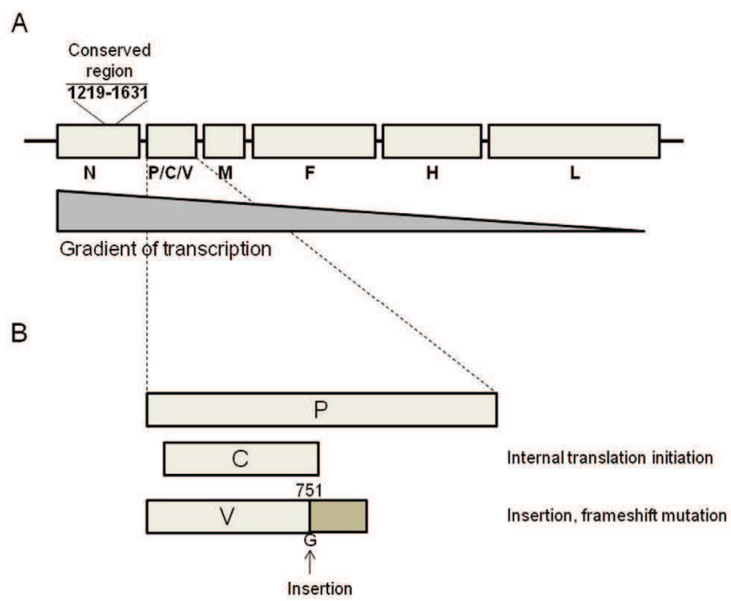

Fig. 2. Schematic diagram of the genome organisation of measles virus.
A. Schematic diagram showing the various genes. Gradient of transcription is indicated below the diagram. Conserved sequence within N gene that is used for molecular epidemiological studies to identify measles virus infection is shown.
B. The three gene products encoded by the P gene and the mechanism used to derive them. P protein is the full length gene product; C protein is translated from an internal open reading frame; V protein arises by the insertion of a non-templated G at position 751, resulting in a frameshift and a protein with a C-terminal high in cysteines

Early on it was recognised that the hyperimmune response in SSPE to MV antigens was directed against all MV proteins except the matrix (M) protein. The M gene of SSPE strains seems particularly vulnerable to mutations, affecting transcription, translation, stability, antigenicity, or function of M protein (Ayata *et al.*, 1989; Cattaneo *et al.*, 1988; Cattaneo *et al.*, 1986). cDNA cloning and sequencing of the entire M coding region established that one of the point mutations leads to a stop codon at triplet 12 of the M reading frame. It is unknown whether this defect, explaining by itself the lack of M protein, is related also to the block of M mRNA formation (Cattaneo *et al.*, 1986). Moreover, in a case of MIBE, 80% of the mutations affecting the viral M gene turned out to be uridine (U) to cytidine (C) transitions (Cattaneo *et al.*, 1988). The biased hypermutation is responsible for all but one of the missense mutations affecting the Biken M protein (a defective virus isolated from a patient with SSPE), which has a much shorter half-life *in vivo* than the M protein of the vaccine Edmonston strain. An extrinsic RNA mutational activity might alter MV RNA and gene

expression in CNS infections (Wong *et al.*, 1989). The structural alterations and instability of the protein were attributed to multiple mutations in the amino and carboxyl regions. In primary neuron cultures, the mutated M protein prevents colocalization of the viral N with membrane glycoproteins, and is associated with accumulation of nucleocapsids in cell cytoplasm and nucleus. Defects in the levels of M protein are mediated by a number of mechanisms and mutations which affect the start codon making the protein unstable, enhance proteolytic degradation or lead to the generation of nonsense mutations (Cattaneo *et al.*, 1989; Hirano *et al.*, 1993). In some cases, translation of the M protein is complicated by a transcriptional defect that leads to an almost exclusive synthesis of dicistronic P-M mRNA (Ayata *et al.*, 1998; Cattaneo *et al.*, 1987; Cattaneo *et al.*, 1986; Seto *et al.*, 1999), due to a single mutation at the P gene end (Ayata *et al.*, 2002). Some SSPE strains have mutations in the F gene that variously result in an elongated or a shortened cytoplasmic domain (Billeter *et al.*, 1994; Ning *et al.*, 2002). A single amino acid substitution in the F protein transformed the non neuropathogenic wild-type MV IC323 strain into a lethal virus similar to the SSPE Osaka-2 strain in hamsters (Ayata *et al.*, 2010).

The demyelination observed in SSPE could be the result of several mechanisms. One possible mechanism involves CSF antibodies, which are produced in an unusually high level in SSPE and have been shown to be capable of lysing brain cells cultured from SSPE patients in vitro (Fujinami & Oldstone, 1980; Oldstone *et al.*, 1975). In addition, *in vivo* studies in rat models demonstrate that anti-measles antibodies not only promote viral persistence (Rammohan *et al.*, 1981) but possibly even decrease viral replication at the transcriptional level (Liebert *et al.*, 1990). Other theories propose that during latency, viral products accumulate in neurons and oligodendroglia and eventually lead to cell death and demyelination (Ikeda *et al.*, 1995). Furthermore, infiltration by CD4+ and CD8+ T cells and the release of inflammatory cytokines such as IFN-γ and TNF-α has been demonstrated, suggesting that cell-mediated damage to infected cells may also play a role (Hofman *et al.*, 1991).

5. Opportunistic infections

One major side-effect of MV induced immune-suppression (discussed below) is the plethora of opportunistic infections that follow. Multiple complications occur, such as diarrroea, pneumonia, laryngotracheobronchitis, otitis media, stomatitis and even encephalitis when measles virus spreads to the corresponding organ. More than half of measles cases in children aged under 5 years experienced acute respiratory infection and/or diarrhoea in the 30 days following rash onset in sub-Saharan Africa (Grais *et al.*, 2007). Measles related blindness is of multifactorial aetiology. While acute measles triggers corneal ulceration through viral proliferation in the cornea, nutritional keratomalacia is often the cause of blindness in the post-measles period. Although timely use of local antibiotic therapy to the eyes and administration of vitamin A supplements offer protection to the child who already has measles, vaccination is the best way to reduce the incidence of MV related eye disease. Live attenuated measles vaccine has been found to be safe and effective in malnourished children (Bhaskaram, 1995). The most common secondary infections following measles are caused by *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Candida albicans*, *Haemophilus influenzae*, *Escherichia coli*, *Enterobacter cloacae*, and *Acinetobacter baumannii* (Yu *et al.*, 2009).

6. MV induced immune suppression

Measles is a major cause of childhood mortality in developing countries which is mainly attributed to the ability of MV to suppress general immune responses (Moss *et al.*, 2004). In most individuals, virus-specific immunity is efficiently induced and the immune response is successful, which eventually leads to clearance of MV from the host and confers long-lasting protection against re-infection. However, infection is also associated with persistence of viral RNA and development of immune-suppression, which can last up to 6 months after an acute infection (Kerdiles *et al.*, 2006b). Paradoxically, the induction of intense immune response in measles does occurs simultaneously with clinically relevant immune-suppression, a phenomenon that is not yet clearly understood. MV related immune-suppression includes loss of of delayed type hypersensitivity (DTH) responses (Garenne & Aaby, 1990; Katz, 1995) in immune individuals for several weeks following the rash, impaired proliferation of peripheral blood lymphocytes (Hirsch *et al.*, 1984) and allospecific cytotoxicity, which increases susceptibility to secondary infections while immune responses towards other pathogens are strongly impaired. This transient MV-induced immune-suppression is of important clinical significance, as it permits opportunistic infections to develop in infected children, leading to high infant morbidity and mortality (Kerdiles *et al.*, 2006b). The molecular basis for MV-induced immune-suppression is not completely understood. MV related severe immune-suppression includes both innate and adaptive immune responses and is probably caused via multiple mechanisms (Karp, 1999; Schneider-Schaulies *et al.*, 1995; Schneider-Schaulies & ter Meulen, 2002). Suppression of mitogen-induced lymphocyte proliferation can be induced by MV infection of lymphocytes or by lymphocyte exposure to a complex of the H and F surface glycoproteins without infection. Dendritic cells (DCs) are susceptible to MV infection and can transmit infection to lymphocytes. Apart from its direct effects on the immune system, MV also has indirect, longer-lasting effects on the immune system, in which the interaction between several viral proteins and the human host seems to play a role (Kerdiles *et al.*, 2006a; Kerdiles *et al.*, 2006b). MV-infected DCs are unable to stimulate a mixed lymphocyte reaction and can induce lymphocyte non-responsiveness through expression of MV glycoproteins.

Evidence of a role for many of these mechanisms was obtained *in vitro*, however, much has still to be learned about MV tissue tropism and its interactions with particular host cells such as DCs *in vivo* (Schneider-Schaulies *et al.*, 2001). Thus, multiple factors may contribute both to measles-induced immune-suppression and to the establishment of durable protective immunity. The mechanisms which contribute to the loss of the allostimulatory function of DCs include both virus release and active suppression mediated by MV-infected DCs, independent of virus production. Data from several studies suggest that carriage of MV by DCs may facilitate virus spreading to secondary lymphoid organs and that MV replication in DCs may play a central role in the general immune-suppression observed during measles. Therefore, contributions of measles virus to immune-suppression are likely multifactorial and include reduced DTH responses, T lymphocyte functional deficits, altered cytokine levels, inhibition of DC function, reduced immunoglobulin production, and inhibition of IFN-γ up-regulation of MHC-II molecules (Kerdiles *et al.*, 2006a).

Leopardi et al (Leopardi *et al.*, 1993) showed that in measles-infected monocytes, there was a 10-fold increase in the expression of MHC class II molecules. However, they

showed that MV inhibited the IFN-γ-induced effect on HLA-DR expression in a human monocytic cell line. They also showed that MV affects presentation of exogenous antigen. Thus like HIV and influenza virus, MV interferes with class II processing by suppressing the production of class II molecules or impeding antigen trafficking (Peters & Sperber, 1999).

6.1 Lymphopenia

MV immune-suppression is associated with a pronounced lymphopenia as well as decreases in neutrophils and monocytes (Okada *et al.*, 2000). Measles is associated with suppression of mitogen-induced proliferative responses and lymphocyte response to monocyte signals is suboptimal (Griffin *et al.*, 1987) in measles infection in children (Esolen *et al.*, 1993; Griffin *et al.*, 1986), and in animal models (Hahm *et al.*, 2003; Niewiesk *et al.*, 2000). Monocytes persistently infected with MV exhibit suppression of NFκB activation, which represents a potential strategy of escape from the host immune system by MV via induced immunological silencing (Indoh *et al.*, 2007).

6.1.1 T lymphocytes

It is reported that MV infection results in remarkable lymphopenia in all measles cases with reduction in cell numbers of CD4+ T cells, CD8+ T cells, B cells, neutrophils, and monocytes in circulation, increased lymphocyte activation, and increased susceptibility to cell death of lymphocytes in children (Ryon *et al.*, 2002), in young adults (Okada *et al.*, 2000; Vinante *et al.*, 1999), in cultured peripheral blood mononuclear cells (PBMC) (Salonen *et al.*, 1989), and in animal models (Hahm *et al.*, 2003). Interestingly, in Chinese adult measles patients with no vaccination history, a general decrease in CD4+ and CD8+ T cells was not observed, although there was a trend toward lower levels compared with healthy donors (Yu *et al.*, 2008). An increase in the total CD3+T cells in PBMCs of Chinese adult measles patients was reported, possibly due to expansion of a CD3+CD4-CD8- T cell subset that defines a double negative Treg phenotype (Chen *et al.*, 2004), and can inhibit immune responses by directly killing effector T cells in an Ag-specific fashion, and produce IFN-γ and TNF-α in addition to other cytokines. The lymphopenia results primarily from depletion of infected and noninfected B and T lymphocytes. Profound lymphoid depletion may also occur in the thymus, lymph nodes, and spleen. With CD4+ T cell counts dropping, host defences may be bolstered by a compensatory increase in natural killer (NK) cell activity (Okada *et al.*, 2000). Similar to other immunosuppressive viruses, MV is lymphotropic and viral nucleic acid and proteins are detectable in PBMCs. It is considered central to MV-induced immune-suppression that PBMC isolated from patients largely fail to proliferate in response to antigen specific and polyclonal stimulation. The low abundance of MV-infected PBMC suggests that MV-induced immune-suppression is not directly caused by infection-mediated cell loss or fusion, but rather by indirect mechanisms such as deregulation of cytokines or surface contact-mediated signalling which may lead to apoptosis or impair the proliferative response of uninfected PBMC. In classical measles cases, infected lymphocytes detected as a minor population during the incubation period disappeared soon after onset of rash, whereas in the cases of serious illness, the infected cells persisted longer after the rash, correlating with reduction in cell numbers of CD4+ T cells, CD8+ T cells, B cells, neutrophils, and monocytes.

6.1.2 B lymphocytes

Mc-Chesney et al. found that MV infection of B cells leads to decreased antibody production when B cells are stimulated by mitogen (Casali *et al.*, 1984; McChesney *et al.*, 1986). More recently, Ravanel et al. have shown that the N protein of MV can bind to B cells through the Fcγ receptor and inhibit immunoglobulin (Ig) synthesis (Ravanel *et al.*, 1997). In contrast, MV-infected T cells still have the ability to produce cytokines required to help uninfected B cells differentiate into plasma cells and secrete Ig (McChesney *et al.*, 1987). Lack of HLA diversity may limit the range of peptides that can be presented to T helper or T cytotoxic lymphocytes, resulting in a decreased immune response to viral infections, as in children with a cumulative effect of increasing HLA homozygosity, in which homozygosity at increasing numbers of loci results in progressively lower measles-specific antibody levels (Jacobson *et al.*, 2003).

Significant lymphopenia due to apoptosis of uninfected cells is one of the principal causes for immune-suppression induced by MV infection, and is correlated with age-dependent severity of the disease (Okada *et al.*, 2000).

6.2 Modulation of T cell response

The initial T-cell response includes CD8+ and Th1 CD4+ T cells important for control of infectious virus. As viral RNA persists, there is a shift to a Th2 CD4+ T-cell response that likely promotes B-cell maturation and durable antibody responses but may suppress macrophage activation and Th1 responses to new infections. Type 2 polarisation of cytokine responses with an increase in the production of interleukin 4 (IL-4) and decrease in IL-2 and IFN-γ occurs during late stages of measles (Griffin & Ward, 1993). Production of the pro-inflammatory cytokine IL-12 is markedly suppressed in measles, providing a unifying mechanism for many of the immunological abnormalities associated with measles infection (Atabani *et al.*, 2001).

The principal players in the early nonspecific immune response are interferon α/β (IFN-α/β) induction, complement activation, natural killer cell (NK) and macrophage activation, and IFN-γ and interleukin-12 (IL-12) production. Although MV infection of cell lines *in vitro* has been shown to induce IFN (Volckaert-Vervliet & Billiau, 1977), the results with wild-type MV infection *in vivo* are conflicting and inconclusive. Active IFN-α/β has been documented *in vivo* after natural infection by MV in one study and shown to be absent in another (Crespi *et al.*, 1988; Shiozawa *et al.*, 1988; Tilles *et al.*, 1987). Levels of serum IFN and of the IFN-inducible oligoadenylate-synthetase (2-5OAS) gene transcript have been shown to rise after MV immunization with the live attenuated vaccine (Tilles *et al.*, 1987). With regard to other innate defence mechanisms, MV does not appear to hamper either complement activation *in vitro* or IFN-γ production *in vivo* (Patrick Sissons *et al.*, 1979). However, MV has been shown to depress IL-12 synthesis *in vitro* and to dampen NK cell activity *in vivo* (Griffin *et al.*, 1990b; Karp *et al.*, 1996). In addition to their antiviral function, IFN-α/β have potent effects in regulating specific immune response. They are thought to enhance differentiation of dendritic antigen-presenting cells and to contribute to prolonging T-lymphocyte lifespan (Luft *et al.*, 1998; Marrack *et al.*, 1999).

Viruses have evolved mechanisms to counter the antiviral effects of IFN or, in some cases, to suppress its production. Resistance to the antiviral effects of IFN is mediated by active inhibition of IFN-inducible gene function. IFN-resistant and -sensitive strains of MV can be isolated by cell culture, and it has been suggested that IFN-resistant strains of MV can

contribute to the establishment of persistent infection of the CNS (Carrigan & Knox, 1990). This is relevant to the rare cases of persistent MV infection of the CNS giving rise to SSPE. It is not known which MV products contribute to IFN resistance, but studies in the closely related Sendai virus have shown that the nonstructural C protein counteracts the IFN-mediated antiviral state (Garcin *et al.*, 1999). MV infection *in vitro* has been shown to depress IL-12 production in both macrophages and DCs (Fugier-Vivier *et al.*, 1997). Macrophages, DCs, epithelial cells, and NK cells provide the initial sources of IFN-α/β, IL-12, and IFN-γ. MV may have established a redundancy of mechanisms to slow the innate immune response to allow early dissemination.

6.3 Cytokines in measles

Despite chemokines directing the migration of T cells to infected neurons, chemokine neutralization revealed that migration is not required for viral clearance, suggesting a cytokine-mediated antiviral mechanism. An increase in IFN-γ in MV-infected children compared with healthy controls has been observed in other studies and it may serve to inhibit viral growth and limit the spread of infection (Griffin *et al.*, 1990a). Children with measles display a transient increase in both IL-2 and IFN-γ, lasting for a few days following rash (Griffin & Ward, 1993; Ryon *et al.*, 2002), followed by sustained IL-4 production (Ryon *et al.*, 2002). A similar response was observed when a clinical isolate of MV was used to infect PBMCs (Dhiman *et al.*, 2005b). In contrast, adult patients demonstrate a sustained increase of IFN-γ and poor IL-4 secretion; an early IL-4 gene induction that was not reflected in protein secretion may be due to uptake of secreted IL-4 by cells, and does not necessarily reflect lack of protein production. Similar findings have been reported in a study where PBMCs from previously immunized adults were infected with MV. All subjects produced IFN-γ, and in subjects who produced both IFN-γ and IL-4, maximal IFN-γ production *in vitro* always greatly exceeded that of IL-4 (Dhiman *et al.*, 2005b). In Zambian children plasma IL-5 levels were lower in patients compared with controls (Ryon *et al.*, 2002). In contrast, a significant upregulation of IL-5 mRNA has been reported among seropositive adult donors after vaccination (Li *et al.*, 2001). The role of IL-5 in MV infection is not clear and data may be complicated by the underlying allergic status of the subjects.

Sustained high levels of IL-10 during convalescence suggest a role for this immunoregulatory cytokine in MV-induced immune-suppression. Plasma levels of IL-10 remain elevated for weeks in children with MV infection (Ryon *et al.*, 2002). The increased IL-10 levels may also be implicated in the decrease in IL-5 expression, because IL-10 is known to inhibit IL-5 production by T cells and in mouse models of allergic disease (Staples *et al.*, 2000). IL-10 has been shown to display a range of immune suppressive effects, including inhibition of APC function, induction of anergy, differentiation of Treg, and control of the expansion of other T cell populations (Kingsley *et al.*, 2002), and may be key to the observed decrease in monocyte/macrophages and innate immune responses observed in MV infection.

In brain tissue, IFN-γ is both necessary and sufficient to clear MV. Secretion of IFN-γ is stimulated by IL-12 in the brain, as neutralization of IL-12 results in loss of antiviral activity and stimulation of leukocytes with IL-12/IL-18 enhances their immune effector function of viral clearance. The IFN-γ signal is transduced within brain explants tissue by the Jak/STAT signalling pathway, as inhibition of Jak kinases results in a loss of antiviral activity driven by either brain-derived leukocytes or recombinant IFN-γ. These results reveal that primed T

cells directly act to clear MV infection of the brain by using a noncytolytic IL-12- and IFN-γ-dependent mechanism in the CNS and that this mechanism relies upon Jak/STAT signalling.

6.4 Effects on DC function

As sensitisers of pathogen encounter and instructors of the adaptive immune response, DCs may play a decisive role in the induction and quality of the MV-specific immune activation. The ability of MV wild-type strains in particular, to infect DCs *in vitro* via the receptor binding H protein is clearly established. DC maturation is induced early after MV infection and is likely to be of crucial importance for the induction of MV-specific immunity. Several *in vitro* studies have demonstrated that MV infection of human DCs affects their phenotype and functions. Different types of DCs including Langerhans cells (Grosjean *et al.*, 1997), peripheral blood DCs (Schnorr *et al.*, 1997), CD34+-derived DCs (Grosjean *et al.*, 1997) and monocyte-derived DCs (Fugier-Vivier *et al.*, 1997) are permissive to MV infection. Viral infection induces formation of DC syncytia, followed by the loss of DC capacity to stimulate naive CD4+T cells (Fugier-Vivier *et al.*, 1997; Grosjean *et al.*, 1997) and acquisition of an active inhibitory function on CD4+ T cell proliferation in response to allogeneic noninfected DC (Grosjean *et al.*, 1997) or mitogens (Schnorr *et al.*, 1997). Inhibition of T-cell functions could be mediated through either transmission of infectious virus to T cells, leading to a block in the cell cycle (Naniche *et al.*, 1999) and/or delivery of inhibitory signals via infected DCs (Grosjean *et al.*, 1997). MV infection was shown to enhance apoptosis of DCs and to inhibit their CD40 ligand dependent terminal differentiation (Servet-Delprat *et al.*, 2000; 2000b). In addition, it induced cytotoxic activity by activation of the TNF-related apoptosis-inducing ligand (TRAIL) synthesis in DC and monocytes (Vidalain *et al.*, 2000). Although the infection of DCs is an attractive hypothesis to explain MV-induced immune-suppression, direct evidence for the presence of MV-infected DCs in children during measles remains to be demonstrated. Analysis of the presence of MV-infection in different cells of the immune system during measles suggests that the major mechanism for the induction of immune-suppression may not be a direct effect of virus replication in these cells. In fact, despite the small amount of virus-infected peripheral blood cells during measles (less than 1%), the severe suppression of the immune system can last for weeks (Borrow & Oldstone, 1995). Moreover, a number of immunological alterations during natural measles also occur to a lesser magnitude after vaccination with attenuated MV (Fireman *et al.*, 1969; Hussey *et al.*, 1996). Therefore, it is likely that MV-induced immune-suppression is induced not only by direct viral replication in haematopoıetic cells, but also by indirect immunopathogenic mechanisms. Indeed, numerous recent studies indicate that MV proteins are sufficient to induce different aspects of MV-induced immune-suppression (Marie *et al.*, 2001; Ravanel *et al.*, 1997; Schlender *et al.*, 1996).

6.5 Type I interferons in measles

MV infection of cell lines *in vitro* has been shown to induce IFNα/β (Volckaert-Vervliet & Billiau, 1977), the results concerning wild-type MV infection *in vivo* are conflicting and inconclusive. Active IFNα/β have been documented *in vivo* after natural infection by MV in one study and shown to be absent in another (Crespi *et al.*, 1988; Shiozawa *et al.*, 1988; Tilles *et al.*, 1987). IFNα/β induction by MV is probably dependant on passage history of the virus

and the cell type tested (Naniche *et al.*, 2000; Volckaert-Vervliet & Billiau, 1977; Volckaert-Vervliet *et al.*, 1978). Recent studies suggest that wild type MV isolates actively inhibit IFN synthesis and induce poor production of IFNα/β while the laboratory adapted and vaccine strains are potent stimulators (Yu, et al., 2008). Recombinant MV with defective V protein can grow in cell lines that do not produce IFN (Niewiesk *et al.*, 1997), *in vivo* studies demonstrate an important role of the V proteins as virulence factors (Patterson, 2000), and analysis of thymic xenografts revealed that V-deficient virus replication was delayed compared to that of wild-type or V-over-producing viruses (Valsamakis, 1998). MV V protein is capable of inducing cytokine inhibition by causing a defective IFN-induced STAT nuclear accumulation and nuclear redistribution, probably linking innate immune evasion to adaptive immune suppression by MV (Palosaari, 2003). MV C protein has also been shown to be a virulence factor (Escoffier *et al.*, 1999; Mrkic *et al.*, 2000; Patterson, 2000; Valsamakis, 1998) and to bind to the IFNα/β receptor (Yokota *et al.*, 2003); MV C protein inhibited the production of IFNα/β and IFNα/β signalling (Shaffer *et al.*, 2003). IFN-resistant and -sensitive strains of MV can be isolated by cell culture, and it has been suggested that IFN-resistant strains of MV may contribute to the establishment of persistent infection of the CNS (Carrigan & Knox, 1990). Systemic dissemination of C- and V-defective MVs is strongly impaired and upon intra- cerebral inoculation these viruses cause lethal disease less often than the parental strain. The attenuated candidate recombinant MV vaccine strains, which include C- and V-protein-defective viruses still replicate in animals at levels that are high enough to efficiently induce immunity and IFNα/β (Radecke and Billeter, 1996). Furthermore, robust production of IFNα in human myeloid DCs and epithelial cells was associated with increase in the level of virus-specific defective interfering RNA (DI RNA), subviral replicons originating from the viral genome associated with many RNA viruses (Lazzarini *et al.*, 1981). Wild type MV isolates contain undetectable levels of DI RNA and induce significantly lower production of IFN in mDCs.

6.6 Suppression of IL-12

IL-12 production by antigen-presenting cells is central to the orchestration of both innate and acquired cell-mediated immune responses to many pathogens. However, MV has been shown to depress IL-12 synthesis *in vitro* and to dampen NK cell activity *in vivo* (Griffin *et al.*, 1990b; Karp *et al.*, 1996). Production of IL-12 from DCs is also suppressed by MV (Karp *et al.*, 1998). The ability of MV to specifically ablate monocyte/macrophage and DC secretion of IL-12 provides a potentially unifying mechanism for many of the immunological abnormalities associated with MV infection. Specifically, (a) ablation of IL-12 activity, by antibodies or genetic deletion, compromises the ability to respond to a variety of infections; (b) DTH responses depend upon IL-12 production; (c) IL-12 stimulates NK activity; and (d) IL-12 is essential for the development as well as the expression of most Th1 responses. IL-12 failure may thus explain the propensity for developing superinfection, the absence of DTH reactivity, the meager NK cell activity, and the Th2 deviation in cytokine profiles seen in the aftermath of measles. IL-12 suppression would not explain lymphoproliferative defects, however. Although IL-12 is co-mitogenic for activated T and NK cells, it is not necessary for the proliferation of such cells. Interestingly, cytotoxic T cell and overall antibody responses develop normally in IL-12 knockout mice indicating that IL-12 suppression need not hinder the development of an effective anti-MV response.

Importantly, IL-12 production is significantly suppressed during natural infection of children with MV, with suppression lasting for weeks after acute presentation with measles (Karp & Wills-Karp, 2001).

The degree to which IFN-α/β induction and IL-12 synthesis are disrupted by MV may determine the virulence of a particular strain. Such virulent measles strains could thus replicate more efficiently and gain access more rapidly to the bone marrow and, on rare occasions, to the CNS. These hypotheses are based on *in vitro* studies and further studies in existing monkey models (Auwaerter *et al.*, 1999; McChesney *et al.*, 1997) are needed to determine if the pathogenesis of infection *in vivo* mirrors the *in vitro* observations presented.

7. Implications for treatment

Vitamin A treatment for children with measles in developing countries has been associated with a marked reduction in morbidity and mortality. The WHO recommends vitamin A administration to all children with measles in communities where vitamin A deficiency is a recognized problem and where the MV-related mortality rate exceeds 1%. Of note, low serum concentrations of vitamin A are found in children with severe measles in USA. Thus, supplemental vitamin A in patients aged 6 months to 2 years who are hospitalized with measles and its complications (e.g., croup, pneumonia, diarrhoea) should be considered (D'Souza & D'Souza, 2002a; b; Hussey & Klein, 1993; Markowitz *et al.*, 1989).

MV is susceptible to ribavirin *in vitro*. Although ribavirin (either intravenous (IV) or aerosolized) has been used to treat severely affected and immunocompromised adults with acute measles or SSPE (IV plus intrathecal high-dose IFNα) (Gururangan *et al.*, 1990), no controlled trials have been conducted; ribavirin is not approved by the US Food and Drug Administration (FDA) for this indication, and such use should be considered experimental.

For immunocompromised persons, immune globulins (IG) are indicated to prevent measles following exposure. If immediate protection against measles is required for immunocompromised persons with contraindications to measles vaccination, including exposed infants less than 1 year of age, passive immunization with IG, 0.5 mL/kg of body weight (maximum dose = 15 mL), should be administered intramuscularly as soon as possible after exposure. Exposed symptomatic HIV-infected and other severely immunocompromised persons should receive IG regardless of their previous vaccination status (recommended dose is 0.5 mL/kg of body weight if IG is administered intramuscularly; maximum dose = 15 mL), because measles vaccine may not be effective in such patients and the disease may be severe. Intramuscular IG may not be necessary if an HIV patient is receiving 100-400 mg/kg IGIV at regular intervals and the last dose was administered within 3 weeks of exposure to measles. Because the amounts of protein administered are similar, high-dose IGIV may be as effective as IG administered intramuscularly. However, no data are available concerning the effectiveness of IGIV in preventing measles. For immunocompromised persons receiving IG for measles prophylaxis, measles vaccination should be delayed for 6 months following IG administration. For persons receiving IG for replacement of humoral immune deficiencies (320 mg/kg intravenously), measles vaccination should be delayed until 8 months following IG administration (CDC, 1993).

8. Future perspectives

Huge strides have been made in reduction of measles incidence in most parts of the world following WHO global eradication programme, with several countries having interrupted the circulation of endemic virus. Unfortunately, the situation is different in the poorer developing and emerging nations, with high measles prevalence, low vaccine coverage and 500,000 childhood deaths annually. Within the Western Pacific region, of which China and Australia are a part, many countries have achieved success in controlling measles infections; but China and Japan still report localised outbreaks that seem to differ in frequency and in character between the developed and under-developed (poor) regions. A region specific vaccination programme is required to achieve control of the endemically circulating MV in China.

Measles infection very often induces characteristic immune-suppression that can extend for weeks following the acute disease, resulting in potentially fatal opportunistic infections. Despite intense research over the years, the mechanisms of MV induced immune-suppression are not completely defined; it is probably very complex with several mechanisms encompassing both the innate and adaptive responses being involved. The situation is further complicated by the fact that the mechanisms that are known are variably affected in different populations. The best characterised immunological change is the severe lymphopenia following MV infection. Immunosuppressive factors, e.g. IL-10 and suppressive cells, e.g. Treg have been shown to be elevated after acute MV infection in separate studies and may play major roles in causing immune-suppression. In various studies, a role for DCs, IL-12, and type I IFNs has been suggested. To date there is no unifying "model" of immune-suppression to connect all the findings. Additionally, as most studies have been performed in cell culture, it is not clear how many of the immunological findings can be directly co-related to natural infection. Success of the global measles vaccination programs has resulted in very rare occurrences of natural measles in developed nations. Clearly, investigations in the non-human primate model of measles are needed to better elucidate MV induced immune-suppression.

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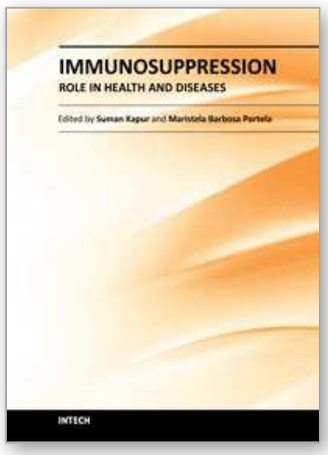

Immunosuppression - Role in Health and Diseases
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A need for a book on immunology which primarily focuses on the needs of medical and clinical research students was recognized. This book, "Immunosuppression - Role in Health and Diseases" is relatively short and contains topics relevant to the understanding of human immune system and its role in health and diseases. Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Therapeutic immunosuppression has applications in clinical medicine, ranging from prevention and treatment of organ/bone marrow transplant rejection, management of autoimmune and inflammatory disorders. It brings important developments both in the field of molecular mechanisms involved and active therapeutic approaches employed for immunosuppression in various human disease conditions. There was a need to bring this information together in a single volume, as much of the recent developments are dispersed throughout biomedical literature, largely in specialized journals. This book will serve well the practicing physicians, surgeons and biomedical scientists as it provides an insight into various approaches to immunosuppression and reviews current developments in each area.

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