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Herpesviruses - a zoonotic threat?

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Abstract

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

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

Introduction

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

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

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

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

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

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

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

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

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Other primate herpesviruses

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

Herpesviruses associated with zoonotic potential

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

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

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

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

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

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

Lowered barriers of transmission - xenotransplantations

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

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

Human to animal transmission

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

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

Concluding Remarks

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

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