

MINIREVIEW

Possible role of different animal species in maintenance and spread of murine gammaherpesvirus 68 in the natureM. WÁGNEROVÁ¹, A. CHALUPKOVÁ¹, Z. HRABOVSKÁ¹, L. ANČICOVÁ¹, J. MISTRÍKOVÁ^{1,2*}¹Department of Microbiology and Virology, Faculty of Natural Sciences, Comenius University, Bratislava, Slovak Republic; ²Institute of Virology, Slovak Academy of Sciences, Dúbravská cesta 9, 845 05 Bratislava, Slovak Republic*Received July 15, 2014; accepted February 9, 2015*

Summary. – Murine gammaherpesvirus 68 (MHV-68), isolated from a bank vole (*Clethrionomys glareolus*) in Slovakia in 1976 is a natural pathogen of wild murid rodents. This review is focused to biological properties of this pathogen, the mode of its maintenance in murid rodents as reservoir animals, mechanisms of its spread to other animals in the same biotope as well as to livestock and household animals. Potential role of ticks as vectors and the possibility of infection of humans with this virus are considered as well. All the above evidence of the virus infection of various hosts is based on serological or molecular analytical data. The presented knowledge indicates important epizootologic consequences, namely harboring and permanent maintenance of the virus in murid rodents as reservoir animals with a real possibility of spread to other animals in the same biotope. These relationships imply a cross-species virus transmission with potential serious consequences for the infected animals or humans.

Keywords: murine gammaherpesvirus 68; murid rodents; reservoir animals; humans; spread; epidemiology

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1. Introduction

The role of individual animal species in emerging viral diseases is not known. It is generally accepted that in case viruses exhibit host-switching, its results may be catastrophic, namely disease and death of animals and humans. Zoonotic outbreaks reflect several factors including increased mobility of human population and demographic and environmental changes caused by globalization. The threat of emerging viruses and the fact that there are no vaccines against the most common viral zoonoses drive research in this field. Transmission of a virus from its natural to other host species with serious outcome may be well documented on the example of herpesvirus saimiri which is not harmful to its natural host, Old world monkey but is even lethal to humans (Blaškovič *et al.*, 1987). Another example can be the pseudorabies virus (Aujeszky's disease virus), non-pathogenic

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Abbreviations: BRHV = Brest herpesvirus; EBV = Epstein-Barr virus; HVS = herpesvirus saimiri; KSHV = Kaposi's sarcoma-associated herpesvirus; LCMV = lymphocytic choriomeningitis virus; MHV-68 = murine gammaherpesvirus 68; VNT = virus neutralization test; WMHV = wood mouse herpesvirus

to pig as reservoir animal but lethal to cattle, deer, pet cats and dogs (Sabó, 1981).

In discussing herpesviruses it should be noted that they represent a spectacular evolutionary success as they have been found in all vertebrates and each of them is associated with a single host species. The host specificity of herpesviruses indicates that they have evolved together with their hosts over long time periods and have adapted to them. Herpesviruses exhibiting high pathogenicity for humans or farmed animals are invariably the result of disequilibrium promoted by human activity (Davison, 2002). The number of newly identified herpesviruses constantly increases so that at present the total of all herpesviruses exceeded two-hundreds. Only eight of these infect humans and cause different diseases (Wágnerová a Mistríková, 2011). This trend implies permanent demands on taxonomic classification of herpesviruses. In this context the former family *Herpesviridae* was recently updated to a new order, *Herpesvirales* consisting now from 3 families, 3 subfamilies, 17 genera and 90 species (Davison, 2010).

One of relatively novel herpesviruses is also the murine gammaherpesvirus 68 (MHV-68) which was isolated from wild murid rodents in Slovakia (Blaškovič *et al.*, 1980) and later in other European countries including UK (Blasdel *et al.*, 2003; Telfer *et al.*, 2007). The objective of this review was to cover the biology of MHV-68 and the role of individual animal hosts species in its maintenance and spread in the nature. Despite herpesviruses represent one of the most intensively studied group of viruses, many aspects of their epidemiology and ecology remain still unknown.

2. The virus

In designating the reviewed virus the most frequently used common name “murine gammaherpesvirus 68” (MHV-68) in preference to formal taxonomic name “murid herpesvirus 4” and to another less frequent common name “mouse herpesvirus strain 68” was chosen.

MHV-68 was originally isolated from wild murid rodents in Slovakia in 1976 as their natural pathogen (Blaškovič *et al.*, 1980). At the same time some more murine herpesviruses, namely MHV-60 and MHV-72 were isolated from bank vole (*Clethrionomys glareolus*) and MHV-76 and MHV-78 from yellow-necked mouse (*Apodemus flavicollis*), all in Slovakia. Later on, further isolates followed: MHV-Šumava from *A. flavicollis* in Bohemia (Mistríková and Blaškovič, 1985) and MHV-4556 and MHV-5682 from the same host in Slovakia (Kožuch *et al.*, 1993). Based on biological properties, MHV-68 was first taken for an alphaherpesvirus (Svobodová *et al.*, 1987), however, later molecular studies including sequencing of the genome indicated that it is a gammaherpesvirus, a member of the subfamily *Gammaherpesvirinae*

(Virgin *et al.*, 1997). A definitive acceptance of MHV-68 as gammaherpesvirus was effected in 1995 by its classification as “murid herpesvirus 4” to a new species, *Murid herpesvirus 4* in the genus *Rhadinovirus*, the subfamily *Gammaherpesvirinae* with synonymic common names “murine gammaherpesvirus 68” and “mouse herpesvirus strain 68” (Murphy *et al.*, 1995). The other murine herpesvirus isolates mentioned above, namely MHV-60, MHV-72, MHV-76, MHV-78, MHV-Šumava, MHV-4556, and MHV-5682 remained so far unclassified and are tentatively considered as gammaherpesviruses.

In 2010, two more gammaherpesviruses were isolated; one from field vole (*Microtus agrestis*) and the other from wood mouse (*Apodemus sylvaticus*). The genome of the latter, designated wood mouse herpesvirus (WMHV) was completely sequenced and showed an 85% nucleotide sequence identity with that of MHV-68. Another gammaherpesvirus named Brest herpesvirus (BRHV), isolated from a white-toothed shrew (*Crocidura russula*) was partially sequenced and gave a 99.25% identity with WMHV. Also the pathogenesis of WMHV in wood mice was very similar to that of MHV-68 (Hughes *et al.*, 2010). Thus WMHV and BRHV were considered strains of a new virus species.

To cover basic molecular biological characteristics of MHV-68 it is a DNA virus with double-stranded genome of ~118 kbp that encodes at least 80 genes and corresponding number of proteins. Based on genome sequences MHV-68 is similar to gammaherpesviruses herpesvirus saimiri (HVS), Kaposi's sarcoma-associated herpesvirus (KSHV) and Epstein-Barr virus (EBV).

The importance of MHV-68 resides in its worldwide use as an experimental model for studying a gammaherpesvirus infection. Gammaherpesviruses are considered archetypal pathogenic persistent viruses. The known human gammaherpesviruses, EBV and KSHV are host-specific and lack a convenient *in vivo* model. This makes the related animal gammaherpesviruses an important source of information. In particular a laboratory mouse infected with MHV-68 is commonly used as a general model of gammaherpesvirus pathogenesis and a tool in the development of therapeutic strategies against these viruses.

3. Maintenance of the virus in reservoir animals

The natural reservoir is an epidemiological term designating natural resource and environment for the persistence of the virus and the disease that occurs among the non-reservoir animals and humans rarely in the form of epidemics and is not present in their population between epidemics. Wild murid rodents represent the reservoir for MHV-68, hantaviruses, tick born encephalitis virus, and lymphocytic choriomeningitis virus (LCMV) (Grešíková *et al.*, 1986; Bardoš, 1965; Lee *et al.*, 1981). Rodents were confirmed as important reservoir

Table 1. Prevalence of serum antibodies to MHV-68 in various hosts

Host	Positivity for serum antibodies (%)	References	
Reservoir animals: wood mouse, bank vole, field vole, yellow-necked mouse, wild mouse	<i>A. flavicollis</i>	0-12.5	Mistríková and Blaškovič, 1985
	<i>A. agrarius</i> , <i>A. sylvaticus</i> , <i>M. arvalis</i>	20.7	Telfer <i>et al.</i> , 2007
	<i>A. flavicollis</i> , <i>A. sylvaticus</i> , <i>M. arvalis</i> , <i>C. glareolus</i>	30-40	Mistríková and Blaškovič, 1985
	<i>A. flavicollis</i> , <i>C. glareolus</i> , <i>M. arvalis</i>	31.4	Klempa <i>et al.</i> , 2001
Non-reservoir wild animals	Wild boar (<i>Sus Scrofa</i>)	7.7	Špajdelová and Sabó, 2009
	Red fox (<i>Vulpes Vulpes</i>)	16.7	Hamzová <i>et al.</i> , 2005
	Fallow deer (<i>Dama Dama</i>)	18.2	Špajdelová and Sabó, 2009
	Red deer (<i>Cervus Elephus</i>)	50	Špajdelová and Sabó, 2009
	European roe deer (<i>Capreolus Capreolus</i>)	12.5	Špajdelová and Sabó, 2009
Farm, domestic and household animals	Hare (<i>Lepus Europeus</i>)	24.4	Špajdelová and Sabó, 2009
	Domestic goat (<i>Capra hircus</i>)	15	Špajdelová, 2009
	Horse (<i>Equus Caballus</i>)	6	Špajdelová, 2009
	Cattle (<i>Bos Primigenius</i>)	8.7	Špajdelová, 2009
	Domestic dog (<i>Canis lupus familiaris</i>)	17.1	Špajdelová and Grmanová, 2010
	Domestic cat (<i>Felis silvestris catus</i>)	12.2	Špajdelová and Grmanová, 2010
Wild house mouse (<i>Mus dommesticus</i>)	3-13	Becker <i>et al.</i> , 2007	
Vector ?	Tick (<i>Ixodes Ricinus</i>)*	1.8	Ficová <i>et al.</i> , 2011
Humans	Laboratory personnel working with the virus	35 (ELISA) 40 (VNT)	Mistríková <i>et al.</i> , 2000
	Hunters	11.1	Hamzová, 2005
	People coming into contact with forest animals	12.5	Špajdelová and Sabó, 2009
	Patients from infectious wards	5	Marková <i>et al.</i> , 2007
	Patients with various diagnoses	16	Mistríková <i>et al.</i> , 2000

Antibodies assayed by VNT, complement-fixation test or ELISA. *MHV-68 positivity by PCR detection.

of 11 viral, bacterial, and parasitic agents including three different hantaviruses, LCMV, orthopoxvirus, *Leptospira* spp., *Borrelia* spp., *Rickettsia* spp., *Bartonella* spp., *Coxiella burnetii*, and *Toxoplasma gondii* in Austria (Schmidt *et al.*, 2014). The pathogenesis of MHV-68 infection in wild murid rodents has been well documented by detection of the virus in various organs and by assay of specific serum antibodies. In this context Klempa *et al.* (2001) detected the virus by PCR in the blood of *C. glareolus* and *A. flavicollis* in Slovakia in 31.4%. An analysis of 381 sera from *A. flavicollis*, *C. glareolus*, *M. arvalis* and *M. musculus* in former Czechoslovakia for specific antibodies by a complement-fixation test revealed 0–12.5% positivity and titers of 8–16 in dependence on the host and locality (Mistríková and Blaškovič, 1985). A more extensive study on 935 sera from 9 different host species showed that specific antibodies in titers of 2–256 were present in *A. flavicollis* and *C. glareolus* from all localities, while those in *A. sylvaticus*, *M. arvalis* and *M. agrestis* were less frequent (Blaškovič *et al.*, 1987).

In studying the incidence of the virus infection in free-living rodents in UK Blasdel *et al.* (2003) found its endemicity in *A. sylvaticus* but not in *C. glareolus* and *M. agrestis*, based on seropositivities of 13–22%, 2.7% and 0%, respectively. Viral DNA was detected by PCR in the lungs

and less commonly in the spleen of these animals. Another study of specific antibodies in *C. glareolus* and *A. sylvaticus* in UK revealed their higher prevalence in the latter host (Telfer *et al.* (2007), thereby supporting a generally accepted view that even though MHV-68 was originally isolated from *C. glareolus*, its major natural host is *A. sylvaticus*. A two-year study of the epidemiology of the virus infection in *A. sylvaticus* and *C. glareolus* by Knowles *et al.* (2012) suggested that (i) male reproductive behaviours of these animals represent an important natural route of transmission of this virus and (ii) this infection may have a detrimental effect on other wild hosts, thus objecting the view that gammaherpesviruses have limited impacts on natural co-evolved host species.

As for the prevalence of the virus infection in wild house rodents, an investigation on *Mus domesticus* in UK using serology showed values of 3–13% (Becker *et al.*, 2007).

In experimental studies of pathogenesis of MHV-68 mostly laboratory mice are employed as model hosts. A comparative study of the virus infection in its natural host, bank vole and laboratory mouse by luciferase imaging and classical virological methods showed that the virus replicated in bank vole approximately 1000-fold less effectively than in mouse (Francois *et al.*, 2010).

In considering the transmission of the virus two basic routes are evaluated: horizontal (between individual animals) or vertical (between mother and fetus or newborn) via placenta or breast milk.

In a study on pregnant Balb/c mice chronically infected with the virus, Štiglicová *et al.* (2011) found the virus in breast milk, tumors in mothers, premature termination of pregnancy and reduced number and size of newborns. All these results indicated vertical transmission of the virus and its teratogenicity. Hricová and Mistríková (2008) detected the virus in lactic glands and breast milk of infected mice already on day 4, in urine and salivary glands on day 9 and in saliva and tear glands on day 14 post infection. These results indicated that intranasal and peroral routes of infection are most probably involved in the virus contraction.

In summary, in considering the maintenance of MHV-68 in reservoir animals the possible way of infection at early age, from infected mother to fetus or newborn is via placenta or breast milk. In adulthood, the transmission is horizontal via air, saliva or urine. There is a real possibility that the virus is transmitted not only to the reservoir animals representing various phylogenetically distant rodents but also to other animal species inhabiting the same biotope. The hypotheses about the likely routes of dissemination of the virus were experimentally confirmed. Thus the respiratory tract appears the main gateway for this virus, i.e. its natural dissemination is carried out by air. After an acute phase of infection that is usually inapparent there follows a chronic phase with lifelong latency and possible reactivation of latent virus. During the infection the virus is excreted via the respiratory tract, saliva, tears, and urine (Hricová and Mistríková, 2008).

4. Spread of the virus to other animal species

With regard to the fact that MHV-68 is capable of infecting different phylogenetically distant species of murid rodents such as *C. glareolus* (the subfamily *Microtinae*) and *A. flavicollis* (the subfamily *Murinae*) it can be hypothesized that this virus could theoretically overstep the species specificity more extensively. This assumption was confirmed by examining the sera of non-reservoir animals occupying a common space with murid rodents.

Thus virus-neutralizing antibodies were detected in sera of wild animals such as fallow deer, red deer, European roe deer, wild boars, daniels, pheasants, mouflons, foxes and hares from different areas in Slovakia (Mistríková *et al.*, 2000; Hamzová *et al.*, 2005; Špajdelová and Sabó, 2009). The detection positivity was partial and varied in dependence on host, place and time (Table 1).

Studies on domestic and farm animals such as horses, cattle, goats, cats and dogs in Slovakia gave similar results (Špajdelová, 2009; Špajdelová and Grmanová, 2010) (Table 1).

A sort of surprise was the finding of the virus in *Ixodes ricinus* (Ficová *et al.*, 2011) that implies the possible involvement of this vector in the spread of the virus in wild mouse in nature. This finding was confirmed experimentally by infected ticks naturally infected with murine herpesvirus sucking on experimentally infected mice. The virus survived metamorphosis ticks, and other developmental stage ticks were transferred to a clean laboratory mice. Murine virus was demonstrated in the salivary glands of ticks which is consistent with biological transmission by saliva of ticks.

Virus survived in ticks without loss of infectivity at least 4 months as demonstrated ability of the virus to multiply in mammalian cells and form plaques. Unlike most pathogenic arboviruses are able to influence MHV-68 infection to ticks, which led to their reduced ability metamorphosis compared with uninfected ticks. This was the first experimental evidence that the herpes virus can be transmitted by blood of suckling arthropod (V. Hajnická, personal communication).

5. Infection of humans with the virus

There is no evidence on the virus infection of humans or on studies on the virus pathogenicity for humans (Mistríková *et al.*, 2000). All the relevant information concerns virus-specific serum antibodies in the persons more or less exposed to the virus. Thus such antibodies were found by ELISA in some percentage in laboratory personnel long time directly working with the virus, hunters coming into contact with the virus indirectly in the wild and even in persons without any real contact to the virus such as patients with various infection or non-infection diagnoses (Mistríková *et al.*, 2000, 2006; Hamzová *et al.*, 2005; Špajdelová and Sabó, 2009; Marková *et al.*, 2007) (Table 1). The only entirely negative group was blood donors from transfusion stations (Mistríková *et al.*, 2006). In view of a relatively high prevalence of antibodies (16%) in the group of patients with various diagnoses we attempted to exclude possible false-positive results caused by cross-reaction of the MHV-68 antigen with antibodies to other human herpesviruses, particularly HSV-1, HCMV and EBV in ELISA. The results obtained by VNT and immunofluorescence assay (IFA) proved a false positivity of the ELISA due to cross-reactivity of MHV-68 with EBV. In addition, a high prevalence of antibodies to EBV was demonstrated in general population (Mistríková *et al.*, 2000; Stewart *et al.*, 1994, 1999; Virgin *et al.*, 1997; Efstathiou *et al.*, 1990).

In the context of the issue of infection of humans with MHV-68 it could be of interest the finding of *in vitro* transformation of human cells with this virus (F. Golais, personal communication).

6. Conclusions

Since we recently face a constant increase in the number of novel virus isolates or even viruses in general and herpesviruses in particular, we principally cannot exclude the emergence of novel viral pathogens of animals or humans. Proving the presence of relatively novel herpesvirus, MHV-68 and/or its antibodies in various hosts enabled identification of its reservoir animals and understanding of mechanisms of its maintenance within the reservoir and spread to other wild, farm or household animals including humans. In general, the knowledge of biology, epidemiology and ecology of this virus can help us to prevent known virus infections and to avoid potential infections caused by so far unknown agents.

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