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I. HISTORY AND NOMENCLATURE

In 1966, Crawford reported the isolation of a passenger virus from a mouse adenovirus stock (Crawford, 1966). It had cell culture, physical, and chemical characteristics that resembled rat virus (Kilham and Olivier, 1959), the prototype virus for the family Paroviridae, including the capacity for autonomous replication. He named the agent minute virus of mice (MVM) and the initial strain MVM-CR. Additional isolates have since been identified, including from naturally infected mice. Two strains in particular have been widely used to investigate parovirus biology: a plaque-purified strain prepared by Tattersall and Bratton (1966) that was initially named MVM-T but was then renamed MVMp (p for “prototype”) and an allotropic strain, MVMi (i for “immunosuppressive”), isolated from a transplantable lymphoma by Bonnard and coworkers (Bonnard et al. 1976). Recently, the International Committee on Taxonomy of Viruses (Van Regenmortel et al. 2000) has considered renaming MVM mice as mouse minute virus (MMV). To the best of our knowledge, this potential change has not been formally accepted. Therefore, we use the acronym MVM in this chapter.

For many years, MVM was viewed as the sole parovirus serotype affecting laboratory mice (Cross and Parker, 1972). During the mid-1980s, however, diagnostic laboratories began to detect mouse sera that reacted with MVM in generic, but not
serotype-specific, tests (A.L. Smith, unpublished data). These findings suggested the existence of a murine parvovirus antigenically distinct from MVM. Subsequently, McKisic and colleagues (McKisic et al. 1993) isolated a lymphocytotropic parvovirus from mice. The newly recognized agent had adverse effects on in vitro immune responses, including lytic growth in a CD8+ T cell clone and inhibition of cloned T cell proliferation after stimulation with antigen or IL-2. Similar parvoviruses were soon isolated from naturally infected mice (Smith, unpublished data; Smith et al. 1993). The new serotype was initially—and unfortunately—named “mouse orphan parvovirus” to convey vague understanding of its biological significance, despite a causative association with immune dysfunction. However, it was subsequently renamed mouse parvovirus (MPV) (Ball-Goodrich and Johnson, 1994) to conform with the nomenclature of parvoviruses in other mammalian species. Retrospective serology suggested that MPV strains had been present in American mouse colonies for at least 20 years (Smith, unpublished data). The discovery of this new serotype, with some properties distinct from MVM, highlights the importance of employing both generic and serotype-specific tests for the identification of murine parvoviruses.

The detection of multiple MPV isolates indicated a need for standardized nomenclature. We proposed adaptation of the system introduced by Parrish to classify canine and feline parvoviruses (Parrish, 1990). Thus, the prototype strain of MPV was designated MPV-la, and two subsequent isolates were named MPV-lb and MPV-lc, with additional isolates to be named in alphabetized sequence (Jacoby et al. 1996). Isolates of additional parvovirus serotypes would be designated MPV-2a and so on. Strong sequence homology between conserved regions of the MVM and MPV genomes encoding for nonstructural proteins suggests that the name MPV could encompass all strains of both serotypes and facilitate a unified nomenclature based on the Parrish system. Because of their similarities, we describe the properties of MVM and MPV collectively, except where drawing distinctions between them is warranted.

II. MOLECULAR ANALYSIS

Murine parvoviruses are small (15–28 nm), non-enveloped single-stranded (ss) DNA viruses (Cotmore and Tattersall, 1987; Ward and Tattersall, 1982). As with other autonomous parvoviruses, they require cellular factors expressed during cell division and differentiation for productive replication. These factors are thought to account for their predilection for mitotically active cells. Genomic analysis has shown that the 5-kb genome is bracketed by terminal palindromes involved in replication (Fig. 4-1). The plus-sense strand of the double-stranded replicative intermediate contains two large and several smaller open reading frames (ORF). The larger ORFs are driven by promoters at map positions 4 and 38 and utilize alternative splicing to generate multiple transcripts. The P4 transcripts encode two nonstructural proteins, NS1 and NS2, that are involved in viral transcription and replication and are highly

![Fig. 4-1](image_url) Physical and genetic map of a murine parvovirus.
conserved among the rodent parvoviruses. The P38 transcripts encode the two major viral (capsid) proteins, VP1 and VP2, which are serotype-specific. All of VP2 is contained within VP1, but VP1 contains an additional 143 amino acids at the N terminus. VP3 is generated by cleavage of 19 N-terminal amino acids from VP2, and is present in differing amounts in virions. The virion coat is composed of 60 copies of VP1, VP2, and VP3, 54 of which are VP2 or VP3.

III. REPLICATION

MVM replicates in monolayer cultures of mouse fibroblasts (A9 cells), C6 rat glial cells, SV40-transformed human newborn kidney (324K cells), T cell lymphomas (S49 and EL4 cells), and rat or mouse embryo cells and produces cytopathic effects that can include the development of intranuclear inclusions (Tattersall and Cotmore, 1986). MPV, by contrast, is very difficult to cultivate in vitro. L3, a line of cloned CD8+ T lymphocytes, is the only line known to support MPV with any degree of reliability (McKisic et al. 1993), although there is preliminary evidence that MPV will replicate in 324K cells after serial passage (S. Jennings, personal communication). Nevertheless, the identification of simpler and hardier in vitro cultivation methods for MPV remains a challenge for parvovirus research.

The replication of murine parvoviruses has been determined primarily through in vitro studies of MVM infection (Cotmore and Tattersall, 1987; Tattersall and Bratton, 1983; Tattersall and Cotmore, 1986) and consists of four outcomes, one representing productive infection and three representing nonproductive infection. Productive infection, the most common outcome, begins with the binding of the virion to an undefined cell surface receptor(s). The virus is internalized by endocytosis, transported to the nucleus, and the positive strand is synthesized to form a duplex DNA replicative intermediate. Viral transcription and translation result in the production of NS proteins, which up-regulate the synthesis of both NS and VP proteins. A burst of viral DNA replication, through duplex DNA intermediates, occurs a short time later. VP1 and VP2 self-associate to form capsids, and predominantly minus-sense viral ssDNA is packaged. Additional functions defined for NS1 and NS2 include modulation of transcription from cellular promoters and cytostatic and cytotoxic functions presumed to down-regulate cellular processes not required for viral replication (Brandenberger et al. 1990; Legendre and Rommelaere, 1992). Replication typically leads to cell lysis and the release of newly synthesized virions.

For nonproductive infection, restrictive infection has been demonstrated for two MVM strains. Thus, MVMp and MVMi undergo productive infection in fibroblasts and lymphocytes, respectively, but the growth of each strain is restricted in the reciprocal cell type. Abortive infection may occur when MVM infects cells of a different species. Significant viral transcription and protein synthesis occur with limited or no genomic DNA replication or production of infectious virus. Cryptic infection may occur in nonreplicating cells that are normally capable of supporting productive infection. Since nonreplicating cells do not proceed through S phase, virus replication is inhibited until the cell is stimulated to divide. Because nonproductive infections have been demonstrated only for MVM and only in vitro, their influence on the health or experimental performance of mice with natural parvovirus infections is currently unknown.

The unique replication strategy of parvoviruses has been utilized to characterize viral tropisms and replication in vivo. Single-stranded genomic probes of either plus-sense, which detect double-stranded (ds) DNA replicative intermediates and ssDNA, or minus-sense, which detect dsDNA replicative intermediates and RNA transcripts, can distinguish between actively infected cells in which replication and viral transcription are occurring from those in which only genomic DNA or dsDNA are present (Bloom et al. 1989; Jacoby et al. 1995).

IV. ANTIGENIC AND PHYSICOCHEMICAL PROPERTIES

Sequence analysis of the MPV genome indicates that regions encoding NS proteins are strongly homologous to those of MVM (Ball-Goodrich and Johnson, 1994). This homology is conserved at the protein and antigenic level, since immune sera to MVM NS proteins also detect MPV NS proteins. NS1 and NS2 proteins are equivalent in size and ratio in both MPV- and MVM-infected cells. The capsid proteins, which are more divergent, provide serotype specificity.

Parvoviruses are highly resistant to many classical methods of inactivation such as dessication, heating, and exposure to lipid solvents or chaotropic agents, including urea and sodium dodecyl sulfate (Harris et al. 1974; Tattersall and Cotmore, 1986). This feature is due to their small size, stable construction, and lack of a lipid envelope. A recent study showed that exposure to wet heat (90°C) for at least 10 minutes was required to inactivate MVM; infectious virus was present in samples treated for 1 hour at temperatures up to 80°C (Boschetti, 2003). This study also showed that NaOH concentrations 0.1M (pH 12.8) were required for efficient (1 minute) inactivation of filtered (dissociated) MVM. However, MVM aggregates were resistant even to prolonged (60 minute) NaOH treatment. Parvoviruses appear to be inactivated by formalin and oxidizing agents such as sodium hypochlorite and sodium chloride (Saknimit et al. 1988). Although these studies assessed only rat and canine parvoviruses, there is no reason to suspect that these agents would not be equally effective against murine parvoviruses. There does not appear to be documented information addressing the virucidal capacity of chlorine dioxide, which is widely used as an
oxidizing disinfectant in animal resource facilities, nor did we find information on the virucidal effectiveness of oxidizing agents during common application such as by spray or wipe.

V. CLINICAL SIGNS

Natural parvovirus infections of mice, for all intents and purposes, are clinically silent, regardless of host age. Therefore, the most common evidence of infection is seroconversion, which occurs, in immunocompetent mice, 7 to 14 days after initial exposure to the virus (Jacoby et al. 1995). The absence of clinical signs also is generally characteristic for experimental infections, even in immunodeficient mice. However, experimental infection of neonatal BALB/c, SWR, SJL, CBA, and C3H mice with MVM(i) has led to morbidity and mortality due to internal hemorrhage and/or accelerated involution of hepatic hematopoiesis (Brownstein et al. 1991). An early study demonstrated granulopralvial cerebellar hypoplasia after combined intracerebral and intraperitoneal inoculation of neonates with MVM, and also reported cerebellar hypoplasia in several contact-exposed control mice (Kilham and Margolis, 1970). More recently, the intranasal inoculation of MVMi into newborn BALB/c mice caused neurological signs associated with active replication in proliferative centers of the cerebrum and in young cerebellar neurons (Ramirez et al. 1996). Nevertheless, the incidence of brain lesions in naturally infected mice should be considered extremely low.

VI. EPIZOOTIOLOGY

The mouse appears to be the primary and sole natural host of murine parvoviruses. Although a large proportion of rat sera tested by Parker contained low-titer reactivity to MVM (Parker et al. 1970), it disappeared after kaolin treatment, illustrating that the reactions were nonspecific. MVM can infect rats and hamsters inoculated parenterally or during fetal development, but such conditions are far removed from natural exposure (Kilham and Margolis, 1970, 1971). An MPV-like virus has been detected in hamsters, but its potential for cross-infection of mice is unknown (Besselsen et al. 1996, 1999).

The prevalence of murine parvoviruses is attributable to their infectivity, persistence (at least for MPV) in infected mice, resistance to environmental inactivation, and contamination of biologicals used for animal inoculation (Parker et al. 1970; Nicklas et al. 1993). A U.S. survey conducted in 1997 (Jacoby and Lindsey, 1997) found that parvovirus infections were present in about 25% of barrier-maintained mouse colonies and 45% of conventional colonies among leading U.S. biomedical research institutions. No comparable surveys of commercial colonies have been reported, but there is anecdotal evidence that they endure occasional outbreaks (S. Compton, personal communication). Several European laboratories have reported parvoviruses as common contaminants in specimens of mouse origin (Kraft and Meyer, 1990; Nicklas, 1993).

Natural murine parvovirus infections appear to result from oroanal exposure, but parenteral inoculation of contaminated biologicals, such as transplantable tumors, are potential sources of infection. Oral exposure facilitates primary replication in the small intestine followed by systemic spread. Viral DNA can be detected in kidney, intestine (and feces), and lung during acute infection (Brownstein et al. 1991; Jacoby et al. 1995; Smith et al. 1993) suggesting that excretion occurs in urine, feces, and, potentially, exhaled air. These results also imply that the alimentary tract is a portal for viral entry. Significant excretion through the respiratory tract seems doubtful, since virus-positive cells are sparse in this organ system. Therefore, the transmission of infection probably occurs primarily by ingestion of contaminated food, bedding, or feces. Further, the comparatively slow rate of cage-to-cage spread suggests that transmission is primarily by contaminated fomites.

MVM appears to produce self-limiting infection in infant and adult mice. Thus, no infection or transmission was detected beyond 4 weeks after oroanal inoculation of neonatal or adult mice (Smith, 1983; Smith and Paturzo, 1988). In contrast, MPV appears to persist among infant and adult mice after the development of humoral immunity. For example, mice inoculated neonatally transmitted virus to cagemates for up to 6 weeks, and mice inoculated as young adults transmitted infection for up to 4 weeks (Smith et al. 1993), despite the onset of seroconversion 7–10 days after inoculation. There is some corollary data from a natural enzootic suggesting that juvenile animals present a greater hazard than older mice for spread of infection (Shek et al. 1998). Further, molecular hybridization studies indicate that MPV DNA can persist in lymphoid tissues of adult mice for at least 9 weeks (Jacoby et al. 1995) whereas no evidence of MVM was found after 3 weeks (Jacoby et al. unpublished data). Preliminary evidence from mouse antibody production tests using samples from naturally infected mice imply that MPV DNA-positive lymphoid tissues harbor infectious virus (Shek et al. 1998). We add the possibility that although continuous contact exposure to infected animals or soiled bedding induces seroconversion within 3 weeks, periodic exposure to low doses of virus may extend this interval (S. Compton, unpublished data). Suckling mice in enzootically infected colonies are protected from infection with homologous virus by maternally acquired immunity, which generally decays within 2–3 months. Subsequent infection of such mice as adults elicits active immunity. However, immunity to MVM may not confer cross-immunity to MPV (Hansen et al. 1999). There is no evidence that murine parvoviruses are transmitted in utero after infection of dams by a natural route. As noted above, parvoviruses resist environmental inactivation, which prolongs risks for the spread and duration of epizootic and enzootic infections.
VII. PATHOLOGY AND PATHOGENESIS

Despite in vitro evidence that productive parvovirus replication leads to cell death, necrosis is not an obvious feature of active infection in mice. This fact, coupled with low sensitivity of immunostaining, has led to reliance on in situ hybridization (ISH) for contemporary pathogenesis studies. Although MPV and MVM infections, especially in adult mice, are similar, they are described separately to emphasize several differences.

A. MPV

As noted above, MPV infection appears to begin in the small intestine, since parvovirus-specific ISH signal can be detected among enterocytes in the small intestine within several days after oral inoculation of virus (Jacoby et al. 1995) (Fig. 4-2). However, virus-positive cells rapidly become more prominent among mononuclear cells and capillary (or lymphatic) endothelium in the lamina propria. Acute infection extends to Peyer's patches, lymph nodes, thymus, spleen, lung, kidney, and liver (Figs. 4-3 and 4-4). Thus, lymphocytotropism occurs early in infection, and may contribute to viremic dissemination. This also suggests that at least some virus-positive cells in intestinal lamina propria are intra-epithelial lymphocytes, a notion compatible with the in vitro tropism of MPV for T cells.

Seroconversion during the second week of infection marks a gradual decrease in virus-positive cells in all infected tissues. However, positive cells can be detected in lymph nodes and splenic white pulp through at least 9 weeks, primarily among germinal centers (Figs. 4-5 and 4-6). It is unclear whether virus targets specific lymphoid cell subsets in vivo. The random distribution of virus-positive cells during acute infection, which includes paracortical regions of lymph nodes and periarteriolar lymphoid sheaths in spleen, followed by the localization of virus during persistent infection suggests that multiple lymphoid cell types can be infected. This possibility also is supported by the characteristics of immune dysfunctions associated with MPV infection (see below). Infection of hematopoietic tissue (splenic red pulp) is sparse and appears limited to early stages.
of infection. Thus, hematopoietic cells are not conspicuous targets as they can be in MVM infection of neonates or immunodeficient adults (Segovia et al. 1999).

During persistent infection, lymphoid tissues contain virion-positive cells but no evidence of viral transcripts or dsDNA. This suggests that virus is quiescent, or that replication is occurring at levels undetected by ISH. Therefore, signal amplification strategies such as polymerase chain reaction (PCR) and reverse transcriptase PCR (RT-PCR) may be required to detect viral transcription and replication during persistent infection.

**B. MVM**

MVM infection in adult mice reveals patterns similar to those for MPV; that is, enterotropism followed by lymphocytotropism (Jacoby et al. unpublished data). However, hybridization signal is rarely detected after 3 weeks, consistent with the concept that MVM is a self-limiting infection in immunocompetent mice (Smith, 1983). As noted above, neonatal mice of several strains are subject to hemorrhagic lesions after experimental inoculation of MVMi (Brownstein et al. 1991). These include infarction of the renal papilla in BALB/c,
SWR, SJL, CBA, and C3H mice. Further, DBA/2 neonates can develop intestinal hemorrhage and accelerated involution of hepatic hematopoiesis. In contrast, C57BL/6 neonates appear resistant to vascular disease. MVMi replicates equally well in resistant (C57BL/6) and susceptible (C3H) mice, but in situ hybridization and immunohistochemistry have shown that fewer target cells (endothelium, lymphocytes, and erythropoietic precursors in the liver) are infected in resistant mice. One explanation offered for these findings is that genetic susceptibility facilitates the accumulation of NS proteins, which are known to be cytotoxic in vitro. This possibility was supported by studies with an MVMi NS2 mutant that revealed that the pathogenicity of MVMi depended on expression of NS2 (Brownstein et al. 1992). Companion studies with intertypic recombinants between MVMi and MVMp indicated that the pathogenicity of MVMi also depended on allotropic determinant(s) encoded by the capsid genes. This region of the MVMi genome, which determines tropism in vitro, also appears to determine lymphotropism and endotheliotropism in vivo.

Kimsey and coworkers compared the effects of MVMp and MVMi (Kimsey et al. 1986) and found that neither strain affected T cell function in adult mice. However, MVMi caused disseminated infection, running, and mild immunodeficiency in mice inoculated as neonates, effects attributed to lymphocytotropism.

MVM appears to be more pathogenic for hematopoietic tissue than MPV. In vitro and in vivo studies complementary to those described above for neonates have demonstrated infection of hematopoietic stem and committed progenitor cells by MVMi (Lamana et al. 2001; Segovia et al. 1995, 2003). MVMi replicated in primary myeloid cells of long-term bone marrow cultures, resulting in high titers of infectious virus and acute myelosuppression in the cultures. In vivo infection of newborn BALB/c mice resulted in a significant decrease in
femoral and splenic cellularity and delayed myeloid depression. In immunodeficient SCID mice, MVMi infection resulted in suppression of myeloid and erythroid progenitors in the bone marrow and lethal leukopenia (Segovia et al. 1999). Hematopoietic tropism aside, MPV and MVM share a predilection for the intestine and lymphoid tissues, but MPV infection persists significantly after serocconversion, whereas MVM infection appears to be more self-limiting. These findings increase concerns not only about the epizootiology of MPV infection, but also about long-term influences of MPV on immune function.

VIII. DIAGNOSIS

The simple structure of rodent parvoviruses has stimulated development of valuable reagents to detect infection. These include generic and serotype-specific antigens for use in serological tests, antibodies to viral proteins for use in immunohistochemistry, PCR primers for detection of viral DNA in infected tissues and feces, and strand-specific molecular probes that help distinguish sites of active viral replication (Jacoby et al. 1995; Besselsen et al. 1995, 1998). In practical terms, however, the detection of parvovirus infection continues to rely heavily on serologic assays for anti-parvovirus antibodies. Generic serological tests capitalize on extensive cross-reactivity among conserved (NS1) antigens. Therefore, MVM NS proteins can be used to detect antibodies to both MVM and MPV. This feature is exploited in immunofluorescence assays (IFA) and enzyme-linked immunosorbent assays (ELISA) using virus-infected cells (Riley et al. 1996; Smith, 1985; Smith et al. 1982). In addition, the NS1 ELISA utilizes recombinant (r) MVM NS1 protein as antigen and serves as a useful screening test for parvovirus infection (Riley et al. 1996). Although ELISAs using whole parvovirus virions or rNS1 as antigen are comparably specific, the latter appears to be more sensitive for generic detection of antibodies to murine parvovirus (Riley et al. 1996). However, the rNS1 ELISA may give false negative reactions if NS proteins are not elicited uniformly among strains and ages of infected mice (Besselsen, 2000). VP2 antigens, because they are serotype-specific, are essential for the serological differentiation of MVM infection from MPV infection. In this context, recently developed ELISAs utilizing recombinant MPV and MVM VP2 proteins or empty virions offer sensitivity and specificity that render the HAI assay outmoded. (Ball-Goodrich et al. 2002; Livingston et al. 2002).

While current serological assays to detect and differentiate murine parvoviruses have great diagnostic value, we add a cautionary note: They may not be reliably applicable to newly recognized strains. This concern is exemplified by a preliminary report that a putative antigenically distinct strain of MPV, designated MPV-2, may not be detected by serological assays for MPV-1 (Dhawan et al. 2004).

The mouse antibody production (MAP) test can be used to detect parvovirus infections in mouse tissues or tissue products, but it is time-consuming and expensive (de Souza and Smith, 1989). Virus isolation has similar drawbacks, but it is a valuable option to confirm MVM infection. Established cell lines frequently used for MVM isolation include A9 murine fibroblasts, NB324K human kidney cells, C6 rat glial cells, and BHK-21 cells (Tattersall and Bratton, 1983; Cotmore and Tattersall, 1987). MPV, as mentioned previously, grows efficiently only in selected T cell lines and clones. Tissue explantation culture, where small segments of tissue harvested from suspect hosts are cultivated for several weeks to allow amplification of virus prior to inoculation and testing of indicator monolayer cultures, is an additional option to detect MVM (Smith and Paturzo, 1988). Neither this option or co-cultivation of lymphoid cells has been tested systematically to detect MPV infection.

More recently, molecular diagnostics have replaced MAP testing and virus isolation for specific and sensitive detection of parvovirus infection. A generic PCR assay, which amplifies a conserved portion of the NS1 gene, detects MVM and MPV (Riley et al. 1996). Virus-specific PCR assays amplify gene segments within the capsid protein genes (Ball-Goodrich and Johnson, 1994; Besselsen et al. 1995; Redig and Besselsen, 2001; Yagami et al. 1995). Both assays are effective in assessing feces as well as tissues from infected animals for parvoviral DNA. Testing of DNA from mesenteric lymph nodes by PCR can be especially useful because the nodes are a consistent site of acute and persistent infection. There also is recent evidence that PCR assays can be used to monitor ventilated cage racks for the presence of parvovirus-infected mice by testing filters placed strategically in the exhaust plenum for parvoviral DNA (Compton et al. 2004). While it is too soon to conclude that such monitoring will play a major role in the early detection of parvovirus infection, this approach illustrates emerging possibilities for molecular diagnosis in rodent preventive medicine. ISH with strand-specific probes is valuable for detecting genomic and replicative viral DNA in paraffin-embedded tissues (Jacoby et al. 1995). Immunostaining of paraffin-embedded tissues has, thus far, proved less reliable for histologic evaluation of infection.

IX. EFFECTS ON RESEARCH

The effects of murine parvoviruses on research are attributable to their predilection for mitotically active cells. The prevalence of clinically silent infections implies that interference will most likely be manifested as distortions of biological responses that depend on cell proliferation. Their historical association with transplantable neoplasms exemplifies this phenomenon, but the clearest demonstrations of the potential impact of parvovirus interference pertain to immune dysfunction.
A. MVM

Early reports showed that MVMi suppressed lymphocyte proliferation in vitro in response to mitogens, abrogated the generation of cytolytic T cells in primary mixed lymphocyte cultures, and inhibited T cell–dependent B cell responses in vitro (Bonnard et al. 1976; Engers et al. 1981; McMaster et al. 1981). These effects were attributed to virus-induced cytolysis. However, as noted previously, the immunosuppressive effects of MVMi were mild in vivo and observed only in infant mice (Kimsey et al. 1986). Further, MVMi has the specific potential to interfere with the hematopoietic system in newborn or severely immunocompromised mice. MVMp, which is not lymphocytotropic, was not immunomodulatory in vitro or in vivo. MVM contamination of transplantable neoplasms is a demonstrable risk. Therefore, infection can be introduced to a colony through inoculation of contaminated cell lines. Failure to establish long-term cell cultures from infected mice or a low incidence of tumor “takes” should alert researchers to the possibility of MVM contamination.

B. MPV

MPV can interfere with the ability of cloned T cells to thrive and proliferate (McKisic et al. 1993). Further characterization of the immunosuppressive properties of MPV showed that infection reduced both cytokine- and antigen-induced T cell proliferation in vitro, apparently without affecting cell viability (McKisic et al. 1996). These results suggested that infection need not be patently lytic to alter effector functions. Virus replication was essential to perturb immune functions since heat inactivation abrogated these effects. These experiments also suggested that MPV infection impaired a signaling event common to both cytokine- and antigen-stimulated proliferation.

MPV infection of adult mice can cause immune dysfunction that can persist after seroconversion. Both CD4+ and CD8+ T cell–mediated responses are altered during acute MPV infection. Modulation of ovalbumin-induced CD4+ T cell proliferation was observed in BALB/c mice as early as 3 days after virus inoculation, although this function was restored within 2 to 3 weeks (McKisic et al. 1996). Additionally, MPV appears to modulate immune responses differentially, depending on the anatomical source of T cells. Specifically, the proliferative responses of splenic and popliteal lymph node cells obtained from infected, ovalbumin-primed mice were suppressed, while proliferation of mesenteric lymph node cells was augmented.

Inoculation of BALB/c mice with MPV resulted in abnormal CD8+ T cell rejection of tumor and skin allografts for at least 3 weeks post-infection (McKisic et al. 1996, 1998). Adult BALB/c mice infected 1, 2, or 3 weeks prior to receiving an inoculum of sarcoma I cells developed smaller tumors that were rejected more quickly compared to uninfected controls. Similarly, MPV infection, either before or after skin transplantation, potentiated the rejection of full thickness allografts. The alteration of tumor and skin graft rejection was not due to virus infection of the tumor or the graft. Also, the specific proliferative and cytolytic capacity of alloantigen-reactive lymphocytes from tumor- and skin-graft-sensitized infected mice was diminished. Therefore, MPV appeared to accelerate graft rejection while inducing dysfunction of alloreactive T cells. Surprisingly, syngeneic grafts on MPV-infected mice were rejected at the same rate as allogeneic grafts, whereas mice inoculated with MVMi, MVMp, or heat-inactivated MPV-1 did not reject syngeneic grafts. Depletion of T lymphocytes prior to grafting or passive immunization with anti-MPV immune serum prevented the rejection of syngeneic grafts. Thus, MPV infection of skin-grafted mice appeared to disrupt normal mechanisms of peripheral tolerance. Modulation of immune responses by MPV raises concerns about the full potential for such effects on immunologic research using mice.

X. CONTROL AND PREVENTION

Because MVM does not persist in immunocompetent mice, control and elimination should employ quarantine for at least 1 month, combined with thorough disinfection of the environment. Quarantine also assumes that MPV infection has been ruled out. If serotyping of virus remains problematic, i.e., if MPV infection remains a possibility, more stringent approaches may be preferable. Elimination (depopulation) of infected mice should be considered if they are an immediate threat to experimental or breeding colonies and can be replaced. For mice that are not easily replaced, persistent infection coupled with low risk for transplacental transmission favor Cesarean rederivation or embryo transfer as attractive options to eliminate infection.

Thorough decontamination is applicable to all parvovirus outbreaks because of the environmental stability of these viruses. Chemical disinfection of suspect animal rooms and heat sterilization of caging and other housing equipment are prudent. While fogging contaminated rooms with formalin may be useful, it also presents increased risk for inadvertent chemical exposure. We have been encouraged by the effectiveness of sequential washing of surfaces, followed by chlorine dioxide and several days of drying. Prevention is based on sound serological monitoring of mice and surveillance of biologicals destined for inoculation of mice.
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