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Murine Norovirus

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Noroviruses are nonenveloped RNA viruses with high environmental resistance and belong to the family Caliciviridae, genus Norovirus. They were first identified after an outbreak of acute gastroenteritis at a school in Norwalk/Ohio (USA) in 1968 and cause about 90% of nonbacterial epidemic gastroenteritis in humans. Noroviruses found in animals include bovine, porcine, canine, feline and murine noroviruses. Noroviruses are not known to cross species.

The first norovirus to infect mice was described in 2003 (1). Experimental inoculation studies with this murine norovirus (MNV-1) show that duration of infection and disease manifestation vary depending on the mouse strain (1-3). In immunocompetent strains, MNV-1 infection is variable in length (e.g. ≥ 7-14 days in 129S6 mice, ≥ 5 weeks in Hsd:ICR mice) and does not induce clinical signs. Infection is associated with mild histopathological alterations in the small intestine (increase in inflammatory cells) and spleen (red pulp hypertrophy and white pulp activation) of 129S6 mice. However, infection can cause lethal systemic disease (encephalitis, vasculitis, meningitis, hepatitis and pneumonia) in certain immunodeficient lines with defects in the innate immune system (interferon-$\alpha\beta\gamma$ receptor-/- and Stat1-/- mice) or persist without symptoms in mice with defects in the acquired immune system (≥ 90 days in Rag1-/- und Rag2-/- mice). These findings indicate that components of the innate immune system are critical for resistance to MNV-1 induced disease. Consistent with this hypothesis, Wobus et al. (4) demonstrated that MNV-1 replicates in macrophages and dendritic cells. Meanwhile, many additional strains of MNV with diverse biological properties were isolated (5-9). An analysis of 26 MNV isolates revealed 15 distinct MNV strains that comprise a single genogroup and serotype (6).

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genogroup and serotype (6). Experimental inoculation studies show that several MNV strains are able to persist in various tissues (small intestine, caecum, mesenteric lymph node, spleen) of immunocompetent (C57BL/6J, Hsd:ICR, Jcl:ICR) and immunodeficient (C.B-17-Prkdcscid) mice with viral shedding in faeces for the duration of at least 35-60 days (5, 6, 10). MNV is transmitted via the faecal-oral route and is efficiently transferred to sentinel mice by soiled bedding (11, 12).

Embryo transfer (11) and hysterectomy (10) are effective means of eliminating MNV from mouse colonies. Since 1- to 3-day-old pups are resistent to infection, elimination of MNV may also be achieved by transferring neonates from infected dams to uninfected foster dams ("cross fostering") (13-15). This transfer should ideally be performed within 24 hours after birth.

MNV infection can be detected directly by RT-PCR on faecal pellets or tissue specimens (see above) and indirectly by serology (1-3, 5, 10, 16). Detection is facilitated by high stability of MNV RNA in faeces (at least 2 weeks at room temperature) (12) and by broad serological cross-reactivity among different strains of MNV (5, 6). Health surveillance data from North America (2, 17), Western Europe (16, 18, 19) Australasia (20) and Japan (21, 22) demonstrate a high prevalence of MNV infections in laboratory mice. In the hitherto largest survey (17), 32.4% of 44,876 mouse serum samples examined had antibodies against MNV. Various studies indicate that MNV is also circulating in wild rodents (23-26).

The impact of MNV on animal experiments remains to be evaluated. Recent studies show that MNV is immunmodulatory and may alter disease phenotypes in mouse models of inflammatory bowel disease (27-29). Furthermore, MNV modestly lowered the CD8 T cell response to murine cytomegalovirus infection in BALB/c and C57BL/6 mice (30), increased the duration of faecal mouse parvovirus shedding in BALB/cByJ and C57BL/6J mice (31), and increased atherosclerotic lesion size in B6.129S7-Ldlrtm1Her mice fed a high-fat diet (32). Other studies did not reveal any impact of MNV on experimental outcomes in mice (33-37).

In norovirus research, MNV is used as a model system to study aspects of norovirus biology and pathogenesis in vitro and in vivo (38, 39). It further serves as a surrogate for (non-cultivable) human noroviruses to evaluate chemical and physical methods of inactivation (40, 41).

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