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Simian herpesviruses and their risk to humans

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Abstract

A high level of genetic and physiological homology with humans has rendered non-human primates (NHP) an essential animal model for biomedical research. As such NHP offer a unique opportunity to study host-pathogen interactions in a species that closely mimics human biology but can yet be maintained under tight laboratory conditions. Indeed, studies using NHP have been critical to our understanding of pathogenesis as well as the development of vaccines and therapeutics. This further facilitated by the fact that NHPs are susceptible to a variety of pathogens that bear significant homology to human pathogens. Unfortunately, these same viruses pose a potential health issue to humans. In this review we discuss the simian herpesviruses and their potential to cause disease in researchers that come into close contact with them.

INTRODUCTION

Non-human primates (NHP) represent an invaluable resource for elucidating and understanding disease processes in humans, as humans and NHP share close developmental, physiological and evolutionary relationships [1]. For infectious disease research, NHP have historically played an important role as they are either susceptible to infectious agents that cause disease in humans or harbor infectious agents that are closely related to those that infect and cause disease in humans. For vaccine research, NHP, in particular rhesus macaques (RM), represent the gold standard for evaluating potential vaccines to inhibit HIV infection, and are essential to test virulence of live vaccines for other viral pathogens that are dangerous to humans. Additionally, the recent elucidation of the RM genome sequence [2] will enrich our understanding of primate biology with respects to infectious disease and how primates respond to disease-causing microorganisms not only at the cellular level, but now the genetic level. With this type of information available for infectious disease researchers, the utilization of RM in biomedical research is anticipated to increase significantly.

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As essential as NHP are for infectious disease research, it is important to remember that NHP harbor pathogens that are potential biological hazards to humans. For example, NHP harbor herpesviruses that are genetically more closely related to human herpesviruses than other mammalian herpesviruses. These simian herpesvirus homologues, which include alpha (α), beta (β) and gamma (γ)-herpesviruses, are capable of causing similar, if not identical, disease manifestations in their natural host, which makes them excellent models to dissect the complicated host-pathogen interactions that lead to disease. Unfortunately, one simian herpesvirus, specifically Herpes B virus can induce fatal encephalomyelitis in humans if humans are exposed to biological fluids or tissue from NHPs harboring the virus. Given the biosafety hazards to biomedical researchers and animal care technicians utilizing NHPs and the need to provide animals free of viruses that can potentially compromise AIDS vaccine and pathogenesis research, the National Centers for Research Resources (NCRR) of the National Institutes of Health (NIH) initiated a program in 1988 to breed RM that are classified as Specific Pathogen Free (SPF). These animals are screened to be antibody negative of herpes B virus, simian immunodeficiency virus (SIV); Type D simian retrovirus; and simian T-lymphotropic virus. The remainder of this review will discuss representative simian herpesviruses and their utility as models of human disease and the potential biosafety hazard these viruses pose to humans.

ALPHA-HERPESVIRUSES

Herpes B virus

Cercopithecine herpesvirus 1, also known as B virus (McHV1), and more recently designated as McHV1 [3] is an alpha-herpesvirus indigenous in Asiatic macaques. In its natural host, McHV1 infection is very similar to that of HSV-1 and HSV-2 in humans. However, transmission of McHV1 to non-macaque primates, including humans, can result in serious and often fatal encephalomyelitis. Below, we discuss the genetic similarities between McHV1 and HSV-1/2, pathogenesis in the natural host and the pathology associated with human infection.

Genome organization—McHV1 is an enveloped double stranded DNA virus that shares extensive genetic similarities with HSV-1 and -2. Like all alpha-herpesviruses, the McHV1 genome is composed of a unique long (UL) and a unique short (US) segment delimited by a repeat L (RL) and a repeat S (RS) repeat sequence [4,5]. The genome of McHV1 is closest in size and G+C content to that of HSV-2 and analysis of the McHV1 genome reveals the presence of 72 unique open reading frames (ORFs) that share significant sequence homology and genetic organization with HSV ORFs [6-8].

Pathogenesis and dissemination—In its natural host, McHV1 infection produces a disease that resembles HSV infection in humans. Primary infection can be associated with the development of vesicular lesions that are similar to those observed during primary infection with HSV-1 in humans. These lesions occur at mucosal surfaces (around the mouth and in the oral cavity), skin and conjunctiva [9]. The lesions associated with primary infection produce mild localized signs in monkeys and heal without scarring within 14 days of erupting [10]. Like HSV-1, McHV1 establishes latent infection in sensory ganglia. Periodic shedding can occur in bodily secretions such as saliva and urine, and genital secretions. Viral shedding can occur spontaneously in the absence of clinical signs of disease; or as a result of stress such as the onset of breeding season [11] or due to relocation [12] and immune suppression. Seroprevalence of McHV1 is associated with increasing age in macaques. A survey found that only 22% of juveniles were seropositive compared to over 80% in the adult population [13]. McHV1 transmission is believed to occur through sexual contact or bite wounds since newborn macaques of seropositive mothers are not infected with McHV1 until they get older [14,15]. McHV1 infection of other monkey species can be fatal. For instance, the transmission of

McHV1 from lion-tailed macaques caused an outbreak in a colony of De Brazza's monkeys with high mortality [16]. Furthermore, McHV1 has been shown to cause fatal disease in capuchin monkeys [17] and common marmosets [18].

Risks to humans—Although McHV1 causes a benign infection in macaques, it can cause a fatal encephalomyelitis in humans. McHV1 infection can be acquired through exposure to contaminated bodily fluids at mucosal surfaces through scratches, bite wounds, needle sticks, injuries by infected cages, or contact with infected tissues. In addition, there is one documented case of person-to-person transmission [19]. Patients can develop dermal lesions at wound sites that resemble HSV primary infection or herpes zoster. Symptoms include fever, pain, fatigue, headaches, and nausea. In most cases, neurological complications develop that include: ataxia, hyperthesia, ascending flaccid paralysis and agitation. Encephalitis occurred in 88% of the documented cases. It is unclear whether McHV1 can establish latency in humans with periodic shedding. However, a serological survey of over 300 animal handlers, amongst whom 166 reported potential exposures, showed that none were McHV1-seropositive [20]. This study suggests that the likelihood that McHV1 causes asymptomatic disease in humans is negligible. Another study estimated that 1:50 to 1:250 contacts with macaques have the potential to result in exposure to McHV1 [21]. Several additional observations suggest that the type of exposure and the time lapse between exposure and cleaning of the site are crucial determinants of the risks for developing disease [21].

The diagnosis of McHV1 infection relies on the isolation of the virus from the animal/cage/tissue and/or the identification of McHV1-specific antibodies in the serum. The high antigenic cross-reactivity between McHV1 and HSV renders serological diagnosis of McHV1 infection difficult. Several diagnostic methods have recently been developed to facilitate this distinction. An ELISA that specifically measured antibody responses to glycoproteins D (gD) from herpes B, and gG from HSV-1 and -2 was found to have high sensitivity [22]. Alternatively, diagnostic PCR using primers specific for the highly variable gG gene of McHV1 can also be used [23].

Prevention of McHV1 exposure involves following guidelines established by the Centers for Disease Control and Prevention (CDC) [24]. These include: 1) enhancing workers' awareness of B virus and its dangers; 2) screening and maintenance of a B virus-free colony; 3) physical or chemical restraint of the animals before obtaining samples; 4) enforcing the use of personal protective clothing; 5) proper incident reporting and wound management. Currently the administration of acyclovir or gancyclovir is the recommended treatment against McHV1 treatment although they are ten-fold less efficacious in preventing McHV1 replication as HSV-1 in tissue culture [18,25]. The duration of acyclovir treatment has not been established. A vaccine that could prevent or limit McHV1 infection in macaques would lessen occupational risk and might reduce disease severity. DNA vaccines against gB and gD were investigated in mice and macaques [26,27] and a recombinant vaccinia vaccine expressing gD was investigated in rabbits [28]. All vaccines generated cellular and humoral immune responses but only the vaccinated rabbits were challenged with McHV1 to evaluate the efficacy of the vaccine.

Simian Varicella Virus

Simian varicella virus (SVV) was discovered in the late 1960's following a series of outbreaks in several primate facilities [29]. Causative agents were identified as herpes viruses based on their size and morphology of enveloped viral particles [30]. Serological assays later determined that these viruses shared significant homology to human varicella zoster virus (VZV) [31,32]. Below, we discuss the utility of SVV as a model of VZV infection and potential risk to humans.

Genome organization—SVV and VZV are evolutionarily related with an estimated 70-75% DNA homology [33-36]. Like other alpha-herpesviruses, the SVV genome consists of a long component (L) covalently linked to a short component (S). The S component includes terminal and internal terminal repeat sequences (TRS, IRS), which bracket the unique short segment. A total of 69 distinct SVV ORFs were identified, each of which shares extensive homology to a corresponding VZV gene, which ranges from 75.4% (ORF 31, glycoprotein B) to 27.3% (ORF 1).

Pathogenesis and transmission—In the years between 1967 and 1974, several simian varicella outbreaks occurred involving African Pates monkeys, African green vervet monkeys, Cynomolgus macaques, pigtail macaques, and Japanese macaques. Although the severity of disease varied, most outbreaks were associated with high morbidity and mortality, which in some cases reached 40% [2]. The vast majority of our understanding of SVV pathogenesis is derived from studies involving experimental inoculation of African green monkeys and Cynomolgus macaques. In these animals, infection is followed by a 7-10 day incubation period during which viremia disseminates the virus throughout the body. Clinical disease is characterized by fever and vesicular skin rash on the face, abdomen and extremities that appears on day 10 post-infection [37]. As described for VZV, pneumonia, hepatitis and hemorrhagic skin rash occur during more severe cases. During or after acute infection, and similar to VZV infection in humans, SVV establishes latent infection in sensory ganglia [38] of surviving monkeys. As described for VZV, SVV can reactivate [29,39-41] to cause secondary disease and viral transmission to susceptible monkeys. However, experimental inoculation of African green monkeys and Cynomolgus macaques with SVV results in persistent viremia that can last for years [42,43], which has limited the use of these models to investigate VZV latency and suggest that these NHP species may not be the natural host of SVV. To address this limitation, a model of natural infection was developed. Unlike experimentally inoculated animals, naturally infected animals are not persistently viremic, but seroconversion and viremia were only observed in a small percentage of animals [40,44].

Risks to humans—Despite the high genetic and clinical similarities between SVV and VZV, very little data supports the ability of SVV to cause clinical disease in humans. Nevertheless, individuals working with SVV or infected animals should take appropriate precautions to protect against possible transmission. Like VZV, SVV is shed in saliva and can therefore be transmitted by inhaled aerosolized droplets, which is the basis for the natural infection model [44]. This risk is heightened when studying inoculated African green monkeys or Cynomolgus macaques since they remain persistently viremic. In addition to standard personnel protective equipment (PPE), the biosafety recommendation at the Oregon National Primate Research Center requires persons working with SVV-infected macaques to have their VZV antibody titer verified since VZV-specific antibodies have been shown to cross-neutralize different SVV isolates. Should a rash develop, prompt diagnosis using polymerase chain reaction assay employing SVV-specific primers and probes can quickly ascertain the presence/absence of SVV and antiviral treatments can be initiated.

BETA-HERPESVIRUSES

Rhesus cytomegalovirus

Several NHP cytomegaloviruses (CMVs) with similarity to human CMV (HCMV) have been identified, with rhesus CMV (RhCMV) emerging as the prototypical animal model to study pathogenesis of HCMV in a primate model [45]. RhCMV not only shares a great deal of homology to human CMV at the genetic level, but also appears to induce similar disease in infected macaques as seen with HCMV. In this section, we will discuss RhCMV disease in immune competent and deficient animals and potential threat to humans.

Genetic organization—The complete genomic sequence of RhCMV strain 68.1 was recently been acquired [46], and demonstrated the high genetic similarity of this virus to HCMV. The RhCMV 68.1 genome, which is typical of other known CMVs, contains a predicted 230 ORFs, of which 138 are homologous to those found in HCMV. Other isolates of RhCMV have also been sequenced, including RhCMV strain 180.92, and a virus obtained directly from naturally infected rhesus macaques without in vitro passage. [47,48]. These studies indicate that there is a high genetic similarity amongst the different isolates of RhCMV, although some sequence variations exist due to apparent instability and frequent mutation of the viral genome during in vitro passage, a finding similar to what is seen with HCMV.

Pathogenesis and transmission—RhCMV is found in the majority of captive rhesus macaques, with infection rates approaching close to 100% and most macaques seroconverting by the time they reach one year of age [49,50]. Similar to human CMV, RhCMV infections of healthy macaques are generally asymptomatic, with no overt signs of disease and persistence of the virus for the lifetime of the host but accompanied by frequent shedding of virus in saliva and urine [12,51,52].

Since congenital CMV infection in humans presents a serious risk for the development of birth defects [53], RhCMV infection of fetuses in utero was developed as a model to study viral and host factors that contribute to the development of these defects. In these models, RhCMV infection of the fetus produces disease of the central nervous system similarly to what occurs with congenital HCMV infection in humans [54,55]. RhCMV infection of SIV-infected macaques was also found to be a robust model of HCMV infection in AIDS patients, with the development of complications such as encephalitis, respiratory disease, and orchitis, as well as ocular CMV infection, and disseminated CMV disease [56,57]. Further, there is evidence that simultaneous co-infection with SIV and RhCMV may promote the development of simian AIDS [58].

Risk to humans—There has been some speculation that primate CMVs may be capable of infecting humans, thus posing a potential threat to human health. It is known that simian CMVs, including RhCMV, can infect human cells in vitro [51,59,60], and there is some evidence suggesting that primate CMVs may be capable of infecting humans. In one instance, a strain of CMV was isolated from a child that had developed encephalopathy [61], and was confirmed to be of African green monkey origin [62]. Also, a link between chronic fatigue syndrome and simian CMV infection has been suggested [63]. However, it is important to note that these are isolated incidences, and to date no definitive link between simian CMV infection and human disease has been confirmed. The risk for occupational exposure is likely a greater threat for human infection with primate CMVs; in particular, those who work closely with infected animals or samples of infected animal tissue could potentially be exposed to primate CMVs. However, in a screening done of employees at one primate center, it was found that none of the workers tested were positive for the presence of antibodies against any simian CMVs, despite their exposure to infected animals [49]. Regardless, unless RhCMV infection of humans can be definitively disproven, and given the frequent shedding of RhCMV, even in asymptomatic animals, precautions should always be taken to prevent exposure to this virus.

GAMMA-HERPESVIRUSES

The *Gamma-herpesvirinae* are lymphotropic viruses that infect and replicate mainly in lymphoid cells, and are capable of causing cellular transformation. This subfamily can be further divided into the *lymphocryptovirus* (or γ-1) genus and the *rhadinovirus* (or γ-2) genus, based on genomic organization and sequence homology. In humans, the *lymphocryptovirus* genus is represented by Epstein-Barr Virus (EBV), while the *rhadinovirus* genus is represented by Kaposi's sarcoma-associated herpesvirus (KSHV). Lymphocryptoviruses and

rhadinoviruses with similarity to EBV [64,65] and KSHV [66-71] have been identified in many species of Old and New World monkeys. In the following section we will discuss rhesus lymphocryptovirus as well as two rhadinoviruses: herpes Saimiri and rhesus macaque rhadinovirus.

Lymphocryptovirus

Genetic organization—In rhesus macaques, two lymphocryptoviruses (Type 1 and Type 2) have been identified [72], and the complete rhesus LCV-type 1 genome has been sequenced [73]. The nucleotide homology between the rhesus LCV and EBV genomes is 65%, and the genetic organization of these viruses appears to be colinear. Rhesus LCV encodes 80 ORFs, all of which share some level of homology to genes in human EBV, with the average homology between EBV and rhesus LCV ORFs being 75.6% [74].

Pathogenesis and transmission—Experimental infection of naïve rhesus macaques with rhesus LCV results in acute and persistent infection, similar to what is seen with primary EBV infection of humans. Oral inoculation of rhesus macaques with rhesus LCV results in the development of lymphadenopathy, lymphocytosis, and an increase in CD23+ B cells, which closely mimics the symptoms of primary EBV infection and mononucleosis in humans [75]. Also similar to human EBV, it was found that rhesus LCV persists in the peripheral blood of these animals after infection, with the shedding of virus in oral secretions. Importantly, it has been demonstrated that cynomolgus macaques naturally infected with LCV that are also infected with simian immunodeficiency virus (SIV) develop malignant B cell lymphomas that contain DNA sequences similar to human EBV [76,77]. Further, squamous epithelial proliferative lesions in SIV-infected rhesus macaques have been found to contain EBV-like sequences by immunohistochemistry and *in situ* hybridization [78,79]. The relevance of this animal model is further underscored by the work of Wang et al., at the New England National Primate Research Center, where they reported that Rhesus LCV immortalized B cells were capable of inducing lymphoma in 1 out of 4 animals [80].

Risks to humans—Attempts to infect Old World primates such as baboons and rhesus macaques with human EBV have thus far been unsuccessful [81,82], suggesting that there is a species restriction. Although no evidence exists that any primate LCVs are capable of infecting humans, if it were possible, the potential oncogenic nature associated with an infection by LCVs could pose a threat of the development of lymphoproliferative abnormalities in infected individuals. Although exposure to LCVs from species such as rhesus macaques may be less likely to pose a significant health risk to humans, it could become more of a concern in regards to exposure to LCVs from primates more closely related to humans, such as chimpanzees.

Herpes saimiri

Herpesvirus saimiri (HVS, Saimirine herpesvirus 2) is the prototypical rhadinovirus, the natural host of which is the squirrel monkey (*Saimiri sciureus*) [71]. Most squirrel monkeys are infected with HVS early in life, remaining persistently infected for their lifetime without the development of any overt disease [71]. Although infections of squirrel monkeys with HVS are asymptomatic, the virus can cause fatal T cell lymphomas in other New and Old World primates [83].

Genetic organization—HVS strains are classified into three subtypes (A, B, and C), based on their pathogenic qualities and genomic similarity. Subtype C viruses possess the highest oncogenic properties, and can immortalize human, rabbit and rhesus macaque lymphocytes, and cause fulminant lymphomas in Old as well as New World primates. The genomes of HVS strains A11 and C488 have been fully sequenced [84,85], with both HVS genomes containing

76-77 ORFs. The genome encodes four oncogenes that have been shown to play a critical role in transforming T cells.

Pathogenesis and transmission—In the wild, squirrel monkeys are infected via saliva within the first two years of life and remain asymptomatically and persistently infected for the remainder of their lives [71]. In fact, HVS can be isolated from peripheral blood cells of persistently infected squirrel monkeys by coculture with permissive cell lines such as owl monkey kidney cell line (OMK, reviewed in [86]).

Risks to humans—Currently, there is no evidence that HVS can infect humans naturally or induce disease, although it is obvious that more information will be necessary before it is assumed the virus poses no threat to human health. Since the virus is capable of infecting and transforming human T cells *in vitro* to continuous growth [83,87], there is the possibility that the virus could infect T cells or possibly other cell types *in vivo* if a human exposure occurred. Given that HVS appears to induce disease in NHP species, it could be possible that HVS would be pathogenic in humans as well.

Rhesus Macaque Rhadinovirus

Rhesus macaque rhadinovirus (RRV) is a recently identified gamma-herpesvirus of rhesus macaques, which has been shown to be closely related to human herpesvirus 8 (HHV-8)/ Kaposi's sarcoma-associated herpesvirus (KSHV). RRV possesses high genetic similarity and pathogenic properties to KSHV and, therefore, has become a robust animal model to study KSHV disease development in vivo, particularly in the setting of SIV-induced immunodeficiency.

Genetic organization—An RRV strain (RRV_{17577}), was obtained from a simian immunodeficiency virus (SIV)-infected macaque that had developed B cell hyperplasia, and upon isolation and characterization of this herpesvirus isolate, the RRV_{17577} genome was found to be essentially co-linear with HHV-8, retaining many of the ORFs believed to be involved in the pathogenesis of HHV-8 [88]. The general structure of the RRV_{17577} genome is similar to other herpesviruses and consists of a long unique region (LUR) of ~131 kb in length, flanked on both ends by regions of terminal repeats.

Pathogenesis and transmission—RRV is a natural pathogen of macaques, with greater than 90% of captive rhesus macaques having been found to be seropositive for RRV [89]. RRV transmission between susceptible hosts is believed to occur via shedding in saliva (White et al., Comparative Medicine 2009, in press) and, similar to KSHV, RRV is capable of establishing a latent infection in B cells [90]. Experimental inoculation of rhesus macaques with RRV_{17577} that have previously been infected with SIV_{mac239} promotes the development of B cell hyperplasia, persistent lymphadenopathy, splenomegaly, and hypergammaglobulinemia [90,91]. The hyperplastic lymphoproliferative disorder (LPD) in RRV-infected macaques closely resembles the plasma cell variant of multi-centric Castleman's disease B cell hyperplasia seen in humans infected with KSHV. More recently, RRV infection has also been associated with lymphomagenesis in SIV-infected rhesus macaques [92].

Risks to humans—The ability of RRV to infect humans is unknown and, therefore, the risks of exposure to this virus remain undefined. However, given the fact that KSHV does not appear to infect other primate species during experimental inoculation, it seems likely that species specificity of RRV may also exist, and prevent infection of humans with RRV. Regardless, precautions should be taken to prevent exposure to RRV, especially given its oncogenic potential in primates.

DISCUSSION

The importance of NHPs, in particular RM, in research has grown considerably since the discovery of HIV-1 as the causative agent for AIDS, and the identification and isolation of a related simian virus capable of inducing AIDS-like disease in RM. As research to develop a vaccine to prevent HIV-infection intensifies, one thing remains clear; the absolute need for more RM for biomedical research is critical [93] as is the required infrastructure to adequately house and care for this valuable animal model. Equally important is the necessity for more SPF RM [94]. What is less well documented is the importance of specific guidelines, policies and procedures required for individuals working with RM to prevent zoonotic infections in humans. Some information can be found in the 5th Edition of the Biosafety in Microbiological and Biomedical Laboratories, published by the CDC and NIH, but most NPRCs have rigorous education, training programs and protocols in place to ensure the safety of animal care staff, veterinarians and biomedical researchers who work working closely with RM to prevent zoonotic infection by simian herpesviruses, simian foamy virus or other yet unknown and identified viral pathogens [95,96].

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Table 1

Comparison of primate herpesviruses and associated diseases with their human herpesvirus counterparts, and the potential risk of primate viruses to human health. NA (not applicable).

	Human Herpesviruses		Non-Human Primate (NHP) Herpesviruses		
subfamily	**Virus**	**Human Disease**	**Virus**	**Primate Disease**	**Risk to Humans**
alpha	HSV-1/2	generally asymptomatic; can cause oral or genital lesions	Herpes B Virus	generally asymptomatic	transmissible to humans; infection can cause encephalomyelitis, fever, neurological complications; can be fatal
	Varicella-Zoster Virus (VZV)	chickenpox; shingles	Simian Varicella-Virus (SVV)	vesicular rash; severe cases can include pneumonia and hepatitis	unknown
beta	Human Cytomegalovirus (HCMV)	generally asymptomatic; persistent infection with frequent shedding of virus; common cause of congenital birth defects and other complications	Rhesus Cytomegalovirus (RhCMV)	generally asymptomatic; persistent infection with frequent shedding of virus; capable of causing birth defects and other complications	unknown
	Epstein-Barr Virus (EBV)	acute and persistent infection; mononucleosis; lymphoproliferative disorders	Lymphocrypto-virus (LCV)	acute and persistent infection; lympadenopathy; lymphocytosis; B cell lymphoma	unknown
gamma	NA	NA	Herpesvirus Saimiri (HVS)	fatal T cell lymphoma in non-host species	unknown
	Kaposi's Sarcoma-Associated Herpesvirus (KSHV)	Kaposi's sarcoma, B cell disorders, lymphoma	Rhesus Rhadinovirus (RRV)	lymphoproliferative disorders; lymphoma	unknown