Received: 15 October 2024 | Accepted: 18 January 2025

DOI: 10.1002/ame2.12575

REVIEW

Animal models of human herpesvirus infection

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Funding information
National Natural Science Foundation of China, Grant/Award Number: 82222041 and 82241068; CAMS Innovation Fund for Medical Sciences, Grant/Award Number: 2021-I2M-1-037 and 2023-I2M-2-001; National Key Research and Development Project of China, Grant/Award Number: 2023YFC2309000; Beijing Natural Science Foundation, Grant/Award Number: Z220018

Abstract

Human herpesvirus, a specific group within the herpesvirus family, is responsible for a variety of human diseases. These viruses can infect humans and other vertebrates, primarily targeting the skin, mucous membranes, and neural tissues, thereby significantly impacting the health of both humans and animals. Animal models are crucial for studying virus pathogenesis, vaccine development, and drug testing. Despite several vaccine candidates being in preclinical and clinical stages, no vaccines are current available to prevent lifelong infections caused by these human herpesviruses, except for varicella-zoster virus (VZV) vaccine. However, the strict host tropism of herpesviruses and other limitations mean that no single animal model can fully replicate all key features of human herpesvirus-associated diseases. This makes it challenging to evaluate vaccines and antivirals against human herpesvirus comprehensively. Herein, we summarize the current animal models used to study the human herpesviruses including α-herpesviruses (herpes simplex virus type 1(HSV-1), HSV-2, VZV), β-herpesviruses (human cytomegalovirus (HCMV), γ-herpesviruses (Epstein–Barr virus (EBV)) and Kaposi's sarcoma herpesvirus (KSHV)). By providing concise information and detailed analysis of the potential, limitations and applications of various models, such as non-human primates, mice, rabbits, guinea pigs, and tree shrews, this summary aims to help researchers efficiently select the most appropriate animal model, offering practical guidance for studying human herpesvirus.

KEYWORDS
animal models, EBV, HSV, human herpesvirus, KSHV, VZV

1 | INTRODUCTION

Herpesviruses constitute a class of enveloped DNA viruses characterized by linear, double-stranded DNA genomes. Herpesviruses consist of three subfamilies: α-herpesviruses, β-herpesviruses, and γ-herpesviruses. Of the many herpesviruses, nine are known to infect human and can lead to various acute diseases. The α-herpesviruses include herpes simplex virus type 1 (HSV-1), HSV-2, and varicella-zoster virus (VZV). The β-herpesviruses encompass human cytomegalovirus (HCMV), human herpesvirus 6A (HHV6A), HHV6B, and HHV7. In the γ-herpesviruses subfamily, Epstein–Barr virus (EBV) and Kaposi's sarcoma herpesvirus (KSHV) are prominent.[1–3]

Herpesvirus can establish lifelong latent infections in their hosts.[4] The herpesviruses undergo two distinct replication phases: the lytic and latent. In the lytic phase, herpesviruses produce infectious particles capable of infecting other cells, whereas during latency, gene expression is limited and infectious virus particles are seldom productive.[5] While acute infections typically do not cause serious consequences in healthy individuals, they can lead to severe complications in those with compromised immune systems, such as herpes genitalis, chickenpox, primary effusion lymphoma (PEL), and multicentric Castleman's disease (MCD). Thus, it is critical to investigate disease pathogenesis and develop novel vaccines and therapeutic interventions.[6–8] Current research focuses on several key areas, including the virus's pathogenic mechanisms and host-virus interactions, immune responses, vaccine development, and antiviral therapy. However, there are still significant gaps in the field, such as insufficient understanding of latency and recurrence mechanisms, and differences between clinical and experimental research. Therefore, the role of various pathogenic animal models in understanding the mechanism of herpesvirus infection, host-virus interaction, and latency and reactivation processes is crucial. Except for HSV, human herpesviruses exhibit pronounced species specificity for humans, complicating the establishment of appropriate animal models for research.

In this review, we describe the animal models used to investigate human herpesviruses, discuss current limitations, and suggest potential improvements, providing valuable insights for establishing and selecting appropriate models for human herpesviruses infections in the future.

2 | α-HERPESVIRUSES

2.1 | HSV

HSV infections are widespread, with over 80% of the global population infected.[9,10] HSV is classified into HSV-1 and HSV-2. HSV-1 is usually responsible for most orofacial infections, whereas HSV-2 is more commonly linked to genital infections.[11–13] They can establish latency in peripheral sensory neurons, featuring periodic reactivations at the position of infection.[14] The latent virus reactivates and moves along sensory nerves to reach the skin and mucous membranes, causing cold scores or genital rashes, followed by viral keratitis, which may progress to herpes viral encephalitis, leading to irreversible neurological damage or even death.[15]

The genome of HSV is enclosed by an envelope containing glycoproteins. During HSV infection of host cells, the glycoproteins interact with receptors and fuse into membrane. The capsid then enters the cell nucleus, followed by the linear DNA. The tegument protein then enters the nucleus and IE genes start transcription, helping viral genome replication. When enough copies of the viral genome are produced, the L gene products assist in DNA encapsidation. Finally, capsids leave the nucleus and enter its envelope.[5]

2.1.1 | Non-human primate (NHP) models

NHP models for studying the pathogenic characteristics and mechanisms of HSV-1 are rarely reported. One study found that, through oral infection, the virulent HSV-1 caused a low-level infection and triggered modest immune responses in NHP.[16] The main method for establishing an infection model of HSV-2 is intravaginal inoculation. Ming Lo et al. established a rhesus macaque model recapitulating characteristics of subclinical infection in women. The data demonstrated acute HSV-2 infection and persistence, as well as spontaneous reactivation. The inflammatory response in the genital tract raises hope that the model could be valuable for exploring the mechanisms involved in immune control of HSV-2 at mucosal sites.[17,18] Recently, a study innovatively used *Cebus apella*, a New World primate, to evaluate an HSV-2 induced genital infection model. The animals exhibited symptoms including genital vesicular lesions and T cell responses.[19] Moreover, HSV-2 infection elevated the rate of vaginal simian-human immunodeficiency virus (SHIV-RT) infection, creating the first relevant co-infection model of HSV-2/SHIV-RT in primates.[20] Studies have evaluated vaccines and antiviral compounds through intravaginal infection in rhesus monkeys and guinea pigs, because of the limited number of animals involved, the data are more supportive than conclusive.[21,22]

2.1.2 | Mouse models

Specific inoculation methods are effective for establishing HSV latency, including the mouse corneal scarification model. Systemic disease can occur when HSV is administered intraperitoneally or intravenously, whereas peripheral infections can be initiated through ocular, vaginal, skin, nasal, or oral routes. Encephalitis can be induced by injection of the virus into the brain.[23–28] Among different mouse strains, C57BL mice showed the greatest resistance to HSV-1, while BALB/c mice exhibited intermediate susceptibility, and AKR and SWR mice were the most susceptible to HSV-1.[29] The IL-27 receptor knockout mice have proved the crucial role of IL-27 in controlling HSV-1 shedding.[30] In addition, IFNAR-deficient A6 mice infected with HSV-1 demonstrate the repression of IFN-I signaling associated with brain atrophy.[31] Moreover, researchers have demonstrated that the expression of receptors differs across different tissues and influences the tropism of both HSV-1and HSV-2 through various inoculating methods.[32,33] These studies illustrate the value of mutant mice for understanding the contributions of receptors to disease. HSV-1 infected mouse models are also frequently used to study postherpetic neuralgia (PHN), and the reactivation of HSV-1 in the sensory ganglia leading to herpes simplex suggests that herpes simplex may effectively simulate VZV-induced PHN.[34–39]

The commonly used animal models for evaluation of HSV-2 candidate vaccines are mice and guinea pigs.[40] Mice were intravaginally challenged after being treated with progesterone, and

successful infection was demonstrated through local lesions and viral replication.[41–43] In HSV-2-infected SV129 mice and mice on a SV129 background lacking the IFN-alpha/beta receptor, it was found that IFN-alpha/beta receptor signaling is critical in antiviral defense.[44]

2.1.3 | Rabbit models

Rabbits have been used as a model for ocular studies because their eyes are larger, which makes it easier to examine the cornea and image corneal lesions. The larger eyes provide sufficient ocular tissue for assessment, and the abundant tear production facilitates the collection process. Rabbits commonly used in ocular herpes studies include the New Zealand White, Dutch Belted, and others. For vision research, rabbits with non-pigmented eyes are typically preferred. Several methods have been used to induce herpetic corneal lesions in rabbits.[45–47] However, compared to mice, rabbits are more expensive and difficult to raise.[48,49]

2.1.4 | Guinea pig models

The guinea pig model was selected to explore the role of immune responses, and evaluate the effectiveness of vaccines targeting genital herpes.[44,50–55] Guinea pig models are challenged with genital infections to mimic the similar characteristics in humans, including vesiculoulcerative skin eruption, urinary retention, asymptomatic viral shedding, recurrent disease, and ganglionic latency.[56–59] Recurrent infection produced by intravaginal HSV-2 inoculation followed by UV radiation exposure is a useful tool for evaluating the effectiveness of antiviral treatments.[58] The guinea pig model serves as a clinically relevant animal model for assessing drug effectiveness and is a reliable predictor of acyclovir's efficacy.[60–63] Nevertheless, the decreasing frequency of recurrences and recurrent shedding constrain the evaluation of vaccines that requires longer observation periods to determine their effectiveness.[64]

2.1.5 | Tree shrew models

The tree shrew (*Tupaia belangeri*), a small mammal in the Tupaiidae family, resembles a squirrel and is susceptible to many human viral pathogens.[65] Importantly, genomic analysis suggests that tree shrews are considered to be more closely related to primates than to rodents.[66,67] Darai and his research team found that juvenile tree shrews are susceptible to HSV, exhibiting hepatitis-like symptoms and high HSV titers in the liver and spleen.[68,69] Darai and Rosenwolff reported a study on HSV abdominal infection in tree shrews.[70,71] More recently, Li and colleagues demonstrated that tree shrews inoculated with HSV-1 showed encephalitis symptoms, further confirming the susceptibility of tree shrews to HSV.[72]

2.2 | VZV

Varicella-zoster virus (VZV) is a human neurotropic herpesvirus that causes varicella and herpes zoster (shingles).[73] The VZV genome encodes at least 71 unique open reading frames (ORFs).[74] Once it reaches mucosal epithelia, VZV infects the host and local replication occurs. This is followed by spread to the tonsils and other regional lymphoid tissues, where the virus infects T cells. Infected T cells transport the virus to cutaneous sites. Then VZV establishes latency in sensory ganglia. Primary VZV infection leads to varicella, characterized by fever and a generalized pruritic vesicular rash.[75,76] Reactivation of latent infection leads to herpes zoster, which presents as a localized, painful, vesicular rash.[77–79] While VZV has the capability to infect NHP and certain small animals, it does not induce diseases similar to those observed in humans.[80]

2.2.1 | NHP models

Simian varicella virus (SVV) shares morphological and genetic similarities with VZV. The rhesus macaque model of SVV is the only animal model that faithfully mimics the key characteristics of varicella zoster virus infection observed in humans, including varicella, latency, and reactivation. Even months after intrabronchial inoculation of rhesus macaques with SVV, viral DNA remained detectable in the ganglia.[81] Notably, Traina-Dorge successfully induced reactivation in rhesus macaques.[82] SVV data from the rhesus macaque model of indicate that $CD4^+$ T cell responses play a crucial role in managing varicella and herpes zoster in humans.[4,83] Overall, the NHP model of VZV infection offers important insights into the processes that drive or contribute to the mechanisms underlying viral reactivation from latency.[84]

2.2.2 | Humanized mouse models

In immunocompetent mice, VZV infection leads to seroconversion but there is no evidence of VZV replication. Although VZV DNA has been identified in non-neuronal cells after corneal inoculation with the virus, these results have not been consistently reproduced in subsequent studies.[85] To investigate VZV pathogenesis, researchers have employed the severe-combined immunodeficient-humanized (SCID-hu) mouse model, which is created by implanting a combination of human fetal thymus and liver tissue (thy/liv) into a SCID mouse.[86] Moffat et al. pioneered the utilization of SCID-hu mice and demonstrated tropism of VZV toward human T lymphocytes, highlighting its ability to induce viremia during natural infection.[87] Additionally, some studies have utilized the SCID-hu mouse model implanted with human fetal dorsal root ganglia (DRG) inoculated with VZV to study VZV neurotropism.[86,88] However, a notable constraint of is that the DRG is inoculated directly with the virus, rather than through natural viremia or transmission from infected cells to DRG.[89]

2.2.3 | Guinea pig models

Early studies using guinea pig models of VZV infection reported viremia and seroconversion after nasal inoculation,[80,90,91] and later an ocular infection model was also developed.[92] These models have since been extensively used to study the cellular immune response to VZV and identify the viral antigenic targets.[93–95] Recently, increased attention on enteric zosterhas revived interest in using guinea pigs to study VZV infection and persistence within the enteric nervous system.[89,96–98] The detection of VZV DNA in enteric neurons has proved a link between VZV and gastrointestinal disorders.[91,99] Studies show that the guinea pig is the most effective small animal model for investigating VZV latency and reactivation.[97] Using the guinea pig model, a study evaluated an mRNA shingles vaccine that induces strong immune responses and provides effective protection against VZV challenges.[100] However, the application of the guinea pig model is limited, because the transcriptional profile during latency in sensory ganglia remains unclear.

2.2.4 | Rat models

Rat models have been utilized to study VZV latency and VZV-associated pain.[101,102] Fleetwood Walker confirmed that plantar inoculation with VZV could induce abnormal painful behavior in rats.[103] Subsequent studies by Dalziel revealed that rats exhibited prolonged abnormal pain that eventually progressed into chronic mechanical pain.[104] Although these models of PHN are based on acute VZV infection and do not fully replicate the transition from latent to active infection or all the clinical features of PHN in patients, they still provide a platform for investigating novel therapies for PHN.[34,105]

3 | β-HERPESVIRUSES

3.1 | HCMV

Human cytomegalovirus (HCMV), belongs to the category of β-herpesviruses.[106] The CMV viral glycoproteins bind to specific cellular receptors, initiating endocytosis. Once inside the host cell, the viral nucleocapsid is transported along microtubules toward the nucleus, where the CMV DNA is released. In the nucleus, the viral genome is transcribed and translated to produce proteins that are crucial for replication. As the replication progresses, Late (L) proteins are synthesized and assembled. Membrane-associated proteins are processed and assembled, which contributes to the maturation of new virions. Finally, mature viral particles are released through budding.[6] The reactivation of the HCMV virus can infect tissues and organs such as nerves, blood vessels, and myofascial muscles, leading to mental retardation, seizures, and encephalitis.[102,107] The risk of infection with HCMV during pregnancy is particularly high, causing viral congenital disability.[108]

3.1.1 | NHP models

Rhesus macaque cytomegalovirus (RhCMV), biologically and immunologically homologous with human cytomegalovirus,[109] is the most extensively studied NHP CMV.[110,111] Barry established a rhesus monkey model of RhCMV infection by intrauterine injection, with the aim of delving into the pathogenesis of HCMV infection and developing new therapies to prevent prenatal infection with HCMV.[112] Despite its strengths, this model has certain drawbacks, such as the paucity of RhCMV-seronegative animals due to the universality of RhCMV infection.[113]

3.1.2 | Mouse models

Despite CMV virus being efficiently transmitted from infected SCID mice, the immunosuppressed background of the mice limits the model's utility.[114] The mouse orthologue herpesvirus, murine cytomegalovirus (MCMV), has many features in common with HCMV.[115] Emphasis in MCMV research has been placed on identifying cell types where the virus becomes latent. John Roback and colleagues developed a mouse model of BALB/cByJ mice, elucidating the mechanism by which humans can be infected with transfusion-transmitted cytomegalovirus.[116] Scientists have also delved into congenital infection with HCMV using MCMV. Recently, several studies have utilized intracranial infections in gestational embryos or intraperitoneal infections in neonatal pups.[117] One notable advantage of mouse models infected with homologous virus is that the characteristics are similar to those of HCMV infection in humans.[118,119] In addition, this model offers homologues of many HCMV genes; and the MCMV genome is highly amenable to genetic manipulation, allowing the deletion or replacement of specific genes with ease.[113] However, it is essential to address the limitation of the resistant placental barrier to CMV transmission.[120]

3.1.3 | Humanized mouse models

Humanized murine models have advanced research on HCMV infection.[107] Use of early humanized mice models was limited by their lack of viral dissemination. In addition, the inability to establish latency and reactivation prompted researchers to develop more suitable models using other cells that better replicate the human immune system.[121] Crawford et al. established a hu-BLT model with hematopoietic progenitor cells (HPCs) and human fetal liver and thymus tissue.[122] HCMV-specific human T cell responses and neutralizing antibodies were observed. However, this model cannot provide a platform for monitoring the maturation of T and B cell. There are several models created by engrafting human $CD34^+$ hematopoietic stem cells (HSCs) from cord blood into the bone marrow of NSG mice, allowing for the detection of HCMV infection in myeloid cells.[3,123] Recently, Wahl and coworkers established a model called 'human lung only mice' (LoM), by transplanting pieces of the human fetal lung into NSG mice. Then, they combined LoM and BLT into a model called BLT-L model. This

modeling strategy successfully monitored the production of affinity mature antibodies and enabled the HCMV-specific adaptive response in vivo.[124] However, the ethical concern about fetal tissue transplantation is a problem that needs to be considered.

3.1.4 | Guinea pig models

For congenital HCMV infection research, the rhesus macaque CMV and guinea pig CMV are both suitable.[125] Placental transmission and vertical transmission have both been well described in guinea pigs.[126–128] Additionally, fetal sequelae such as intrauterine growth retardation and maternal and pup mortality are evident.[129] Labyrinthitis and sensorineural hearing loss were also observed.[130–132] Lower cost, genomic similarity between GPCMV and HCMV and the capacity of the virus to cross the guinea pig placenta make guinea pigs an excellent model for designing vaccines aimed at preventing transplacental transmission of infection.[127,133] Some studies using guinea pigs infected with GPCMV suggest that subunit gB vaccination could be effective in providing protection against CMV-related diseases.[134–136] However, studies to date are limited by availability of immunologic reagents, prolonged gestational periods and small sample sizes.[113] Nonetheless, the guinea pig model for congenital CMV infection is of great value because there is no other rodent model that can replicate its features, making it unique in this regard.[137]

4 | γ-HERPESVIRUSES

4.1 | EBV

EBV, a gama-1 herpesvirus, was the first tumor virus isolated in 1964 and is strictly human-tropic.[138–140] In B cells, entry requires gp42 binding to HLA class II proteins as a co-receptor, while in epithelial cells lacking HLA class II, entry is mediated solely by the gH-gL complex. During replication, gp42 interacts with the gH-gL complex.[141] Primary EBV infection can cause a febrile syndrome called infectious mononucleosis (IM). Eventually, the acute viremia can be controlled by the immune response of the infected hosts, but the latent virus persists in the peripheral blood B cells and cannot be completely cleared.[142] Reactivation leads to proliferation of B cells into malignant lymphomas, including nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin's lymphoma and pyothorax-associated lymphoma.[143–145]

4.1.1 | NHP models

Most NHP are naturally infected with a lymphocryptovirus (LCV), which shares immunological cross-reactivity with EBV, which may explain their low natural susceptibility to EBV.[146] Immunologically, rhesus LCV (rhLCV, the genome is homologous to EBV gene) infection in rhesus macaques is very similar to EBV infection in humans.[147] Lymphomas, including lymphoblastoid tumors and plasma cell tumors, were successfully induced in cotton-top tamarin monkeys with high titers of EBV suspensions.[111] The similar T cell immune responses to EBV in rhesus macaques and humans suggest that the rhLCV rhesus macaque model is a useful model for evaluating novel vaccines.[148–150] But it must be noted that significant distinctions exist between these two viruses and their host species. The New World monkeys, as the closest EBV animal model to humans, cannot be infected with EBV through normal oropharyngeal inoculation and do not develop lymphomas.

4.1.2 | Mouse models

EBV infects humans and exhibits biological similarities with murine gammaherpesvirus68 (MHV68). MHV68 is more closely related to KSHV in terms of genomic structure, as both are classified as gamma-2 viruses, whereas EBV is a gamma-1 virus.[151] Despite these differences between them, MHV68 and EBV exhibit similar biological features when infecting their hosts. In mice, MHV68 infection establishes lifelong latency in B cells, mainly within the lungs and spleen, with occasional reactivation and lytic infection. Consequently, MHV68 has been utilized to investigate the potential neuroinvasive properties of EBV. However, the pathology induced by EBV infection does not fully mirror the pathology observed in multiple sclerosis (MS) in humans, as EBV-associated experimental autoimmune encephalomyelitis (EAE) in mice does not entirely replicate MS pathology.[152–154]

4.1.3 | Humanized mouse models

In 1988, Mosier established a human SCID mouse (hu-PBL-SCID mice) model by inoculating the human peripheral blood lymphocytes (huPBLs) infected with EBV virus in vitro, obtaining numerous novel results related to the biology of EBV-induced lymphoproliferation.[155] Additionally, researchers highlighted the crucial role of lytic EBV infection in the process of developing B cell lymphomas in a SCID mouse model, where EBV was introduced alongside CD34+ cells for immune reconstitution.[156]

The EBV-related cleavage protein (BZLF1) was shown to be a target antigen for developing EBV vaccines by establishing the hu-PBL-SCID mouse model.[157] Additionally, a nanoparticle vaccine activates a protective neutralizing antibody response targeting EBV in mice with humanized immune systems, demonstrating significant potential for preventing EBV infection.[158] However, the human immune system in humanized mice is dysfunctional, especially the mucosa-associated lymphoid tissue, which complicates the exploration of the complex network of interactions between various immune components and EBV infection.

4.1.4 | Tree shrew models

In a reported study, ten tree shrews were intravenously innoculated with EBV and EBV infection was detected in eight of the tree shrews.

In addition, the EBV copy number and its antibodies were found to be increased to different degrees, and enlarged livers, spleens, and mesenteric lymph nodes were observed.[65] Interestingly, EBV DNA was found in the genitals of 67% of the tree shrews, suggesting that this model could be valuable for studying the sexual transmission of EBV.[159,160] As a new model animal, the tree shrew is ideal for EBV infection studies because of its rapid reproduction, small size, ease of handling, low cost, and its ability to be infected with a variety of viruses related to human diseases.

4.2 | KSHV

KSHV, a gamma-2 herpesvirus, has been found in Kaposi's sarcoma (KS).[161] KSHV virions have icosahedral nucleocapsids surrounded by a lipid bilayer envelope, with the tegument located between the capsid and the envelope. KSHV DNA is a linear duplex approximately 165 kb in length.[162] Many details of the KSHV lifecycle need further exploration, especially regarding the mechanisms of virus-host cell interaction, immune escape strategies, and the transition mechanisms between the latency and lytic cycles. The main target cell of KSHV is the B cell.[163] It is known to cause malignant cancerous tumors,[164] including Kaposi's sarcoma (KS), the B-cell malignant proliferative neoplastic cancer disease primary effusion lymphoma (PEL), KSHV inflammatory cytokine syndrome (KICS) and multicentric Castleman's disease (MCD).[165] Additionally, studies have reported that Burkitt's lymphoma (BL), genital lymphoproliferative disorders (GLD), multiple myeloma (MM), and other diseases are closely related to KSHV infection.[2]

4.2.1 | NHP models

KSHV is also strictly tropic for humans. Although KSHV can infect rhesus macaques, the virus replicates at low levels, and no viral gene expression is observed. Therefore, the absence of a direct KSHV animal model has prompted the development of a NHP model using rhesus macaque rhadinovirus (RRV; a gamma-2-herpesvirus).[166] Two identified strains show distinct pathogenic potential.[167] Strain H26-95 has not been linked to any diseases. In contrast, strain 17577 is associated with B cell lymphoma and a mesenchymal proliferative lesion, retroperitoneal fibromatosis, which is closely related to Kaposi's sarcoma in SIV-infected rhesus monkeys.[168,169] In a study, Chang established a NHP model, suggesting that KSHV can establish an effective persistent infection in NHP.[170]

4.2.2 | Mouse models

MHV68-infected mice have previously served as an effective mouse model for studying EBV infection and pathogenesis.[171] In wild-type mice, high titers of MHV68 in spleen and lung have been observed.[172] However, wild-type mice infected with MHV68 do not develop lymphoma and skin lesions or imitate the development of endothelial tumors characteristic of KSHV infections upon natural infection, and the MHV68 model fails to replicate the development of endothelial cell tumors associated with KSHV infections.[173] The biggest strength of these models lies in their capacity for engineering mutations in the murine genome. Therefore, they are highly effective for investigating tissue tropism, latency, and the immune response of MHV68 infection, especially with mice lacking specific host genes.[174]

4.2.3 | Genetically engineered mouse models (GEMM)

Transgenic mouse models have been established for confirming the function and mechanism of KSHV proteins in oncogenesis. Currently, several GEMM were established for KSHV latent proteins (e.g. LANA, vCyclin, vFLIP) and KSHV-encoded lytic oncoproteins (e.g. vIL-6, K1, ORF36/vPK, vGPCR).[175] While these transgenic mouse models are useful tools for studying the mechanism of KSHV-induced tumorigenesis, the function of proteins and individual susceptibility genes, there is still no model that fully recapitulates KSHV related cancers in humans. Only a few cases of carcinogenic potential have been confirmed in vivo using transgenic mouse models.

4.2.4 | Nude mice models

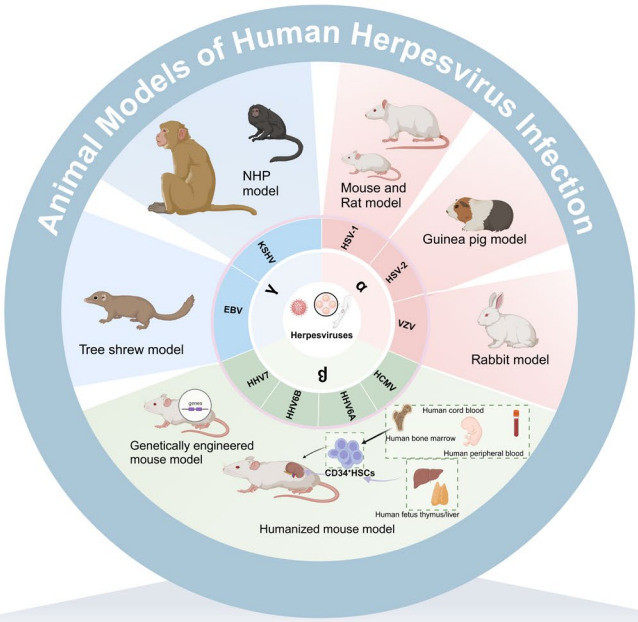
Mutlu and colleagues transfected KSHVBAC36 virus into murine bone marrow endothelial cells to construct the mECK36 cell line, which can cause KS-like tumors in mice.[176] In addition, An et al. successfully established a KS nude mice model with KSHV telomerase-immortalized human umbilical vein endothelial cells.[177] However, the cumbersome techniques for constructing the animal models and their inability to realistically simulate the immune response of KSHV-infected organisms means their application remains limited.

4.2.5 | Humanized mouse models

SCID and nonobese diabetic-severe combined immune deficient (NOD/SCID) have been widely used in the successful establishment of KSHV infection. Foreman injected KSHV viruses into SCID mice implanted with normal human skin and found that 60% of the mice developed morphological and phenotypic lesions similar to those seen in human skin KS, but the infection was mostly confined to tissues of human origin.[178] In NOD/SCID mice infected with KSHV cells, the presence of viral DNA was detected in immune organs and peripheral blood, and rapid tumor growth of both single and multiple solid tumors was observed.[179–181] However, the symptomatic characteristics of many tumors differ from those of patients with PEL. Notably, Wang successfully infected humanized BLT-NOD/SCID/IL2rγ(NSG) mice with KSHV.219 virus via the oral and vaginal routes and the infections were mostly focused on human B cells and macrophages, which could be useful for understanding the pathogenesis of KSHV.[182]

5 | DISCUSSION

Establishing suitable animal models is necessary to replicate the pathological process of herpesvirus comprehensively. Herein, we review infection models of herpesvirus in NHP, mice, especially humanized mice, and other animal species. Figure 1 provides an overview of the relevant animal models for studying human herpesviruses infections, and Table 1 summarizes the general strengths and limitations of each model for specific research objectives. Despite previous and ongoing efforts to develop effective vaccines, none have succeeded so far. Recently, gene-editing technologies have shown the potential to impact the development of animal models. This technology allows for precise editing of the herpesvirus genome, facilitating the study of gene functions, the identification of potential therapeutic targets, and the exploration of drug resistance and viral escape mechanisms. With the advancement of new technology, future research can overcome the limitations of traditional animal models by enabling more precise experimental designs, ultimately providing more reliable and reproducible data. As our understanding of host immune responses to herpesviruses continues to grow, we can anticipate further breakthroughs in developing animal models for human herpesvirus infections.



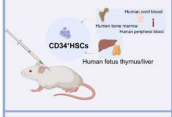
Animal species	Virus	Strain of virus	Route of inoculation	Inoculum Dose
	HSV-2	HSV-2 G	Vaginal	1×10^7 PFU
	SVV	SVV WT/ VZV KMcC	Intrabronchial	1×10^4 PFU
	RhCMV	RhCMV strain UCD52	Intracranial/ Vaginal/ *i.v.*	1×10^5~10^6 PFU
	RhLCV	RhLCV naive	Oral/ *i.v.*	1×10^6 ~ 10^8 PFU
	RRV	RRV 17577	*i.v.*	5×10^6 PFU
	HSV-1	HSV-1 McKrae	*i.p.* / *i.v.* / *i.c.* / *s.c.* / Mucosal	1×10^1~10^6 PFU
	MCMV	MCMV Smith	*i.p* ./ *i.v.* / *s.c.* / Intracranial	1×10^6 PFU
	MHV68	MHV68 WUMS	*i.p.*	1×10^6 PFU
	HSV-2	HSV-2 186	Vaginal	1×10^5~10^6 PFU
	VZV	VZV VR-1433TM	Cutaneous	5×10^5 PFU
	GPCMV	GPCMV 22122	*s.c.*	$1\sim4\times10^5$ PFU
	HSV-1	HSV-1 McKrae	Ocular	$2\sim4\times10^6$ PFU
	VZV	VZV Mck	Corneal intrastromal	1×10^5 PFU
	EBV	EBV B95-8	*i.v.* / Oral	1.1×10^8~1.8×10^9copies
	VZV	VZV-S and pOka	Lateral ventricle	$2\sim8\times10^3$ PFU
	HCMV	HCMV TR	*i.p.*	1×10^5 PFU
	EBV	EBV B95-8	*i.v.*	1×10^3 TD_{50}
	KSHV	rKSHV.219	*i.p.* / Oral/ Vaginal	2.5×10^5PFU
	HSV-1	HSV-1 17+/ HSV-1 McKrae	Ocular	1×10^6 PFU
	HSV	HSV-1 Thea	*s.c.* / *i.v.* / *i.p.*	1×10^5 PFU
	EBV	EBV B95-8	*i.v.*	1×10^8 copies

FIGURE 1 Animal models of human herpesvirus infection. *i.c.*, intracutaneous; *i.p.*, intraperitoneal; *i.v.*, intravenous; PFU, plaque-forming units; *s.c.*, subcutaneous.

TABLE 1 Advantages and limitations of human herpesvirus infection animal models.

Virus classification	Viral species	Animal models	Advantages/Achievements	Limitations	Reference
α-herpesviruses	HSV	NHP	Genetically close	Expensive; Does not experience acute or recurrent genital disease	[17]
		Mouse	Inexpensive; Available immunologic reagents; Latent infection; Function of viral genes; T cell response	Lethal; Absence of spontaneous reactivation; Inapplicable to reproductive tract infections	[183]
		Guinea pig	Moderate price; Immunogenic permitting rapid assessment; Scorable primary disease; Spontaneous recurrences;	Poor immunogenicity of naked DNA in human; Differences in pathogenesis between host species; Limited time of frequent recurrences	[184]
	VZV	NHP	SVV causes varicella, latent infection and zoster; Closest to humans genetically; Recapitulates crucial clinical and virological features	Expensive; Reactivation of SVV leads to a rash affecting the entire body, whereas reactivation of VZV causes a localized dermatomal rash; SVV genome not present in VZV	[84,185,186]
		Guinea pig	Establishment of latent infection; VZV infects guinea pig cells and can proliferate; Less expensive; To prevent concerns about postmortem reactivation, ganglia can be promptly removed following euthanasia;	Inoculated through unnatural process; Long gestation period; Expensive to breed, Studying congenital VZV is difficult	[89]
		Mouse and rat	The PHN model	Induced through unnatural process	[103–105]
		Humanized mouse	Effective VZV neurotropism ; Less expensive ;	Deficient immune system ; Lack of adaptive immune responses ; Complicated surgery procedure;	[86,87,187]
β-herpesviruses	HCMV	NHP	Closest to humans genetically; Immunologic reagents	Expensive; Paucity of RhCMV-seronegative animals; The lytic replication without latency	[111,112]
		Mouse	Cellular tropism; Congenital infection; Similar characteristics	Role of specific private genes	[24]
		Guinea pig	Congenital infection; Low cost	Limited immunologic reagents; Prolonged gestational periods; Small litter sizes	[113]
		Humanized mouse	$CD4^+$ and $CD8^+$ cell responses; IgM and IgG antibodies; Long productive replication	Invisible T and B cell maturation	[123,124]
γ-herpesviruses	EBV	NHP	Similar virologic and immunopathological event; Acute IM-like syndrome	Expensive	[188–190]
		Rabbit	LPD; Peripheral blood EBV DNA; Specific antibodies	Less effective	[191,192]
		Mouse	B-cell lymphoma, Persistent infection	Lack of human immune system	[173]
		Humanized mouse	Immune responses; IM-like syndrome; B-cell LPD; Hodgkin-like lymphoma; RA-like arthritis;	Immature T cells	[193–196]
		Tree shrew	Low cost of feeding; Similar anatomical and physiological features; Closely related to primates	Short lifecycle; Low reproductive rate; Short reproductive cycle; Lack of specific antibodies and reagents;	[159,160]

TABLE 1 (Continued)

Virus classification	Viral species	Animal models	Advantages/Achievements	Limitations	Reference
	KSHV	NHP	KS-like skin tumor	Expensive	[146,170]
		Mouse	IM-like syndrome; persistent infection; B-cell LPD/lymphoma; Genome engineering	Lack of human immune system; Role of private gene	[151,197]
		GEMM	Target individual susceptibility genes; Evaluating drugs targeting viral proteins	Lack of overall human infection environment; Lack of fully recapitulated KSHV related cancers	[175]
		Humanized mouse models (BLT-NSG mice) (Endothelial model)	Similar characteristics; Infection to B cells and macrophages	Engraftment rates; Suboptimal innate immune function; B cell maturation; Elevated mortality rate; Increased costs	[182,198]

6 | CONCLUSION

While existing animal models can replicate many aspects of human herpesvirus infections, there are still limitations in different areas. Nonetheless, animal models are essential in further exploring how herpesviruses evade host immune surveillance mechanisms. Another key area for future investigation is the mechanisms of latent infection and reactivation of herpesviruses. Further research aimed at unraveling the underlying molecular mechanisms of latency and reactivation will provide valuable insights, potentially leading to the development of more effective antiviral therapies and vaccines.

AUTHOR CONTRIBUTIONS

Ziqing Jia: Writing – original draft; writing – review and editing. **Dong Zhang:** Writing – review and editing. **Lin Zhu:** Writing – review and editing. **Jing Xue:** Writing – review and editing.

ACKNOWLEDGMENTS

The authors have nothing to report.

FUNDING INFORMATION

This work was funded by the National Key Research and Development Project of China (2023YFC2309000), the National Natural Science Foundation of China (82222041, 82241068), the Beijing Natural Science Foundation (Z220018), and the CAMS Innovation Fund for Medical Sciences (2021-I2M-1-037, 2023-I2M-2-001).

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

ETHICS STATEMENT

None.

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How to cite this article: Jia Z, Zhang D, Zhu L, Xue J. Animal models of human herpesvirus infection. *Anim Models Exp Med*. 2025;8:615-628. doi:10.1002/ame2.12575