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Rhesus Monkeys for a Nonhuman Primate Model of Cytomegalovirus Infections

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Abstract

Human cytomegalovirus (HCMV) is the leading opportunistic viral infection in solid organ transplant patients and is the most common congenitally transmitted pathogen worldwide. Despite the significant burden of disease HCMV causes in immunosuppressed patients and infected newborns, there are no licensed preventative vaccines or effective immunotherapeutic treatments for HCMV, largely due to our incomplete understanding of the immune correlates of protection against HCMV infection and disease. Though CMV species-specificity imposes an additional challenge in defining a suitable animal model for HCMV, nonhuman primate (NHP) CMVs are the most genetically related to HCMV. In this review, we discuss the advantages and applicability of rhesus monkey models for studying HCMV infections and pathogenesis and ultimately informing vaccine development.

Introduction

Human cytomegalovirus (HCMV) is a ubiquitous herpesvirus that establishes persistent infection in its host. While infection of healthy individuals is generally asymptomatic, primary HCMV infection or viral reactivation in immunosuppressed patients, such as AIDS and transplant patients, can lead to dissemination and life-threatening end-organ diseases [1,2]. Congenital HCMV (cCMV) infection can also cause severe clinical outcomes to the developing fetus and impacts ~1 in every 150 (0.7%) newborns, making it the most common congenitally transmitted pathogen worldwide [3–5]. In the United States alone, an alarming

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Conflict of Interest Statement

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40,000 congenital infections occur annually and nearly 7,000 infants develop permanent neurological sequelae including microcephaly, sensorineural hearing loss (SNHL), and cognitive impairment [3–5].

Despite the significant global health impact of cCMV and opportunistic HCMV infections, there are no licensed vaccines or effective immunoprophylactic measures to prevent these infections, as clinically tested vaccine candidates have not been successful enough to move forward towards licensure [6,7]. One major challenge of studying HCMV infections and testing vaccines preclinically is that HCMV, like all β-herpesviruses, does not infect non-human species. Therefore, animal models rely on species-specific CMVs, which vary in their biological relevance to HCMV [8]. In this review, we discuss the suitability and application of the rhesus monkey (*Macaca mulatta*) nonhuman primate (NHP) model for studying CMV infections and disease and for testing immunotherapeutic and prevention strategies.

NHP CMV Genomic and Functional Relevance to HCMV

Because CMV evolution has paralleled mammalian speciation, primate CMVs are more closely related to each other than to CMVs in small animals, such as rats, mice, and guinea pigs [9,10]. Chimpanzee CMV and rhesus CMV (RhCMV) genomes are most similar to HCMV, though chimpanzees are a less accessible animal model due to their endangered population status [10]. Genomic sequencing and annotating of RhCMV isolates 180.92 and 68.1 revealed that 60% of RhCMV open reading frames are homologous to HCMV proteins — notably those encoding structural, immune evasion, replicative, and regulatory proteins [10,11]. For instance, subunits of the pentameric complex (PC; glycoproteins gH/gL and UL128-131A), which is involved in epithelial and endothelial cell tropism and has been reported as the target for the most potently neutralizing antibodies against HCMV, are conserved in RhCMV [10–13]. As with HCMV, the RhCMV subunits interact as a pentamer and are essential for epithelial cell viral entry [13–15]. Vaccination of rhesus monkeys with a vector coexpressing the RhCMV pentamer subunits induced neutralizing antibodies against RhCMV infection of epithelial cells and fibroblasts, which reduced plasma viral loads and supports a functional similarity between RhCMV and HCMV PCs [13]. Due to these findings, a similar vector was designed to coexpress the HCMV pentamer subunits, and rhesus monkeys vaccinated with this vector stimulated antibodies that neutralized HCMV infection of human epithelial cells, placental macrophages, and fibroblasts [16]. Interestingly, RhCMV 68.1, which lacks regions homologous to HCMV UL128-131A, has been used as a vector to express simian immunodeficiency virus (SIV) proteins and vaccination with this vector induced unconventional $CD8^+$ T cell responses, namely targeting of diverse, highly promiscuous epitopes presented by major histocompatibility complex II molecules [17,18]. Nearly 50% of vaccinated animals were protected after SIV challenge, and unconventional T cell responses only occurred when the RhCMV vector lacked HCMV UL128-131A homologs. Thus, the RhCMV PC bears functional relevance to its HCMV homolog and knockdown of certain regions within the pentamer may be advantageous for vaccine delivery.

Similar to the PC, gB, which is essential for viral entry into all host cell types and is an immunodominant target for neutralizing antibodies, shares 60% identity (75% similarity) between RhCMV and HCMV at the amino acid level [19]. Researchers also found that HCMV monoclonal anti-gB antibodies cross-react and cross-neutralize with RhCMV gB (RhgB) [20]. Anti-RhgB antibodies have been shown to develop following primary RhCMV infection in rhesus monkeys and to possess neutralizing capabilities, which recapitulates humoral responses to HCMV [21]. In fact, a study recently isolated an anti-RhgB monoclonal antibody from a rhesus dam following viral challenge [22]. In light of gB containing numerous neutralizing epitopes and two phase II clinical trials finding that a gB subunit vaccine was partially protective against HCMV acquisition, the genomic and functional similarities between RhCMV and HCMV gB, in addition to the PC, are particularly important for an animal model for CMV infection and vaccine immunity [23, 24]. Because of the accessibility of rhesus monkeys and the parallels between RhCMV and HCMV genomes and proteins' functions, we will focus this review on the rhesus monkey/RhCMV model as an NHP model for CMV infections.

RhCMV Acquisition and Persistence

Like HCMV in humans, RhCMV is largely prevalent among rhesus monkey populations and causes life-long infection [25,26]. Nearly half of rhesus monkey infants in breeding colonies are seropositive for RhCMV by 7 months of age, which is just after maternal antibody wanes, and almost all seroconvert by 1 year of age [27,28]. High frequencies of CMV-specific $CD4^+$ and $CD8^+$ T lymphocytes are detected in naturally-infected CMV-seropositive macaques with prolonged virus shedding and impaired $CD4^+$ T lymphocytes commonly being observed in the first 2–3 years of infection [28–31]. Immune evasion mechanisms that contribute to infection persistence have been found to be similar between rhesus monkeys and humans. Specifically, induction of the cellular interleukin-10 signaling pathway and avoidance of natural killer cell activation, via preventing NKG2D ligand surface expression, contributes to RhCMV and HCMV viral persistence [32–35].

Despite the ubiquitous and persistent nature of RhCMV, efforts using early weaning of young infants to develop specific pathogen-free rhesus monkey colonies were successful generating RhCMV-seronegative rhesus monkey colonies, which can be used to characterize primary RhCMV acquisition following direct inoculation and to evaluate prophylactic strategies [36]. For instance, prime/boost immunizations containing either RhgB or a combination of RhgB, phosphoprotein 65 (pp65), and immediate-early 1 (IE1) proteins have been tested in RhCMV-naïve, healthy adult rhesus monkeys for their effect on RhCMV acquisition and virus shedding using subcutaneous inoculation with epithelial cell-tropic RhCMV UCD52 [37]. In the mock-immunized controls, challenge virus was detectable in plasma, saliva, and urine within 4 weeks of challenge and high levels of virus persisted in the saliva and urine throughout 21 weeks of observation. This study's immunizations were partially effective, with the combined RhgB/pp65/IE1 vaccine leading to reduced oral shedding in half of the vaccinees. Similar studies have also employed subcutaneous and/or intravenous (IV) inoculation of RhCMV-seronegative monkeys to characterize primary RhCMV infection and to assess prevention strategies, including prime/boost immunizations with the RhCMV PC or with RhgB/pp65/IE1, which both partially reduced RhCMV plasma

viral loads [13,26,38]. Thus, direct inoculation of RhCMV in naïve rhesus monkeys via subcutaneous or IV routes causes quantifiable, persistent infection, which allows assessment of the efficacy of prophylactic strategies. Oral RhCMV challenge and natural vertical transmission models via co-housing with RhCMV-seronegative monkeys are also being trialed as more physiologically-relevant challenge models that can better recapitulate human CMV transmission [39].

CMV Infection in Immune Compromised Populations

RhCMV-SIV Coinfection

Like humans, adult macaques usually manifest with overt CMV disease only under immunosuppressive conditions that result in reactivation of latent RhCMV infection [40–44]. The SIV-rhesus macaque model is the leading animal model of AIDS and recapitulates many features of untreated HIV infection including the occurrence of RhCMV disease in 30–50% of macaques with simian AIDS [45,46]. Both primary and reactivated RhCMV disease are associated with rapid progression of simian AIDS and loss of RhCMV-specific humoral and cellular immunity [46,47]. The profile of simian AIDS-related RhCMV disease is very similar to HIV-HCMV coinfection, with a few notable exceptions. Unlike in HIV-HCMV coinfection, RhCMV retinitis was not observed during SIV-RhCMV coinfection, and progressive, fatal disease with high RhCMV and SIV loads occurred prior to the onset of severe $CD4^+$ T lymphocytopenia [31,46]. In a longitudinal study of SIV-RhCMV coinfected rhesus macaques, intermittent RhCMV reactivation frequently occurred following impairment of RhCMV-specific $CD4^+$ or $CD8^+$ T cell immunity, but overt RhCMV disease only occurred after decline of both RhCMV-specific T cells and neutralizing antibodies [46]. A direct relationship between loss of cellular immunity and RhCMV reactivation in NHPs was also observed following *in vivo* administration of $CD20^+$ and $CD8^+$ lymphocyte-depleting antibodies to SIV-negative pig-tailed macaques and African green monkeys, which experienced a transient increase in RhCMV viremia, while lymphocyte-depleted and SIV-infected pig-tailed macaques developed an irreversible increase in RhCMV viremia and AIDS progression [48]. Overall, SIV-RhCMV coinfection bears many similarities to HIV-HCMV and, like with HCMV, adaptive immunity is critical for immune control of RhCMV infection.

Transplantation-related Studies

High CMV seroprevalence rates in rhesus and cynomolgus macaque colonies ensure that most NHP animals used in transplantation-related studies, whether donor or recipient, will be infected with CMV endemic in the host species [49–51]. While there has not been a systematic review of CMV reactivation in immunosuppressed NHPs, accumulating anecdotal reports indicate that CMV reactivation is a frequent cause of morbidity and mortality in transplant-associated studies. As persistent CMV infection is asymptomatic in healthy immune competent animals, CMV sequelae following immune suppression in NHP has direct relevance for a better understanding, prevention, and treatment of HCMV reactivation, disease, and organ rejection in humans.

Like HCMV infection in humans, detectable RhCMV is cleared from plasma after resolution of primary infection and detectable RhCMV in plasma is rare during persistence [13,51–53]. Thus, the reappearance of RhCMV DNA in plasma is indicative of viral reactivation, caused by impaired immune control of persistent reservoirs of RhCMV-infected cells. Reactivated CMV infections are common in immunosuppressed NHP studies [44,54–64]. Limited studies also indicate that reactivated CMV infections occur in immunosuppressed pigtailed macaques [65] and baboons [43,66,67]. Studies to date suggest that the frequency and severity of reactivation are related to the degree of immune suppression and/or the extent of allogeneic exposure. Moreover, there is seemingly contradictory evidence that reactivation can occur despite prophylactic antiviral treatment, and that reactivation can resolve in the absence of antivirals.

There is no consensus prevention or treatment strategy in NHP for anti-CMV inhibitors, and studies have generally adopted dosing and treatment schedules used in human transplant settings, including the use of ganciclovir (GCV), phosphonoformic acid (PFA; foscarnet), cidofovir (CDV), and valganciclovir (valgan). *in vitro* studies demonstrate that the effective concentrations of GCV [68], PFA [60], and CDV (Barry, unpublished) that inhibit RhCMV replication by 50% (EC50) are comparable to the EC50 values reported for HCMV [69–72]. Valgan is delivered orally to treat HCMV infections, and the L-valine ester in valgan must be cleaved *in vivo* by liver and intestinal cells to release the bioactive GCV form of the drug, a cleavage process that occurs in NHP after oral delivery [73].

The frequencies of CMV reactivation and, most importantly, disease vary between studies, ranging from ~14 –89% [44,54–57,59–66]. While it remains unclear what causes the wide disparity, variables between studies potentially include the type of tissue transplanted, the presence of prophylactic anti-CMV drugs, the stringency of the immune suppression regimen, and the parameters used to assess CMV reactivation and/or disease. Some studies prospectively measure CMV viral loads in blood while others determine viral genome copies in plasma or serum. Likewise, some investigators have used clinical sequelae (*e.g.*, pneumonitis, gastroenteritis) as a measure of CMV reactivation while others have performed retrospective analyses based on pathognomonic histopathology and/or immunohistochemical staining for CMV antigens.

As more NHP transplantation studies are performed, it is likely that CMV reactivation will remain a confounding variable in assessing transplant efficacy until there are more efficacious prevention and treatment strategies, uniform diagnostic modalities, and better understandings of the relationship between modes of immunosuppression, allogeneic stimulation, and CMV reactivation. As NHPs are strong predictors of outcomes in humans, these studies can directly improve human prevention and treatment regimens.

Congenital CMV

Congenital HCMV Transmission

Despite HCMV being the most common congenitally transmitted pathogen, major gaps remain in our understanding of HCMV *in utero* transmission and maternal correlates of protection. While infection may ascend from the maternal genital tract to the fetus, more

studies have supported the hematogenous route of cCMV transmission, which considers that infection spreads from maternal uterine blood vessels to the villous core and fetus via the placenta [74–76]. A comprehensive understanding of these infection events would aid in rational maternal HCMV vaccine design to prevent congenital transmission. Additionally, defining maternal immune correlates of protection would inform cCMV vaccine strategies. cCMV transmission occurs in 30–40% of women who acquire primary HCMV infection during pregnancy, whereas only 1–2% of infants born to seropositive mothers are congenitally infected [3]. Though vertical transmission rates during maternal HCMV super-infection remain unclear, maternal immunity appears to have a protective role against cCMV transmission. Among maternal immune factors that contribute to partial protection against cCMV, maternal $CD4^+$ T cell frequency and lymphoproliferative response, in addition to high-titer and avidity antibodies, have been correlated with reduced cCMV transmission [12,75,77–81]. Despite the associations gained from human cohorts, a relevant cCMV animal model would enable studies to control immune factors and consequently identify protective correlates and cCMV transmission routes.

Congenital RhCMV Transmission and Pathogenesis

A comprehensive CMV animal model must accurately recapitulate cCMV infection and sequelae. Although rhesus monkey pregnancy is divided into 55-day trimesters as opposed to 90-day trimesters in humans, placental and fetal development is temporally, with most organ development occurring in the first trimester [82]. Multiple studies employing direct RhCMV fetal inoculation *in utero* found that inoculation led to spontaneous abortions or infected fetuses developed brain and neurologic defects analogous to human cCMV cases, which provides support that congenital RhCMV clinical manifestations mimic those of human cCMV [83–86].

Because nearly all rhesus infants seroconvert by 1 year of age, it has remained inconclusive whether RhCMV can be naturally congenitally transmitted. Nevertheless, a study demonstrated that systemic RhCMV inoculation of seronegative pregnant dams resulted in congenital RhCMV transmission and fetal infection [87]. Dams were challenged during the second trimester with a swarm of high-titer RhCMV variants, which reflects the setting of cCMV infection in humans. All immunosuppressed ($CD4^+$ T cell-depleted) animals and 2 of the 3 immunocompetent animals were positive for RhCMV DNA in their amniotic fluid, and placental tissue stained positive for RhCMV-IE1 (Figure 1). These findings establish proof-of-concept RhCMV intrauterine transmission and placental infection. Furthermore, 3 of the 4 infected immunosuppressed animals had spontaneous abortions and the last surviving infant displayed cCMV-associated sequelae, such as liver lesions and neutropenia. Thus, congenital RhCMV transmission from maternal systemic inoculation, in addition to direct fetal inoculation, recapitulates human cCMV pathogenesis, rendering rhesus monkeys a suitable model for cCMV transmission and disease.

Other work has employed the NHP model for cCMV and demonstrated its applicability. A study compared the humoral responses between two dams that experienced primary infection during pregnancy that either did or did not congenitally transmit RhCMV and found that the nontransmitting dam had an earlier and more robust plasmablast response

with more RhCMV-specific antibodies [22]. Additionally, another study investigated the efficacy of RhCMV hyperimmune globulin (HIG) on preventing RhCMV congenital transmission in immunosuppressed dams and as a treatment for maternal and fetal CMV infection [88]. In light of conflicting results from small scale studies and phase I/II clinical trials on whether HIG treatment following primary maternal infection is protective and/or therapeutic against cCMV transmission and disease, NHP studies that are assessing the dosage and timing of HIG treatment are particularly relevant [89–93].

Conclusion

NHPs offer a considerable advantage in the studies of CMV pathogenesis due to both their similarities to the human host and the genetic and functional homology of the NHP CMV strains and HCMV. The rhesus monkey/RhCMV model is the most characterized of the NHP CMV models and has been utilized for studying the pathogenesis of CMV infection in adult, immunocompromised, pregnant, and fetal monkeys, determining maternal correlates of protection against cCMV, and testing CMV candidate vaccines (NHP models summarized in Table 1). Future studies can employ the NHP models described in this review to inform rational vaccine design and evaluation preclinically, consequently de-risking clinical trials.

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Highlights

- Nonhuman primate CMVs are most closely related to human CMV (HCMV).
- Rhesus CMV (RhCMV) bears numerous genomic and functional similarities to HCMV.
- RhCMV inoculation of RhCMV-naïve rhesus monkeys mimics acute CMV infection and leads to life-long viral persistence.
- Immune suppression from coinfections or during the setting of transplantation causes viral reactivation and CMV disease.
- Maternal challenge with RhCMV can cause placental infection and intrauterine transmission, and consequent disease from fetal infection, either from direct inoculation or intrauterine infection, recapitulates congenital HCMV pathogenesis.

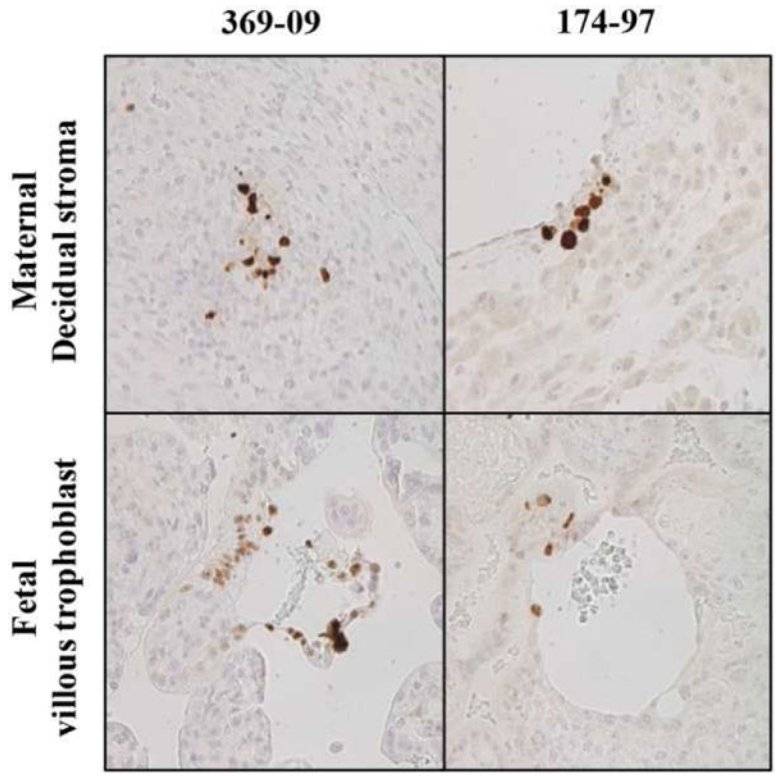

Figure 1.

Rhesus monkey placental tissue stained positively for RhCMV-IE1 protein. Placental tissue pictured was from two immunosuppressed seronegative dams. Adapted from Bialas *et al.*, 2015 [87].

Table 1

NHP Models for CMV Infection.

Model Type	Relevance to HCMV	References
Acquisition and Persistence	• RhCMV causes persistent infection, associated with induction of IL-10 and inhibition of NK cell activation • Direct inoculation in naïve monkeys mimics primary infection for prevention/challenge studies • Infection induces viral shedding in multiple compartments; poses risk for horizontal transmission	• [33] • [32] • [37] • [13]** • [16]* • [38] • [26]
Infection in Immune Suppressed Patients	• SIV-RhCMV coinfection bears many similarities to HIV-HCMV coinfection and progression to AIDS • Type of immune suppression influences risk of CMV reactivation in NHPs • CMV reactivation confounds transplantation outcomes in NHPs	• [46]* • [62] • [59]** • [61]* • [56]
Fetal Infection	• Direct fetal inoculation causes pathogenesis similar to human cCMV • Associated sequelae: microcephaly, limb deformity, central nervous system disease, multiorgan disease	• [83] • [84]* • [85] • [86]
Placental Transmission	• Maternal inoculation can lead to congenital infection • Intrauterine transmission includes infection of placenta, and leads to fetal loss in the setting of maternal $CD4^+$ cell-depletion • Maternal preexisting antibodies may be protective against transmission T	• [87]** • [22]* • [88]*