Monkeys in Measles Research

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1 Introduction

The identification of measles virus (MV) as the causative agent of measles was first described in 1911, when filtered respiratory tract secretions of measles patients were inoculated into macaque monkeys causing measles-like symptoms in these animals (Goldberger and Anderson 1911). It was not until 1954 that the virus could be isolated and adapted to growth in vitro in several cell lines of primate and nonprimate origin (Enders and Peebles 1954; Ruckle and Rogers 1957; Katz et al. 1958; Enders 1962). This provided the basis for extensive biological research on the pathogenicity of MV and led to diagnostic methods for measles and eventually to the development of measles vaccines (Katz and Enders 1959; Enders et al. 1960; Katz 1965). Apart from humans, nonhuman primates proved susceptible animal species for MV infection, either by contracting the infection from humans during captivity or by experimental infection with different clinical specimens. Although marmosets, macaques and several other monkey species have been used in studies concerning the host range and the virulence of different

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strains of MV, macaque species have been studied most extensively. It has been shown that the pathogenesis of MV infection in macaques is similar to that of measles in humans.

Besides different primate species, also rodents (hamster, rat, mice) can be infected experimentally with MV. However, replication of MV in rodents is largely restricted to neuroadapted strains of the virus and to the central nervous system (CNS) of the animals (INAGAWA and ADAMS 1958; WAKSMAN et al. 1962; BURNSTEIN et al. 1964; MATUMOTO et al. 1964; JANDA et al. 1971; GRIFFIN et al. 1974; HERNDON et al. 1975, NEIGHBOUR et al. 1978; CHAN 1985; CARRIGAN 1986; CARRIGAN and KABAKOFF 1987; OHUCHI et al. 1984, 1986; LIEBERT and TER MEULEN 1987; LIEBERT et al. 1988). Therefore, the rodent model may be of special interest to study the pathogenesis of infections with different MV strains, the regulation of viral gene expression, and the contribution of B and T cell mediated immune responses to protection from CNS infection (DRILLIEN et al. 1988; DE VRIES et al. 1988; MALVOISIN and WILD 1990; BANKAMP et al. 1991; BRINCKMANN et al. 1991; NIEWIESK et al. 1993). The selective replication of MV in the CNS also implicates the limitations of the rodent models, since the CNS is rarely involved in clinical manifestations of MV infection of humans.

One of the priorities in MV research is the development of a suitable animal model which may provide more insight into the pathogenesis of measles, the induction of humoral and cellular immune responses and molecular correlates of virus attenuation. Moreover, a suitable animal model will offer the opportunity to evaluate the efficacy and safety of novel generations of measles vaccines and novel vaccination strategies. In this chapter, we review the present knowledge concerning the pathogenesis of MV infection and immune defense mechanisms underlying the disease in monkeys.

2 Pathogenicity of Measles Virus in Monkeys

2.1 Introduction

Following the most early transfer experiments of measles from humans to monkeys (JOSIAS 1898; GOLDBERGER and ANDERSON 1911), blood or throat washings obtained from measles patients were repeatedly transferred to macaque monkeys to confirm the etiology of the disease and to establish a model for measles. Though the response was extremely variable and only observed in part of the inoculated animals, the most frequently occurring clinical signs reported were exanthema and fever (LUCAS and PRIZER 1912; BLAKE and TRASK 1921; DEGWITZ 1927; KRAFT 1932; PLOTZ 1938; HURST and Cooke 1941; SCHAFFER et al. 1941).

After the successful isolation and propagation of MV in vitro (ENDERS and PEEBLES 1954), inoculation experiments were continued in rhesus (Macaca mulatta), cynomolgus (Macaca fascicularis) and in baboon (Papio hamadryas and P. hybridus) monkeys. In these studies not only clinical specimens were used,
but also defined strains of MV (Peebles et al. 1957; Enders et al. 1960; Sergiev et al. 1960; Yamanouchi et al. 1970, 1973; Albrecht et al. 1972, 1977a; Sakaguchi et al. 1986; Kobune et al. 1990; Van Binnendijk et al. 1994). In most of these experiments, clinical manifestations of measles were not observed or the observed symptoms were restricted to mild fever, slight leukopenia and mild respiratory symptoms, although symptoms more characteristic for measles such as conjunctivitis and maculopapular rashes have been reported occasionally (Peebles et al. 1957; Sergiev et al. 1960; Kobune et al. 1990). However, the susceptibility of many monkey species to a variety of MV strains and the close similarity between measles pathogenesis in humans and macaque monkeys were unequivocally demonstrated by a variety of other observations. These included; (1) the presence of viral antigen and multinucleated giant cells of the reticular type in lymphoid organs and in epithelial tissues including the trachea and skin of killed animals (Taniguchi et al. 1954; Sergiev et al. 1960; Nii et al. 1964; Ono et al. 1970; Yamanouchi et al. 1970, 1973; Hall et al. 1971; Sakaguchi et al. 1986; Kobune et al. 1990); (2) the development of a disseminated MV infection in lung macrophages, epithelial cells of the pharynx and in peripheral blood mononuclear cells (PBMCs) during the first 2 weeks of infection (Peebles et al. 1957; Hicks et al. 1977; Van Binnendijk et al. 1994); and (3) the appearance and persistence if virus-specific serum antibodies shortly after the peak of viremia (Enders et al. 1960; Van Binnendijk et al. 1994).

2.2 Outbreaks of Measles in Monkey Colonies

Neither cynomolgus nor rhesus monkeys are infected with MV in their natural environment but they are often exposed to this infection when captured (Peebles et al. 1957; Habermann and Williams 1957; Meyer et al. 1962; Potkay et al. 1966; Shishido 1966; Hall et al. 1971; Remfry 1976; Welshman 1989). Previously it has been described that measles can spread rapidly through a captive population (Meyer et al. 1962; Shishido 1966; Welshman 1989). Only in part of the population could clinical signs be observed, in some cases associated with the development of a maculopapular rash and conjunctivitis (Peebles et al. 1957; Potkay et al. 1966; Hall et al. 1971; Remfry 1976; Welshman 1989). However, in all animals studied, the presence of multinucleated giant cells in skin lesions and in lymphoid organs and the appearance of MV-specific hemagglutination-inhibiting serum antibodies confirmed the etiology of the disease and the spread of virus through the whole population within 3 weeks of captivity (Meyer et al. 1962; Shishido 1966; Potkay et al. 1966; Yamanouchi et al. 1969; Hall et al. 1971; Welshman 1989). Substantial evidence for the contagiousness of measles among monkeys came from experimentally infected marmosets (Saguinus mystax and Saguinus labiatus). Animals infected with two wild-type strains of MV (JM and Edmonston) were capable of rapidly spreading the virus to separately housed MV-seronegative control animals by aerosol, which is also the main mechanism of transmission in humans (Lorenz and Albrecht 1980).
Epizootics of measles in monkeys during captivity are not restricted to marmosets and macaques. Outbreaks of measles have been reported in colobus monkeys (*Colobus guereza*), in which the majority of pathological and clinical symptoms were similar to the disease in macaques, except for the absence of rashes and Koplik spots (Himes and Keymer 1975). From these colobus monkeys virus could also be isolated and neutralized by MV-specific human and macaque antisera (Scott and Keymer 1975). Other examples of nonhuman primate species susceptible to measles during captivity are spider monkeys (*Ateles Spp*), talapoin (*Cercopithecus talapoin*) and chimpanzees (*Pan troglodytes*). Although these latter species often lack the more typical clinical signs of the disease, the occurrence of MV infections have been recognized by the appearance of specific serum antibodies and the presence of multinucleated giant cells in the lungs of fatal cases (MacArthur et al. 1979).

### 2.3 Experimental Measles Virus Infections in Monkeys

Peebles et al. (1957) and Enders et al. (1960) were the first to study experimentally infected monkeys in detail. They infected nine MV-seronegative cynomolgus monkeys by the intranasal and intravenous route with the virulent MV Edmonston strain that had been passaged in human kidney cells. While only four animals developed maculopapular rashes, viremia could be detected in blood specimens of eight animals between days 7 and 11 postinoculation. Adaptation of the virulent MV Edmonston strain by passaging of the virus through chicken embryos in vivo and through chicken embryo cell cultures in vitro resulted in the first preparation of attenuated measles vaccines (Milovanovic et al. 1957; Katz et al. 1958). Infection of monkeys with these attenuated MV strains by either a combined intravenous-intranasal, a combined intracerebral-intracisternal or a subcutaneous route of inoculation appeared to be clinically silent and did not cause a detectable viremia. However, virus could be recovered from the nasal secretions of a number of animals that were infected by the subcutaneous route. Challenge experiments demonstrated that all immunized animals were protected against a subsequent combined intranasal-intravenous infection with the virulent MV Edmonston strain. Though local virus replication still occurred in the upper respiratory tract of these animals after challenge, clinical symptoms were absent and a systemic viremia was not observed (Enders et al. 1960). The initial infection experiments in a primate model provided a basis for attenuated MV strains to be used as safe and effective measles vaccines. Also, it was reassuring that the intracerebral inoculation of monkeys with attenuated strains of MV never elicited neuronal complications commonly associated with acute measles in humans (Enders et al. 1960; Albrecht et al. 1981).

Recently, we and others have infected cynomolgus monkeys with wild-type RVs isolated and propagated in Epstein-Barr virus (EBV)-transformed marmoset and human B lymphoblastoid cell lines (B-LCLs). These cell lines proved to be very sensitive indicator cells for the detection of RVs in clinical specimens of both
humans and monkeys and in this way virulence for cynomolgus monkeys proved to be preserved (Kobune et al. 1990; van Binnendijk et al. 1994). Though the results of these experiments were in principal comparable to those published earlier by Peebles et al. (1957) and by Enders et al. (1960), monkeys showed a higher susceptibility to these wild-type MV isolates. A more extensive replication of the virus in PBMCs and lung macrophages and a more widely distributed giant cell formation in the lymphoid tissues were observed when compared to infections with other laboratory and attenuated strains of MV (Yamamoto et al. 1970; Kobune et al. 1990; Van Binnendijk et al. 1994). In contrast to the findings of Peebles et al. (1957), we were also able to detect a measles viremia in monkeys immunized with standard doses of an attenuated (Schwartz) measles vaccine. This may be related to the use of a more sensitive detection based on human B-LCLs rather than other continuous cell lines for virus isolation (van Binnendijk et al. 1994). Therefore it may be speculated that the virulence of wild-type MVs and their pathogenesis in monkeys may parallel the human situation, but may be strongly dependent on the strain and in vitro passage history of the MV strain used.

2.4 Encephalitogenicity of Measles Virus in Marmosets and Macaques

Whereas measles in macaques can be depicted as a rather mild disease with a normal measles-like pathogenesis, aberrant and fatal measles has been reported in a colony of marmosets, causing hundreds of animals to die within a period of several months. The disease was caused by a MV strain which could be isolated from moribund animals. Many of the animals showed drooping, puffy upper eyelids and mucous nasal discharge prior to a progressive lethargy. Typical measles skin reactions were almost never part of the symptoms. The most characteristic histopathological finding was an interstitial pneumonitis with giant cell formation (Levy and Mirkovic 1971). Lorenz and Albrecht (1980) and Albrecht et al. (1980, 1981) corroborated these findings, showing widespread MV infections in the respiratory, gastrointestinal and other visceral tissues of marmosets of the Saguinus mystax subspecies when these animals were experimentally infected with a wild-type strain of MV (JM) by the respiratory route. Clinical signs and gross pathological findings lacked the characteristic features of measles and most of the infected animals died within 2 weeks due to a widespread gastroenterocolitis (Albrecht et al. 1980). As animals previously vaccinated with inactivated measles vaccines not only survived these infections but developed high titers of MV-specific antibody as well (Lorenz and Albrecht 1980; Albrecht et al. 1980), a primary deficiency in lymphocyte function has been implicated in what are probably the most virulent MV infections reported in monkeys.

The CNS of monkeys is rarely involved after parenterally administered MVs (Enders et al. 1960; Albrecht et al. 1980). However, marmosets infected intracerebrally with either of two wild-type strains of MV (JM and Edmonston), but not with attenuated measles vaccine, developed encephalitis in the absence of other
clinical symptoms (Albrecht et al. 1981). The Edmonston strain was found to be considerably more neurotropic in these animals than the JM strain, causing perivascular cuffs, proliferation of glial cells, multinucleated giant cells and inflammatory response in brain tissues. Most of the animals inoculated with the JM strain showed a milder brain disease but died of the visceral form of measles infection (Albrecht et al. 1980) as was also reported after the parenteral administration of the JM strain (Albrecht et al. 1981). Marmosets thus seem to be a very sensitive indicator of the viscerotropic and neurotropic properties of wild-type and attenuated MVs. However, due to the lack of characteristic features of measles and the postulated immune dysfunction, the use of these animals seems less satisfactory for studies concerning MV pathogenesis and immune responses involved in recovery and protection from the natural disease.

Similar infection experiments carried out with the same wild-type strains and attenuated strains of MV in macaque monkeys did not result in measles encephalitis (Enders et al. 1960; Albrecht et al. 1972). However, intracerebral inoculation of rhesus monkeys with a hamster brain-adapted subacute sclerosing panencephalitis (SSPE) strain resulted in a chronic, progressive encephalitis, resembling characteristic features of SSPE in humans (Albrecht et al. 1972, 1977a). Interestingly, the disease ran a subacute or chronic course only in animals with preexisting immunity and was most vigorously induced with the virus passed through monkey brain. Clinical disease was characterized by ataxia, lethargy and weakness prior to coma, and accompanied by extremely high antibody titers in serum and cerebrospinal fluid which were comparable to those found in SSPE. The striking similarities of the brain disease in monkeys with SSPE may make primates suitable model for studies concerning the mechanisms of SSPE and possible therapeutic approaches for this disease (Albrecht et al. 1977a).

3 Measles Virus-Specific Immunity in Monkeys

3.1 Introduction

Recovery of humans from measles and the subsequent protection against reinfection in humans may depend on virus-neutralizing antibody and virus-specific cell mediated immune responses. Shortly after the onset of the maculopapular rash, which is a hallmark for the development of cell-mediated immune response, MV-neutralizing antibody can be detected in the circulation. The appearance of neutralizing serum antibodies and the protective effect of passively transferred MV-specific antibody preparations to children for measles prophylaxis, demonstrates the importance of antibody-mediated immune response in the protection from MV infection (reviewed by Norrby and Oxman 1990). Passive transfer of polyclonal or monoclonal MV-neutralizing antibodies directed against either of the two MV glycoproteins, the hemagglutinin (H) and fusion (F) proteins
proved to be effective in protecting naive mice and Lewis rats against MV-induced encephalitis (GIRAUDON and WILD 1985; SATO et al. 1989; MALVOISIN and WILD 1990). However, most agammaglobulinemic children seem to develop the normal clinical symptoms after MV infection and to develop protective immunity to reinfection. In contrast, children with functional T cell deficiencies often develop a fatal giant cell pneumonia after infection with MV (GOOD and ZAK 1956; MITUS et al. 1959; BURNET 1968). These observations suggest that cell-mediated immunity, probably in combination with neutralizing antibody, plays a major role in the control of MV infections rather than a unique role for antibody-mediated immune response. Although the transient immunosuppression associated with measles (reviewed by McCHESNEY and OLDSTONE 1989) has initially hampered the investigation of MV-specific cell mediated immunity, recent studies have evaluated the kinetics and role of MV-specific cellular cytotoxic T lymphocytes (CTLs) (reviewed by UYTDEHAAG et al. 1993). From these studies, it was concluded that CTLs of the CD8 rather than of the CD4 phenotype are involved in the clearance of virus infected cells and in recovery from measles, T cells of both phenotypes may function as memory cells in maintaining life-long protection against measles in immune individuals (KRETH et al. 1979; LUCAS et al. 1982; JACOBSON et al. 1984, 1987; VAN BINNENDIJK et al. 1989, 1990). It has been shown that passive transfer of MV-specific CD4+ and CD8+ T cell lines to naive mice and Lewis rats protect them from MV-induced encephalitis (BANKAMP et al. 1991; BRINCKMANN et al. 1991). It is not clear, whether the transferred T cell directly functioned as CTLs in these models. NIEWIESK et al. (1993) have clearly demonstrated that the occurrence of an MV-induced encephalitis correlated with an inefficient induction of MV-specific CD8+ T Cells.

### 3.2 The Immunosuppressive Effects of Measles in Monkeys

MV infection in human is known to exert a transient immunosuppression. It has been suggested that the suppression of T cell mediated lymphoproliferation and antibody production by B lymphocytes to a number of stimulating mitogens and antigens are a direct result of virus replication in these cells during the acute stage of the disease (reviewed by McCHESNEY and OLDSTONE 1989). An as yet unknown autocrine mechanism may be responsible for the observed inhibition, as the effector functions of these cells are dramatically impaired only when they are infected prior to their differentiation. During an outbreak of measles at a primate research center MV was detected in the PBMCs of infected rhesus monkeys. In these monkeys, pokeweed mitogen (PWM)-driven IgM and IgG synthesis was markedly reduced when compared to uninfected control animals. Immunoglobulin secretion was still reduced several months after infection but returned to normal levels within 1 year (McCHESNEY et al. 1989). An enhanced mitogenic response was actually seen shortly after infection, when measles viremia and a marked leukopenia were also reported. Thus MV infection may not disseminate as rapidly through lymphocytes in vivo as it does under in vitro conditions and may
rather activate certain populations of lymphocytes or even alter the circulatory pattern of lymphocytes shortly after infection (Hicks et al. 1977).

Recently, Contreras and Furesz (1992) described the immunosuppressive effects of MV infections on the outcome of the neurovirulence test for oral poliovirus vaccines in a colony of macaques in Canada. Although the origin and history of the MV infections were unknown, the prevalence and increase of high titers of specific serum antibody in these monkeys, which also paralleled the increase in the prevalence of measles in the population of Ontario, highly correlated with a more pronounced severity of poliomyelitis. Taken together, these observations indicate that the mechanisms of MV-induced immunosuppression in humans and macaque monkeys are similar.

3.3 Measles Virus Specific Annses in Macaques

As stated above, it is most likely that both virus-neutralizing antibody and virus-specific CTLs contribute to virus clearance after MV infection and to protective immunity in monkeys. Moreover, successful protection against MV infection induced by immunization with live attenuated measles vaccines may depend on the same immune mechanisms. However, further studies are necessary to define the specific contribution of individual components of the immune system. Since macaques develop clinical signs and a pathogenesis of MV infections similar to measles in humans, they may provide a suitable animal model to study protective immune responses elicited by either vaccination or MV infection and to evaluate the efficacy and safety of measles vaccines.

Epizootics of measles in captive populations of macaque monkeys were always accompanied by the appearance of MV-specific serum antibodies, closely resembling the kinetics of antibody responses after acute measles in humans. The persistence of specific serum antibodies in monkeys after infection may also be part of the protective immune response as no subsequent reinfecions have been reported in the infected populations (Peebles et al. 1957; Meyer et al. 1962; Potkay et al. 1966; Shishido 1966; Hall et al. 1971; Rempfry 1976; Welshman 1989).

Other investigators have reported similar types of MV-specific antibody responses in macaques after the administration of different strains of virulent MV, attenuated measles vaccines and inactivated MV preparations. Strong virus-neutralizing, complement-fixing and hemagglutination-inhibiting antibody responses were detected in the sera of monkeys 1-5 weeks after immunization, which declined to persistent levels over a period of 3 years (Peebles et al. 1957; Enders et al. 1960; Yamanouchi et al. 1969; Hicks and Albrecht 1976; MacArthur et al. 1982; De Vries et al. 1988; Welshman 1989; Van Binnendijk et al. 1994). In contrast to inactivated MV preparations, infectious MVs, especially when administered intranasally or intratracheally, often produced higher levels of virus-neutralizing serum antibodies in monkeys, which may be due to extensive virus replication and dissemination in the cells of the respiratory tract (Hicks et al. 1977; De Vries et al. 1988; Van Binnendijk et al. 1994). MV-infected monkeys also developed antibodies mediating a complement-dependent lysis of MV-infected
target cells (cytolytic antibodies) (Peebles et al. 1957; Hicks and Albrecht 1976). Immunization of monkeys with heat-inactivated MV resulted in very low concentrations or even the absence of cytolytic antibodies, which may be related to the general failure of such preparations to induce functional antibodies against the F glycoprotein of MV (Hicks and Albrecht 1976, reviewed by Norrbry 1985). However, the induction of functional and long-lived F protein-specific antibody responses has been reported in cynomolgus monkeys immunized with the F protein incorporated in an immune stimulating complex (ISCOM) (De Vries et al. 1988). These observations are of major importance as a severe atypical measles syndrome (AMS) has been reported in MV-infected children who had been vaccinated with inactivated measles vaccines 2-4 years before exposure to the virus. These vaccine failures were initially attributed to the inability of inactivated measles vaccines to induce the proper antibody response against the F protein of MV (reviewed by Norrbry 1985), although other mechanisms may be involved. These include an altered immunoglobulin subclass distribution of the antibody response (Mathiesen et al. 1990) and the general failure of inactivated MV to induce a properly balanced T cell response (Van Binnendijk et al. 1990, 1992).

3.4 Cell-Mediated Immune Responses in Macaques

Today, substantial knowledge is available concerning the role of antibody response induced by MV infection in humans and in monkeys; however parameters of T cell-mediated immune responses have only been studied extensively in humans and rodents (reviewed by Uytdehaag et al. 1993). From initial experiments performed in macaques and marmosets (Hicks et al. 1977; Albrecht et al. 1972, 1980), cell-mediated immunity may be considered important in the control of MV infection in monkeys. In these experiments, treatment of rhesus monkeys with the immunosuppressive agent cyclophosphamide or with T lymphocyte depleting drugs resulted in enhanced and prolonged viremia of infected animals.

Recently, we have undertaken a series of experiments in cynomolgus monkeys to study the immune response parameters induced by different measles vaccines and vaccine candidates (Van Binnendijk et al. 1994). In preliminary experiments, MV-seronegative cynomolgus monkeys were inoculated intratracheally with the wild-type strain BIL of MV, which was recently isolated and biologically cloned from a patient with acute measles in The Netherlands. All infected monkeys developed strong virus-specific IgM and long-lasting (virus-neutralizing) IgG serum antibodies (Van Binnendijk et al. 1994). Furthermore, the long-term presence of MV-specific CD4+ and CD8+ T cells were detected in the PBMCs of most infected monkeys using techniques similar to those previously described for MV infections in humans (Van Binnendijk et al. 1990) and for simian immunodeficiency virus (SIV) infections in rhesus monkeys (Miller et al. 1990; Yamamoto et al. 1990). Cynomolgus monkey PBMCs stimulated in vitro with MV-infected B-LCLs resulted in the predominant expansion of primarily MV-specific CD8+ T cells which were capable of destroying virus-infected target cells in vitro (Van Binnendijk et al. 1994). Thus, these studies support the hypothesis that the
induction of a class I MHC-restricted CTL response and memory by CD8+ T cells, as a direct result of virus infection in vivo, may control MV infections by eliminating virus-infected cells in both humans and monkeys (VAN BINNENDIJK et al. 1990, 1992, 1994).

3.5 Measles Vaccination in the Presence of Maternal Antibody

Almost immediately after monkeys have been captured they are usually vaccinat-
ed with live attenuated measles vaccines in order to prevent the high incidence of measles during captivity due to human contacts. Usually good levels of protection will be achieved by vaccination and in most cases without the development of any clinical signs (WELSHMAN 1989). However, it may occur that some animals are already naturally infected with measles prior to vaccination (HALL et al. 1971). Previous studies on the efficacy of measles vaccination in a breeding colony of rhesus monkeys showed that captive-born offspring from wild-born MV-seropositive mothers were unable to respond to vaccination up to 6 months of age. Revaccination of this group from the age of 8-10 months onward resulted in significant MV-specific serum antibody titer rises (MACARTHUR et al. 1982). As in humans, MV-specific serum antibodies, representing maternal antibodies, were detected in the prevaccination sera of these animals and were detectable up to 9-12 months of age (MACARTHUR et al. 1979). In unvaccinated, newborn cynomolgus monkeys, maternal MV-specific serum antibody titers decreased linearly with a half-life time of approximately three and a half weeks. Furthermore it has been shown that these titers never exceeded the MV-specific antibody titers of the mothers (FUJIMOTO et al. 1983b). It is most likely that, as in human babies, the placental transfer of IgG is responsible for the MV-specific antibody titers in the newborns rather than the transfer of Immunoglobulin by breast-feeding (ALBRECHT et al. 1977b; FUJIMOTO et al. 1983a,b).

In developing countries measles is still responsible for high mortality rates among children during their first year of life. Indeed, it is this group of young children who in most cases cannot be vaccinated with live attenuated vaccines due to the interference of maternal antibodies with the attenuated virus replication. Therefore, a suitable monkey model in, e.g., cynomolgus or rhesus macaques would provide the opportunity to study the efficacy and safety of novel generations of measles vaccines able to induce a protective immune response in the presence of maternal antibodies.

4 Concluding Remarks

Several primate species can be infected experimentally with MV. Also spontaneous infections may occur after contacts with humans, after which MV may spread from monkey to monkey and cause serious losses in affected colonies or during
the shipment of animals. In certain species, e.g., cynomolgus and rhesus macaques, infection with wild-type MV causes a disease of varying severity, quite similar to measles in humans. The development of antibody and cell-mediated immunity to MV largely parallels the development of MV-specific immunity in humans. Attenuated MV strains used in human vaccines also proved to be attenuated for primates and upon infection rendered the animals immune to subsequent wild-type MV infection. As in humans, MV-specific passively acquired maternal antibodies interfere with wild-type and attenuated MV infection in macaques. Unlike macaques, marmosets develop a usually fatal infection with wild-type MV upon experimental or contact infection. The infection is not characterized by the signs and symptoms of measles that are typical for the disease in humans. In contrast, experimental infection with attenuated MV vaccine strains does not lead to disease symptoms in marmosets.

Taken together, cynomolgus and rhesus macaques may be considered suitable animals for studying the pathogenesis of and immune-mediated protection from MV infection, induced by natural infection or vaccination. Especially in the light of the eradication strategy of measles, as recently adopted by the WHO, the present availability of a suitable macaque model to study the potential of novel generations of vaccines that may overcome the specific problems related to maternally derived antibodies and atypical measles syndrome is of major importance.

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References

Degwitz R (1927) Etiology of measles J Infect Dis 41: 304
Giraudon P, Wild TF (1985) Correlation between epitopes on hemagglutinin of measles virus and biological activities: passive protection by monoclonal antibodies is related to their hemagglutination inhibiting activity. Virology 144: 46–58
Herndon RM, Rena-Descalzi L, Griffin DE, Coyle PK (1975) Age dependence of viral excretion. Electronic microscopic and immunoperoxidase studies of measles virus replication in mice. Lab Invest 33: 544–553
Hime JM, Keymer IF (1975) Measles in recently imported colobus monkeys (Colobus queraza). Vet Rec 97: 392
Josias A (1898) Recherches experimentales sur la transmissibilite de la rubeole aux animaux. Med Mod 9: 158
Peebles TC, McCarthy K, Enders JF, Holloway A (1957) Behavior of monkeys after inoculation of virus derived from patients with measles and propagated in tissue culture together with observations on spontaneous infections of these animals by agent exhibiting similar antigenic properties. J Immunol 78: 63–74
Plotz H (1938) La rougeole inapparente chez le singe (Macacus rhesus) CR Soc Biol 133: 141
Van Binnendijk RS, Poelen MCM, Kuipers KC, Oosterhaus ADME, UytdeHaag FGC (1990) The predominance of CD8+ T cells after infection with measles virus suggests a role for CD8+ class I MHC-restricted cytotoxic T lymphocytes (CTL) in recovery from measles. Clonal analyses of human CD8+ class I MHC-restricted CTL. J Immunol 144: 2394–2399