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► **To cite this version:**

B. Karsten Tischer, Nikolaus Osterrieder. Herpesviruses - a zoonotic threat?. *Veterinary Microbiology*, 2010, 140 (3-4), pp.266. 10.1016/j.vetmic.2009.06.020 . hal-00556050

HAL Id: hal-00556050

<https://hal.science/hal-00556050>

Submitted on 15 Jan 2011

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Accepted Manuscript

Title: Herpesviruses - a zoonotic threat?

Authors: B. Karsten Tischer, Nikolaus Osterrieder

PII: S0378-1135(09)00304-6
DOI: doi:10.1016/j.vetmic.2009.06.020
Reference: VETMIC 4474



To appear in: *VETMIC*

Received date: 16-1-2009
Revised date: 4-3-2009
Accepted date: 12-6-2009

Please cite this article as: Tischer, B.K., Osterrieder, N., Herpesviruses - a zoonotic threat?, *Veterinary Microbiology* (2008), doi:10.1016/j.vetmic.2009.06.020

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1 **Herpesviruses - a zoonotic threat?**

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18

19 Abstract

20 Herpesviruses are highly host specific and share a long synchronous evolution with their
21 hosts. Only in rare cases, species barriers fall and allow animal to human or human to animal
22 transmission. Among the zoonotic herpesviruses, *Cercopithecine herpesvirus 1* is the most
23 significant and can be transmitted from macaques to human. Conversely, *Human*
24 *herpesvirus 1* is capable of causing severe disease in primates. Besides those two
25 examples, there are several herpesviruses with a certainly limited or only suspected ability to
26 cross species barriers. Those include *Saimiriine herpesvirus 2*, *Phocid herpesvirus 2*, Equid
27 herpesvirus 1, Epstein-Barr Virus, Marek's disease virus, and pseudorabies virus.
28 Concerning xenotransplantations, porcine gammaherpesviruses must be considered as a
29 zoonotic threat.

30

31 **Keywords:** herpes B virus, herpes simplex virus, Marek's disease virus, phocine herpesvirus

32

33 Introduction

34 The *Herpesviridae* are large DNA viruses of humans and vertebrates but members of this big
35 virus family were also isolated from invertebrates such as mollusks (Fields, 2007). The family
36 is part of the order *Herpesvirales* and is divided into three subfamilies, *Alpha-*, *Beta-* and
37 *Gammaherpesvirinae*, with a growing number of identified species, which generally show a
38 long-standing co-evolution of the respective viruses with their hosts. However, there are
39 cases of a transfer of virus lineages between distantly related hosts (Ehlers et al., 2007;
40 Ehlers et al., 2008a). Altogether, the phylogenetic data clearly indicate a very narrow host
41 range and specificity of herpesviruses but show at the same time that there is a residual
42 potential to cross host species barriers and to adapt to new hosts (Ehlers et al., 2008b),
43 which raises the question of the present and possibly future zoonotic potential of
44 herpesviruses.

45 The term zoonosis describes a phenomenon, which is characterized by the ability of a given
46 disease agent to overcome species barriers between human and animals, mainly
47 vertebrates. Zoonoses naturally occur more frequently among closely related host species,
48 but transmissions of disease agents can also be found where barriers of transmission are
49 inherently low or artificially lowered. Examples for such lowering of barriers of transmission
50 are close contacts of humans to animals living in zoos or Safari Parks or situations where
51 pets live in the same household with their owners. Lately, a specialized form of “close
52 relationship” has become more and more important, namely the transplantation of xenogenic
53 organs, particularly the potential use of organs from pigs in man.

54 Only rarely zoonotic infections are able to establish a sustained presence in the new host
55 and often variations of the pathogen are necessary to adapt to the new host system (Parrish
56 et al., 2008).

57 In this review, we will focus on the most important zoonotic infections caused by
58 herpesviruses, which generally are rare because of the usual close and long-standing
59 evolutionary relationship between viruses and their respective hosts.

60

61 ***Cercopithecine herpesvirus 1***. *Cercopithecine herpesvirus 1* (CeHV-1, Herpes B Virus, B
62 virus) is by far the most important zoonotic threat to human health caused by a member of
63 the herpesvirus family (Jainkittivong and Langlais, 1998b). The virus naturally causes a
64 virtually asymptomatic infection in Asian macaques (*Macaca mulatta* and *Macaca*
65 *fascicularis*) (Keeble et al., 1958; Davenport et al., 1994). The clinical picture in the natural
66 host is comparable to *Human herpesvirus 1* (HHV-1, herpes simplex virus type 1) infections
67 in humans with mild mucocutaneous lesions upon primary infection, latency in sensory
68 ganglia, and virus reactivation (Benson et al., 1989; Weigler, 1992b). Virus shedding mainly
69 occurs via bodily fluids, like saliva or other contaminated excretions upon primary infection or
70 reactivation (Weigler et al., 1993b). The seroprevalence of CeHV-1 varies between different
71 studies from 5.3% in urban performance monkeys in Indonesia up to 97% of >2.5 year old

72 monkeys housed at the California Regional Primate Research Center. Generally, the
73 seroprevalence is comparable to that of HHV-1 in humans such that it is lower in younger
74 animals and increases as a function of age (Shah and Morrison, 1969; Weigler et al., 1990;
75 Kessler and Hilliard, 1990; Weigler et al., 1993a; Schillaci et al., 2005; Sariol et al., 2006; Lee
76 et al., 2007). Approximately 40% of seropositive macaques were found to be PCR positive
77 for CeHV-1 sequences in trigeminal ganglia (Oya et al., 2008).

78 While causing mostly very mild or asymptomatic infections in its natural host, CeHV-1 can be
79 fatal in humans. The main route of transmission is exposure to saliva from infected animals
80 by bites and scratches, but needle-stick injuries and even airborne infections were also
81 reported (Palmer, 1987; Holmes et al., 1990; Artenstein et al., 1991; Weigler, 1992a). In
82 addition, one case of human-to-human transmission of CeHV-1 is documented (Centers for
83 Disease Control (CDC), 1989). Although all known CeHV-1 infections are related to animals
84 held in captivity for biomedical research, infections of humans at places that will allow close
85 contact with macaques are possible and remain a potentially serious threat to human health
86 (Cohen et al., 2002c). For that reason, CeHV-1 seropositive animals are sometimes culled,
87 as was done e.g. at Woburn Safari Park (U.K.) (CDR, 2000).

88 The onset of symptoms of CeHV-1 infections and the progress of the disease often depend
89 on the route and the dose of infection. Primary vesicular lesions are mostly found at the site
90 of exposure. Also, itching, pain, numbness and lymphadenopathy are occasionally seen
91 proximal to the site of infection. Usually those primary symptoms are followed by a general
92 flu-like illness. In the majority of the cases in which antiviral treatment was not initiated, the
93 patients developed encephalitis resulting in severe neurological disorders combined with
94 high mortality reaching up to 80% (Jainkittivong and Langlais, 1998a; Cohen et al., 2002b;
95 Huff and Barry, 2003). There is some speculation about asymptomatic human CeHV-1
96 infections, but since no asymptomatic, seropositive contact individuals could be identified so
97 far, those cases might only occur rarely or not at all (Freifeld et al., 1995).

98

99 Other primate herpesviruses

100 Other primate herpesviruses, like *Cercopithecine herpesvirus 2* (simian agent 8) or
101 *Cercopithecine herpesvirus 16* (baboon herpesvirus 2) have also been discussed to have a
102 zoonotic impact; however, neither of the viruses could unambiguously be linked with any
103 cases of human disease (Kalter and Heberling, 1990; Borchers and Ludwig, 1991; Black and
104 Eberle, 1997; Rogers et al., 2006; Ritchey et al., 2006). Yet another herpesvirus that is
105 discussed as a zoonotic agent is *Saimiriine herpesvirus 2* (SaHV-2, herpesvirus saimiri). Its
106 natural hosts are squirrel monkeys, which are usually infected within the first two years of life.
107 The infection in the monkeys is completely asymptomatic and the virus persists in its host for
108 life (Melendez et al., 1968). Upon experimental infection of New World primates, however, T-
109 cell lymphomas can be induced (Melendez et al., 1969b; Wright et al., 1976). In cell culture,
110 human T-lymphocytes can readily be transformed with SaHV-2 subgroup C (Biesinger et al.,
111 1992). Although no human infections with SaHV-2 were reported so far, this member of the
112 *Gammaherpesvirinae*, genus *Rhadinovirus*, presents a clear potential threat for zoonotic
113 infections and raises the bar for the use of SaHV-2 for gene therapy or oncolysis, which is
114 propagated by some investigators due to its lymphotropism that is a desired characteristic of
115 such a tool (Griffiths et al., 2006; Vaha-Koskela et al., 2007). Before SaHV-2 could be used
116 as a gene delivery vehicle, however, extensive testing as to vector safety would have to be
117 completed, especially given the relatively close relationship with *Human herpesvirus 8*, the
118 causative agent of Kaposi sarcoma.

119

120 Herpesviruses associated with zoonotic potential

121 Certainly, herpesviruses that can readily infect human cells in cell culture theoretically
122 represent zoonotic threats. Examples for this category of herpesviruses are members of the
123 *Alphaherpesvirinae* such as Suid herpesvirus 1 (SuHV-1, pseudorabies virus) or equid
124 herpesvirus 1 (EHV-1). The latter was shown to be able to infect a wide spectrum of cells
125 coming from various host species and tissues in vitro, among them human epithelial cells

126 and peripheral blood mononuclear cells. In addition, productive intranasal infection with EHV-
127 1 of other species such as the mouse or Syrian hamster could be shown, thereby
128 demonstrating the potential of EHV-1 to cross species barriers. Since there are no
129 seropositive results from human routinely working with EHV-1 and no human infections were
130 reported so far, the threat seems to largely be theoretical in nature (Trapp et al., 2005).

131 SuHV-1 is the causative agent for Aujeszky's disease in swine and can also break species
132 barriers and establish infections e.g. in sheep, dogs, cattle, panther or mink. Infections of
133 species other than swine invariably results in severe neurological symptoms and death of the
134 affected animals (Kluge et al., 1992; Glass et al., 1994; Marcaccini et al., 2008). Despite an
135 anecdotic report about three cases of PRV infections in man, humans and primates, for
136 unknown reasons, seem to be refractory to infection with this virus. HHV-1, HHV-2 and
137 SuHV-1 were shown to use the same set of cellular receptors for entry into target cells.
138 Consequently, a post-entry restriction of virus growth is likely but has not been investigated
139 in any detail (Mravak et al., 1987; Kluge et al., 1992).

140 Yet another alphaherpesvirus, *Gallid herpesvirus 2* (GaHV-2, Marek's disease virus), was
141 claimed to be involved in human infections. First, a connection was postulated in some
142 reports between GaHV-2 infection and multiple sclerosis (McStreet et al., 1992). Another
143 study reported that human serum samples apparently tested GaHV-2-positive by PCR
144 (Laurent et al., 2001). The results, however, could not be reproduced by other research
145 groups and must therefore be deemed inconclusive (Hennig et al., 1998; Hennig et al.,
146 2003). At least, there is no formal proof or even likelihood of an infection of humans with this
147 avian herpesvirus that is capable of infecting host species other than the chicken, namely the
148 turkey and the quail.

149 Another herpesvirus with a zoonotic potential is a seal gammaherpesvirus, *Phocid*
150 *herpesvirus 2* (PhHV-2). Although gammaherpesviruses usually are narrowly host restricted,
151 PhHV-2 isolates are able to infect a wide variety of cells from different species *in vitro*, also
152 including primate and human cell lines. In addition, experimental infections of mice and even

153 monkeys are possible and virus replication could be confirmed in the upper respiratory tract
154 and in PBMCs (Martina et al., 2007).

155

156 **Lowered barriers of transmission - xenotransplantations**

157 The availability of a sufficient number of suitable donor organs is a decisive bottleneck for
158 human transplantation medicine. For decades, ongoing research has tried to overcome that
159 problem by using xenogenic organs and for many reasons the domestic pig is the species of
160 choice for producing organs for xenotransplantation (Calne, 1966; Deodhar, 1986;
161 Schuurman and Pierson, III, 2008). One of the big concerns for the completion of this dream,
162 besides all the immunological problems that would result in immediate rejection of the
163 transplant, is the transmission of viruses from the donor animal to the recipient by infected or
164 contaminated organs (Isacson and Breakefield, 1997; Fishman and Patience, 2004). Not
165 only would the barrier of transmission be reduced dramatically in patients receiving such an
166 organ from a different species. All organ recipients, regardless of the source of the organ,
167 have to receive immunosuppressive therapy post transplantation to minimize the risk of
168 transplant rejection. Such immunosuppressive therapy, unfortunately, also drastically
169 reduces the ability of the host immune system to restrict persistent or latent viruses present
170 in the transplant. It is therefore well known that e.g. human cytomegalovirus present in the
171 recipient or “incoming” with the organ represent a serious threat in transplantation medicine
172 because immunosuppressive therapy can cause reactivation of the virus (Slifkin et al., 2004).
173 Among the porcine viruses potentially causing problems after xenotransplantation are retro-
174 but also gammaherpesviruses, which potentially pose such a threat. Recently, it was shown
175 that porcine lymphotropic herpesvirus 1 and its close human relatives, *Human herpesvirus 8*
176 (HHV-4, Epstein-Barr Virus and *Human herpesvirus 8*, are capable of transactivating each
177 other. Since co-infection of recipients with HHV-4 and the porcine virus would be highly
178 likely, a double infection of one and the same cells with both gammaherpesviruses cannot be
179 excluded. Consequently, such co-infections, especially under immunosuppressive therapy,

180 may result in reactivation of HHV-4 and present a clear threat to the sustained health of the
181 individual receiving a porcine transplant. It is also conceivable that the porcine viruses adapt
182 to and establish a foothold in humans, thereby causing bona fide zoonotic infection.
183 Therefore, in the case of xenotransplants, one will have to weigh the health of the individual
184 (and right thereto) to the potential health threat to the general population, which presents
185 quite a substantial ethical problem (Santoni et al., 2006).

186

187 **Human to animal transmission**

188 Besides infections of man by animal viruses, zoonotic infections of animals with human
189 herpesviruses have also been demonstrated. There is a report of an HHV-1 infection in a
190 group of marmosets resulting in a mortality of 100% (Matz-Rensing et al., 2003). In addition,
191 infection with HHV-1 of other New World primates was reported, also resulting in fatal
192 disease (Melendez et al., 1969a; McClure and Keeling, 1971). For as yet unknown reasons,
193 Old World primates appear to be less susceptible to HHV-1 and infection results in clinical
194 signs comparable to those after infection of humans (Smith et al., 1969; Emmons and
195 Lennette, 1970; McClure et al., 1980; Heldstab et al., 1981; Ramsay et al., 1982).

196 There is also evidence for potential HHV-4 infection in dogs. Not only can rat and canine cell
197 lines stably be infected with HHV-4, but HHV-4 or and HHV-4 -like infection could be
198 detected in pet dogs serologically, by PCR, nucleotide sequencing and *in situ* hybridization
199 (Yang et al., 2000; Chiou et al., 2005). Taken together, one has to conclude from the studies
200 summarized above that there either is transmission of HHV-4 to dogs or there are canine
201 gammaherpesviruses that are closely related to HHV-4.

202

203 **Concluding Remarks**

204 Overall, herpesviruses have a long-standing, most near-commensal relationship with the
205 species they have co-evolved with. There are only two examples where there is clear
206 evidence for herpesviruses causing zoonoses. One of the viruses is herpes CeHV-1 , which
207 presents a clear threat for people working or getting in close contact with macaques. The
208 second herpesvirus with clear zoonotic potential is the the closely related alphaherpesvirus
209 HHV-1, which is capable to establish productive and lethal infection in primates. All the other
210 examples of putative and suspected herpesvirus zoonoses are of theoretical or sometimes
211 even anecdotal nature. Taken together, herpesviruses are highly species-specific and
212 present an almost negligible zoonotic threat. However, as is the case for certainly almost all
213 infectious agents, the risk for a zoonotic infection is increased when closer contacts to
214 infected hosts are established and barriers of transmission are lowered. These latter
215 scenarios are certainly becoming ever more important with the advent of xenotransplantation
216 and the adaptation of “exotic” companion animals. Therefore, an increased vigilance towards
217 herpesvirus infections of man transmitted by diseases is imperative.

218

219 Acknowledgments

220 Research in the authors' laboratories is supported by the National Cancer Institute of the
221 National Health Institute, the United States Department of Agriculture, the Deutsche
222 Forschungsgemeinschaft and Morris Animal Foundation. .

223

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