

# Kilham Rat Virus (KRV)

## Host species

- natural host: laboratory and wild rats,
- hamsters and other species such as *Mastomys natalensis* can be infected experimentally (KILHAM 1961, RABSON et al. 1961, National Research Council 1991)

## Properties of the virus

- highly temperature resistant (FASSOLITIS et al. 1985)
- highly resistant to environmental conditions like e.g. desiccation (LUM & SCHREINER 1963, TATTERSALL & COTMORE 1986, YANG et al. 1995)
- evidence for virus persistence in rats after natural infection (ROBEY et al. 1968, LIPTON et al. 1973)
- persistent infection after experimental infection of infant and juvenile rats (PATURZO et al. 1987, JACOBY et al. 1991)
- persistent infection in T cell-deficient rats (GAERTNER et al. 1995)
- limited infection in euthymic rats

## Strain susceptibility

- none (JACOBY & BALL-GOODRICH 1995)

## Organotropism

- viral replication only in mitotically active tissues (TENNANT & HAND 1970) like, e.g. embryo, intestines, tumours
- predilection for the developing liver and cerebellum (KILHAM & MARGOLIS 1966, COLE et al. 1970)

## Clinical disease

- infection often asymptomatic (LUM 1970, ROBINSON et al. 1971), but can be severe or lethal, especially in athymic infant rats (GAERTNER et al. 1991)
- cases of spontaneous clinical disease with deaths have been reported (KILHAM & MARGOLIS 1966, COLEMAN et al. 1983)
- fetal and neonatal abnormalities (KILHAM & MARGOLIS 1975)

- cerebellar hypoplasia and ataxia in hamsters after experimental infection (KILHAM & MARGOLIS 1964)
- periodontal disease in hamsters (National Research Council 1991)

## **Pathology**

- haemorrhage and infarction especially in the central nervous system (EL DADAH et al. 1967, COLE et al. 1970, MARGOLIS & KILHAM 1970, BARINGER & NATHANSON 1972)
- intranuclear parvoviral inclusions in areas of necrosis among clinically affected rats (JACOBY et al. 1979, LUSSIER 1991)
- mongoloid-type deformity in new-born hamsters after experimental infection (BAER & KILHAM 1962)
- cerebellar lesions in cats after experimental infection (KILHAM & MARGOLIS 1965)

## **Morbidity and mortality**

- pathogenic in fetal and infant rats (JACOBY & BALL-GOODRICH 1995)
- acute disease in hamsters after experimental infection (KILHAM 1961)
- prenatal infections in rats (JACOBY et al. 1988)

## **Zoonotic potential**

- none

## **Interference with research**

### **Pathology**

- increased leukocyte adhesion in the aortic epithelium (GABALDON et al. 1992)
- hamsters surviving experimental infection develop stunted growth resembling mongolism (KILHAM 1961)

### **Immunology**

- infection of T and B lymphocytes and suppression of various lymphocyte functions (MCKISIC et al. 1995)
- stimulates autoreactive T lymphocytes specific for pancreatic antigens (BROWN et al. 1993)
- virus alters susceptibility to autoimmune diabetes in a rat strain which is normally resistant to this syndrome (GUBERSKI et al. 1991, STUBBS et al. 1994, ELLER-MANN et al. 1996)

- alters cytotoxic lymphocyte activity (DARRIGRAND et al. 1984)
- depresses lymphocyte viability and a variety of T cell functions like, e.g. in vitro lymphoproliferative responses (CAMPBELL et al. 1977 a, b)
- stimulates interferon production (KILHAM et al. 1968)

## Physiology

- inhibition of lipid formation in rat kidney cells in vitro (SCHUSTER et al. 1991)
- increased abortion rate (KILHAM & MARGOLIS 1969)

## Cell biology

- contaminant of cell lines (HALLAUER et al. 1971)
- persistent infection of cell lines and transplantable tumours (WOZNIAK & HETRICK 1969, BASS & HETRICK 1978, National Research Council 1991)
- Teratology
- congenital malformation (MARGOLIS & KILHAM 1975)
- death and resorption of foetuses (KILHAM & MARGOLIS 1966)

## Infectiology

- necrosis in the lung may support secondary colonisation with other microorganisms such as *Pasteurella pneumotropica* (CARTHEW & GANNON 1981)
- KRV together with H-1 and C. piliforme can influence the prevalence rate of Yersinia-induced arthritis in rats (GRIPENBERG-LERCHE & TOIVANEN 1993, 1994)

## Oncology

- contamination of transplantable or chemically induced tumours (KILHAM & OLIVIER 1959, CAMPBELL et al. 1977, NICKLAS et al. 1993)
- contamination of leukaemias or leukaemia virus preparations (KILHAM & MOLONEY 1964, BERGS 1967, SPENCER 1967)
- suppression of leukaemia induction by Moloney virus (BERGS 1969)

## References

- Baer, P. N., and L. Kilham. 1962. Rat virus and periodontal disease. II. Onset and effect of age at time of inoculation. *Oral Surg. Oral Med. Oral Path.* 15:1302-1311.
- Baringer, J. R., and N. Nathanson. 1972. Parvovirus hemorrhagic encephalopathy of rats. Electron microscopic observations of the vascular lesions *Lab. Invest.* 27:514-522.
- Bass, R., and F. M. Hetrick. 1978. Persistent infection of a human lymphocyte cell line (Molt-4) with the Kilham rat virus. *J. Infect. Dis.* 137:210-212.
- Bergs, V. V. 1967. Leukemias induced in rats by mammary tumor extracts. *J. Natl. Cancer Inst.* 38:481-490.
- Bergs, V. V. 1969. Rat virus-mediated suppression of leukemia induction by Moloney virus in rats. *Cancer Res.* 29:1669-1672.

- Brown, D. W., R. M. Welsh, and A. A. Like. 1993. Infection of peripancreatic lymph nodes but not islets precedes Kilham rat virus-induced diabetes in BB/Wor rats. *J. Virol.* 67:5873-5878.
- Campbell, D. A., Jr., E. K. Manders, J. R. Oehler, G. D. Bonnard, R. K. Oldham, and R. B. Herberman. 1977a. Inhibition of in vitro lymphoproliferative responses by in vivo passaged rat 13762 mammary adenocarcinoma cells. I. Characteristics of inhibition and evidence for an infectious agent. *Cell. Immunol.* 33:364-377.
- Campbell, D. A., Jr., S. P. Staal, E. K. Manders, G. D. Bonnard, R. K. Oldham, L. A. Salzman, and R. B. Herberman. 1977b. Inhibition of in vitro lymphoproliferative responses by in vivo passaged rat 13762 mammary adenocarcinoma cells. II. Evidence that Kilham rat virus is responsible for the inhibitory effect. *Cell. Immunol.* 33:378-391.
- Carthew, P., and J. Gannon. 1981. Secondary infection of rat lungs with *Pasteurella pneumotropica* after Kilham rat virus infection. *Lab. Anim.* 15:219-221.
- Cole, G. A., N. Nathanson, and H. Rivet. 1970. Viral hemorrhagic encephalopathy of rats. II. Pathogenesis of central nervous system lesions. *Am. J. Epidemiol.* 91:339-350.
- Coleman, G. L., R. O. Jacoby, P. N. Bhatt, A. L. Smith, and A. M. Jonas. 1983. Naturally occurring lethal parvovirus infection of juvenile and young-adult rats. *Vet. Pathol.* 20:49-56.
- Darrigrand, A. A., S. B. Singh, and C. M. Lang. 1984. Effects of Kilham rat virus on natural killer cell-mediated cytotoxicity in Brown Norway and Wistar Furth rats. *Am J. Vet. Res.* 45:200-202.
- El Dadah, A. H., N. Nathanson, K. O. Smith, R. A. Squire, G. W. Santos, and E. C. Melby. 1967. Viral hemorrhagic encephalopathy of rats. *Science* 156:392-394.
- Ellerman, K. E., C. A. Richards, D. L. Guberski, W. R. Shek, and A.A. Like. 1996. Kilham rat triggers T-cell-dependent autoimmune diabetes in multiple strains of rats. *Diabetes* 45:557-562.
- Fassolitis, A. C., et al. 1985. Thermal resistance of three parvoviruses: a possible human isolate, the minute virus of mice, and the latent rat virus. *J. Food. Protect.* 48:4-6.
- Gabaldon, M., C. Capdevila, and A. Zuniga. 1992. Effect of spontaneous pathology and thrombin on leukocyte adhesion to rat aortic endothelium. *Atherosclerosis* 93:217-228.
- Gaertner, D. J., R. O. Jacoby, F. X. Paturzo, E. A. Johnson, J. L. Brandsma, and A. L. Smith. 1991. Modulation of lethal and persistent rat parvovirus infection by antibody. *Arch. Virol.* 118:1-9.
- Gaertner, D. J., R. O. Jacoby, E. A. Johnson, F. X. Paturzo, and A. L. Smith. 1995. Persistent rat virus infection in juvenile athymic rats and its modulation by antiserum. *Lab. Anim. Sci.* 45:249-253.
- Gripenberg-Lerche, C., and P. Toivanen. 1993. *Yersinia* associated arthritis in SHR rats: effect of the microbial status of the host. *Ann. Rheum. Dis.* 52:223-228.
- Gripenberg-Lerche, C., and P. Toivanen. 1994. Variability in the induction of experimental arthritis: *Yersinia* associated arthritis in Lewis rats. *Scand. J. Rheumatol.* 23:124-127.
- Guberski, D. I., et al. 1991. Induction of type 1 diabetes by Kilham rat virus in diabetes-resistant BB/Wor rats. *Science* 254:1010-1013.
- Hallauer, C., G. Kronauer, and G. Siegl. 1971. Parvoviruses as contaminants of permanent human cell lines. I. Virus isolations from 1960 to 1970. *Arch. Ges. Virusforsch.* 35:80-90.

- Jacoby, R. O., P. N. Bhatt, and A. M. Jonas. 1979. Viral Diseases, in: H. J. Baker, J. R. Lindsey & S. H. Weisbroth (Eds.): The laboratory rat, Vol. 1, Biology and Diseases, Academic Press, New York, 1979.
- Jacoby, R. O., D. J. Gaertner, P. N. Bhatt, F. X. Paturzo, and A. L. Smith. 1988. Transmission of experimentally induced rat virus infection *Lab. Anim. Sci.* 38:11-14.
- Jacoby, R. O., E. A. Johnson, F. X. Paturzo, D. J. Gaertner, J. L. Brandsma, and A. L. Smith. 1991. Persistent rat parvovirus infection in individually housed rats *Arch. Virol.* 117:193-205.
- Jacoby, R. O., and L. Ball-Goodrich. 1995. Parvovirus infections of mice and rats *Sem. Virol.* 6:329-337.
- Kilham, L. 1961. Rat virus (RV) in hamsters. *Proc. Soc. Exp. Biol. Med.* 106:825-829.
- Kilham, L., and L. Olivier. 1959. A latent virus of rats isolated in tissue culture. *Virology* 7:428-437.
- Kilham, L., and G. Margolis. 1964. Cerebellar ataxia in hamsters inoculated with rat virus. *Science* 143:1047-1048 .
- Kilham, L., and G. Margolis. 1965. Cerebellar disease in cats induced by inoculation of rat virus. *Science* 148:244-246.
- Kilham, L., and G. Margolis. 1966. Spontaneous hepatitis and cerebellar 'hypoplasia' in suckling rats due to congenital infections with rat viruses. *Am. J. Pathol.* 49:457-475.
- Kilham, L., and J. B. Moloney. 1964. Association of rat virus and Moloney leukemia virus in tissues of inoculated rats. *J. Natl. Cancer Inst.* 32:523-531.
- Kilham, L., C. E. Buckler, V. H. Ferm, and S. Baron. 1968. Production of interferon during rat virus infection. *Proc. Soc. Exp. Biol. Med.* 129:274-278.
- Kilham, L., and G. Margolis. 1969. Transplacental infection of rats and hamsters induced by oral and parenteral inoculations of H1 and rat viruses (RV). *Teratology* 2:111-223.
- Kilham, L., and G. Margolis. 1975. Problems of human concern arising from animal models of intrauterine and neonatal infections due to viruses: a review. I. Introduction and virologic studies. *Progr. Med. Virol.* 20:113-143.
- Lipton, H. G., N. Nathanson, and H. Hodous. 1973. Enteric transmission of parvoviruses. Pathogenesis of rat virus infection in adult rats. *Am J. Epidemiol.* 6:443-446.
- Lussier, G (Ed.). 1991 Detection methods for the identification of rodent viral and mycoplasmal infections. *Lab. Anim. Sci.* 41:199-225.
- Lum, G. S. 1970. Serological studies of rat virus in relation to tumors. *Oncology* 24:335-343.
- Lum, G. S., and A. W. Schreiner. 1963. Study of a virus isolated from a chloroleukemic Wistar rat. *Cancer Res.* 23:1742-1747.
- Margolis, G., and L. Kilham. 1970. Parvovirus infections, vascular endothelium and hemorrhagic encephalopathy. *Lab. Invest.* 22:478-488.
- Margolis, G., and L. Kilham. 1975. Problems of human concern arising from animal models of intrauterine and neonatal infections due to viruses: a review. II. Pathologic studies. *Prog. Med. Virol.* 20:144-179.
- Mckisic, M. D., et al. 1995. A nonlethal parvovirus infection suppresses rat T lymphocyte effector functions. *J. Immunol.* 155:3979-3986.
- National Research Council, Committee on Infectious Diseases of Mice and Rats. Infectious diseases of mice and rats. National Academy Press, Washington, D.C., 1991.

- 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.
- Paturzo, F. X., R. O. Jacoby, P. N. Bhatt, A. L. Smith, D. J. Gaertner, and R. B. Ardito. 1987. Persistence of rat virus in seropositive rats as detected by explant culture. *Arch. Virol.* 95:137-142.
- Rabson, A. S., L. Kilham, and R. L. Kirschstein. 1961. Intranuclear inclusions in *Rattus (Mastomys) natalensis* infected with rat virus. *J. Natl. Cancer Inst.* 27:1217-1223.
- Robey, R. E., D. R. Woodman, and F. M. Hetrick. 1968. Studies on the natural infection of rats with the Kilham rat virus. *Am. J. Epidemiol.* 88:139-143.
- Robinson, G. W., N. Nathanson, and J. Hodous. 1971. Sero-epidemiological study of rat virus infection in a closed laboratory colony. *Am. J. Epidemiol.* 94:91-100.
- Schuster, G. S., G. B. Caughman, and N. L. O'Dell. 1991. Altered lipid metabolism in parvovirus-infected cells. *Microbios* 66:134-155.
- Spencer, H. J. 1967. Recovery of rat virus from a series of chemically induced rat leukemias. *Proc. Am. Assoc. Cancer Res.* 8:62.
- Stubbs, M., D. L. Guberski, and A. A. Like. 1994. Preservation of GLUT 2 expression in islet beta cells of Kilham rat virus (KRV)-infected diabetes-resistant BB/Wor rats. *Diabetologia* 37:1186-1194.
- Wozniak, J., and F. Hetrick. 1969. Persistent infection of a rat nephroma cell line with Kilham rat virus. *J. Virol.* 4:313-314.
- Tattersall, P., and S. F. Cotmore. 1986. The rodent parvoviruses, in: Bhatt, P. N. et al. (Eds.), *Viral and mycoplasmal infections of laboratory rodents. Effects on biomedical research.* Academic Press Inc., Orlando, 1986.
- Tennant, R. W., and R. E. Hand. 1970. Requirement of cellular synthesis for Kilham rat virus replication. *Virol.* 42:1054-1063.
- Yang, F.-C., F. X. Paturzo, and R. O. Jacoby. 1995. Environmental stability and transmission of rat virus. *Lab. Anim. Sci.* 45:140-144.

**Author: Werner Nicklas, DKFZ Heidelberg, Germany**