

# Mouse Hepatitis Virus

## Host species

- mouse

## Organotropism

- polytropic strains: liver, brain, lymphoid tissue, (other organs)
- enterotropic strains: intestine, lymphoid tissue

## Clinical disease

- inapparent in immunocompetent adults
- diarrhea and death in neonates (epizootic infection)
- wasting disease in immunodeficient mice

## Pathology

- polytropic strains: acute necrosis and syncytia formation in liver, spleen and lymphoid tissue; necrotizing encephalitis with demyelination and syncytia formation
- enterotropic strains: villus attenuation, enterocytic syncytia and mucosa necrosis of the terminal small intestine, the cecum and the ascending colon

## Morbidity and mortality

- usually 100% of animals are infected
- mortality close to 100% in neonates (all virus strains, epizootic infection) and in immunodeficient mice (polytropic strains)
- mortality 0% (or very low) in all other cases

## Interference with research

### Oncology

- Contamination of transplantable tumors (Nicklas et al., 1993)

- abnormal tumor invasion pattern, abnormal tumor passage intervals, spontaneous regression or oncolysis of normally stable tumors (Akimaru et al., 1981; Braunsteiner and Friend, 1954; Fox et al., 1977; Manaker et al., 1961; Nelson, 1959)
- rejection of human xenografts (Kyriazis et al. 1979)
- altered response to chemical carcinogens (Barthold, 1986a)

## **Infectiology**

- Confusion about origin of virus isolates: Tettang (Smith et al., 1983), multiple sclerosis (Gerdes et al., 1981), puffinosis (Nuttall and Harrap, 1982)
- Reduced susceptibility for viral infections (PVM, Sendai ) (Carrano et al., 1984)
- Potentiation of subclinical MHV infections by urethane and methylformamide (Braunsteiner and Friend, 1954), halothane (Moudgil, 1973), transplantation of tumors (Barthold, 1986b), concurrent infection with *Eperythrozoon coccoides* (Kraft, 1982)
- enhances resistance to *Salmonella typhimurium* in mice by inducing suppression of bacterial growth (Fallon et al., 1991).

## **Immunology**

- immunodepression and immunostimulation depending on the time of infection (Virelizier et al., 1976).
- MHV replicates in macrophages and with or without lysis in both B and T lymphocytes (Bang and Warwick, 1960; de Souza and Smith, 1991; Lamontage et al., 1989).
- enhanced and suppressed macrophage function (Boorman et al., 1982; Dempsey et al., 1986) and dysfunction of T and B cells (Casebolt et al., 1987; Cook-Mills et al., 1992; de Souza et al., 1991; Smith et al., 1991).
- activation of natural killer (NK) cells and alteration of the interferon responsiveness of infected mice (Schindler et al., 1982; Virelizier et al., 1976).
- reduced levels of cytokines, interleukins and gamma interferon in spleen cells (de Souza et al., 1991).
- recovered mice have complete or partial protection against T cell dysfunctions when re-infected with different strains of MHV (Smith et al., 1992).
- macrophage dysfunctions continue in MHV-recovered mice (Boorman et al., 1982)
- MHV infection can durably modify unrelated T cell responses that are initiated at the time of infection (Coutelier et al., 1991).
- permanent decrease of skin graft rejection and T cell dependent antibody responses after recovering from MHV-A59 infection (Cray et al., 1993).
- enhancement of concomitant autoimmune reactions (Lardans et al., 1996)

## **Physiology**

- alteration of liver enzyme levels, patterns of protein synthesis and other biochemical markers (Barthold, 1986a; Lucchiari et al., 1992.; Piazza, 1969)
- induction of alpha-fetoprotein (Kiuchi et al., 1974) and increase of iron uptake (Tieniwakul and Husain, 1979)
- changes in peripheral blood such as anemia, thrombocytopenia, leukopenia and increased monocyte procoagulant activity (Levy et al., 1981; Piazza et al., 1965).

- decrease of the incidence of diabetes in non-obese diabetic mice (Wilberz et al., 1991)

## **Reproductive technology**

- persistent contamination of embryonic stem (ES) cells without diminishing their pluripotency (Okumura et al., 1996)

## **References**

Akimaru, K., G. M. Stuhlmiller, and H. F. Seigler. 1981. Influence of mouse hepatitis virus on the growth of human melanoma in the peritoneal cavity of the athymic mouse. *J. Surg. Oncol.* 17:327-339.

Bang, F. B., and A. Warwick. 1960. Mouse macrophages as host cells for mouse hepatitis virus and the genetic basis of their susceptibility. *Proc. Natl. Acad. Sci. USA* 46:1065-1075.

Barthold, S. W. 1986a. Research complications and state of knowledge of rodent coronaviruses, p. 53-89. In T. F. Hamm (eds.), *Complications of viral and mycoplasmal infections in rodents to toxicology research testing*. Hemisphere, Washington.

Barthold, S. W. 1986b. Mouse hepatitis virus biology and epizootiology, p. 571-601. In P. N. Bhatt, R. O. Jacoby, A. C. Morse, III and A. E. New (eds.), *Viral and mycoplasmal infection of laboratory rodents: Effects on biomedical research*. Academic Press, Orlando.

Boorman, G. A., M. I. Luster, J. H. Dean, M. L. Cambell, L. A. Lauer, F. A. Talley, R. E. Wilson, and M. J. Collins. 1982. Peritoneal and macrophage alterations caused by naturally occurring mouse hepatitis virus. *Am. J. Pathol.* 106:110-117.

Braunsteiner, H., and C. Friend. 1954. Viral hepatitis associated with transplantable mouse leukemia. I. Acute hepatic manifestations following treatment with urethane or methylformamide. *J. Exp. Med.* 100:665-677.

Carrano, V., S. W. Barthold, D. L. Beck, and A. L. Smith. 1984. Alteration of viral respiratory infections of mice by prior infection with mouse hepatitis virus. *Lab. Anim. Sci.* 34:573-576.

Casebolt, D. B., D. M. Spalding, T. R. Schoeb, and J. R. Lindsey. 1987. Suppression of immune response induction in Peyer's patch lymphoid cells from mice infected with mouse hepatitis virus. *Cell. Immunol.* 109:97-103.

Cook-Mills, J. M., H. G. Munshi, R. L. Perlman, and D. A. Chambers. 1992. Mouse hepatitis virus infection suppresses modulation of mouse spleen T-cell activation. *Immunology* 75:542-545.

Coutelier, J. P., J. T. van der Logt, and F. W. Heessen. 1991. IgG subclass distribution of primary and secondary immune responses concomitant with viral infection. *J. Immunol.* 147:1383-1386.

- Cray, C., M. O. Mateo, and N. H. Altman. 1993. In vitro and long-term in vivo immune dysfunction after infection of BALB/c mice with mouse hepatitis virus strain A59. *Lab. Anim. Sci.* 43:169-174.
- Dempsey, W. L., A. L. Smith, and P. S. Morahan. 1986. Effect of inapparent murine hepatitis virus infections on macrophages and host resistance. *J. Leukocyte Biol.* 39:559-565.
- de Souza, M. S., and A. L. Smith. 1991. Characterization of accessory cell function during acute infection of BALB/cByJ mice with mouse hepatitis virus (MHV) strain JHM. *Lab. Anim. Sci.* 41:112-118.
- de Souza, M. S., A. L. Smith, and K. Bottomly. 1991. Infection of BALB/cByJ mice with the JHM strain of mouse hepatitis virus alters in vitro splenic T cell proliferation and cytokine production. *Lab. Anim. Sci.* 41:99-105.
- Fallon, M. T., W. H. Benjamin, Jr., T. R. Schoeb, and D. E. Briles. 1991. Mouse hepatitis virus strain UAB infection enhances resistance to *Salmonella typhimurium* in mice by inducing suppression of bacterial growth. *Infect. Immun.* 59:852-856.
- Fox, J. G., J. C. Murphy, and V. E. Igras. 1977. Adverse effects of mouse hepatitis virus on ascites myeloma passage in the BALB/c mouse. *Lab. Anim. Sci.* 27:173-179.
- Gerdes, J. C., I. Klein, and B. L. DeVald. 1981. Coronavirus isolates SK and SD from multiple sclerosis patients are serologically related to murine coronavirus A59 and JHM and human coronavirus OC43, but not to human coronavirus 229E. *J. Virol.* 38:231-238.
- Kraft, L. M. 1982. Viral diseases of the digestive system, p. 159-191. In H. L. Foster, J. D. Smith and J. G. Fox (eds.), *The mouse in biomedical research*. Vol. II, Academic Press, New York.
- Kyriazis, A. P., L. DiPersio, J. G. Michael, and A. J. Pesce. 1979. Influence of the mouse hepatitis virus (MHV) infection on the growth of human tumors in the athymic mouse. *Int. J. Cancer* 23:402-409.
- Lamontage, L. M., J.-P. Descoteaux, and P. Jolicoeur. 1989. Mouse hepatitis virus 3 replication in T and B lymphocytes correlate with viral pathogenicity. *J. Immunol.* 142:4458-4465.
- Lardans, V., C. Godfraind, J.T. van der Logt, W.A. Heessen, M.D. Gonzalez, and J.P. Couteiller. 1996. Polyclonal B lymphocyte activation induced by mouse hepatitis virus A59 infection. *J. Gen. Virol.* 77:1005-1009.
- Levy, G. A., J. L. Leibowitz, and T. S. Edgington. 1981. Induction of monocyte procoagulant activity by murine hepatitis virus type 3 parallels disease susceptibility in mice. *J. Exp. Med.* 154:1150-1163.
- Lucchiari, M. A., C. A. Pereira, L. Kuhn, and I. Lefkovits. 1992. The pattern of proteins synthesized in the liver is profoundly modified upon infection of susceptible mice with mouse hepatitis virus 3. *Res. Virol.* 143:231-240.

- Manaker, R. A., C. V. Piczak, A. A. Miller, and M. F. Stanton. 1961. A hepatitis virus complicating studies with mouse leukemia. *J. Nat. Cancer Inst.* 27:29-51.
- Moudgil, G. C. 1973. Influence of halothane on mortality from murine hepatitis virus (MHV 3). *Brit. J. Anaesth.* 45:1236.
- Nelson, J. B. 1959. Emergence of hepatitis virus in mice infected with ascites tumor. *Proc. Soc. Exp. Biol. Med.* 102:357-360.
- Nicklas, W., V. Kraft, and B. Meyer. 1993. Contamination of transplantable tumors, cell lines, and monoclonal antibodies with rodent viruses. *Lab. Anim. Sci.* 43:296-300.
- Nuttall, P. A., and K. A. Harrap. 1982. Isolation of a coronavirus during studies on puffinosis, a disease of the manx shear-water (*Puffinus puffinus*). *Arch. Virol.* 73:1-13.
- Okumura, A., K. Machii, S. Azuma, Y. Toyoda, and S. Kyuwa S. 1996. Maintenance of pluripotency in mouse embryonic stem cells persistently infected with murine coronavirus. *J. Virol.* 70:4146-49.
- Piazza, M. 1969. *Experimental viral hepatitis*. Charles C. Thomas, Springfield.
- Piazza, M. F. Piccinio, and F. Matano. 1965. Hematological changes in viral (MHV-3) murine hepatitis. *Nature* 205:1034-1035.
- Schindler, L., H. Engler, and H. Kirchner. 1982. Activation of natural killer cells and induction of interferon after infection of mouse hepatitis virus type 3 in mice. *Infect. Immun.* 35:869-873.
- Smith, A. L., J. Casal, and A. Main. 1983. Characterization of Tett nang virus: Complications caused by passage of the virus in mice from a colony enzootically infected with mouse hepatitis virus. *Amer. J. Trop. Med. Hyg.* 32:1172-1176.
- Smith, A. L., D. F. Winograd, and M. S. de Souza. 1991. In vitro splenic T cell responses of diverse mouse genotypes after oronasal exposure to mouse hepatitis virus, strain JHM. *Lab. Anim. Sci.* 41:106-111.
- Smith, A. L., M. S. de Souza, D. Finzi, and S. W. Barthold. 1992. Responses of mice to murine coronavirus immunization. *Arch. Virol.* 125:36-52.
- Tiensiwakul, P., and S. S. Husain. 1979. Effect of mouse hepatitis virus infection on iron retention in the mouse liver. *Brit. J. Exp. Pathol.* 60:161-166.
- Virelizier, J.-L., A.-M. Virelizier, and A. C. Allison. 1976. The role of circulating interferon in the modifications of the immune responsiveness to mouse hepatitis virus (MHV-3). *J. Immunol.* 117:748-753.
- Wilberz, S., H. J. Partke, F. Dagnaes-Hansen, and L. Herberg. 1991. Persistent MHV (mouse hepatitis virus) infection reduces the incidence of diabetes mellitus in non-obese diabetic mice. *Diabetologia* 34:2-5.

**Author: F. Homberger**