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Review Articles

RCMV ALL-03 Model and Study of CMV Pathogenesis in Congenital Infection

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Abstract: Cytomegalovirus (CMV) is one of the most commonly studied members of the *Herpesviridae* family. So far several strains have been identified but human CMV (HCMV) remains the most important due to its ability to infect humans and also cross the placenta causing neonatal infection and mortality. However, there are several limitations in the study of this strain which includes availability and use of model animals. Although strains such as Rhesus CMV (RhCMV), Guinea pig CMV (GPCMV) and Rat CMV (RCMV ALL-03) have been shown to cross the placenta and exhibit similar pathogenesis to HCMV, only RCMV ALL-03 can be conveniently used without much limitations as guinea pigs are resistant to antiviral drugs, while rhesus monkeys are seropositive, considered costly and have ethical use restrictions. We therefore propose the use of RCMV ALL-03 as a model for the study of CMV infection.

Keywords: Cytomegalovirus, Animal Model, Congenital Infection, Sensory Neural Hearing Defect (SNHD), Central Nervous System Abnormalitis

Introduction

Cytomegalovirus (CMV) is a member of *herpesviridae* family. Approximately, eight members of this family are well known to cause disease in humans. The differences between these 3 subfamilies lies in their genome sequences and virus biology such as host range, growth kinetics, tissue tropism and ability to transform cells (Pass *et al*., 2009; Roizman *et al*., 1981). CMV is classified as a beta virus because of its unique properties that involves its strict species specificity, salivary glands tropism and slow growth in the cell culture (Britt, 2008; Landolfo *et al*., 2003; Mocarski *et al*., 2007).

Virus Structure and Genome Organization

Like any other herpesvirus, CMV is an enveloped virus with an icosahedral virion (150-200 nm). A proteinious layer is found between the nucleocapsid and envelop, which is well known as the tegument (Mocarski and Courcelle, 2001; Roizmann *et al*., 1992). The virus also contains a core protein viral DNA polymerase and virion structure (major capsid proteins, gp B, H and L (Alba *et al*., 2001), which are conserved among all families members. The genome of CMV is the largest among all herpes viruses (Dolan *et al*., 2004). It is a ds-DNA genome with a length around 230-235kbp (Cha *et al*., 1996). Its linear genome contains two main regions with different length named Unique Long (UL) and Unique Short (US). Different internal repeated sequences are available. The genome structure can be represented as ab-U_L-b`a`c`-$U_S$-ca. in which, ba and b`a` donated $U_L$ and $U_S$ and ca/c`a` indicated the inverted repeats. The Presence of these internal sequences allows the genome regions to orientate, showing four isomers.

Approximately, 220 genes (in wild type) are available in the genome which is named according to their location in the genome. Earlier studies done showed that more than 200 Open Reading Frames were found in both clinical isolates and laboratory strains (Murphy *et al*., 2003a; Murphy and Shenk, 2008; Murphy *et al*., 2003b; Yu *et al*., 2003b). In another report, 19 ORFs were deleted from laboratory strains during their adaption to grow in the fibroblast cell line (Cha *et al*., 1996). Most genes located in the UL are involved in viral structure and replication (Yu *et al*., 2003b), while the US region contains specific genes that encode for immune evasion (Mocarski *et al*., 2007; Yu *et al*., 2003a).

Infection Cycle

CMV replication cycle takes place in the nucleus and cytoplasm. The replication cycle spans 48h to 72 h in the fibroblast cell line (Browne *et al*., 2001). The following steps were recorded in the host nucleus: DNA synthesis, encapsidation, capsid assembly and initial tegumentaion (Mocarski *et al*., 2007), while other steps in the cytoplasm are essential for maturation and release (Das and Pellett, 2011; Das *et al*., 2007; Tandon and Mocarski, 2008).

The first step in the replication is attachment to cell receptor. Presence of different types of glycoproteins on virus envelop give the virus ability to invade a broad range of cells. Moreover, these glycoproteins can arrange in three main complexes gCI (gB homodimer, gCII (gM/gN), gCIII (gH/gL/pO) and gH/gL/pUL (128, 130, 131A), thus the virus has ability to interact with many cellular receptors. Many receptors were reported to facilitate the virus entry to the cell such as Heparin sulphate proteoglycan (Petrik *et al*., 2007; Ryckman *et al*., 2006; Sinzger *et al*., 2008), cellular epidermal Growth Factors Receptor (GEFR) (Wang *et al*., 2003), intergin as co receptors (β1, β2 intergens) (Feire *et al*., 2010; Isaacson *et al*., 2007; Soroceanu *et al*., 2008; Wang *et al*., 2005) and platelet-derived growth factor receptor-α (PDGFRα) (Boyle and Compton, 1998). Comparison between clinical isolate and laboratory strains showed that laboratory adapted strains lost their ability to infect epithelial, endothelial and monocyte-macrophages, which resulted in development of mutation in UL128, UL130 and UL 131(Cha *et al*., 1996; Dolan *et al*., 2004; Hahn *et al*., 2004). Following viral entry the viral envelope will fuse with the endosomal membrane, releasing the nucleocapsid and the teguments proteins in the cytoplasm and is mediated by glycoprotein complex gH/gL (Connolly *et al*., 2011). Next, the nucleocapsid is delivered to the nucleus, the main place for the virus replication steps. Both cellular microtubules and the motor system help in the delivery of the viral capsid into the nucleus (Radtke *et al*., 2010), mediated by pUL47 (Bechtel and Shenk, 2002) and pUL48 proteins. In addition, pUL69 can interact with the capsid and facilitate nucleocapsid translocation into the nucleus (Radtke *et al*., 2010).

The viral nucleic acid is then released and enters the nucleus through the nucleus pore to start its transcription to the mRNA and microRNAs (miRNA). The transcription of the viral genome is mediated by the cell RNA polymerase II in the presence of host transcription factors. The virus encodes for miRNA, which plays a special role in the control the gene expression in order to facilitate virus replication. During the productive infection, the transcription of the viral genes appears in three phases. There are intermediate early (IE or α) (0 to 2 h), early (E or β) (24 h) and late (L or γ) (>24 h) proteins (Stinski, 1978). The expressions of these genes start directly without stimulation from any synthesized protein (Rodems and Spector, 1998), under control of Major IE Promoter (MIEP) (Cherrington and Mocarski, 1989; Pizzorno *et al*., 1988). The first two proteins expressed are IE1 and IE2 (UL123 and UL122 gene products that were known as IE 72 and IE86). They play a role to get a suitable environment to support viral replication since they contain sequence specific DNA binding and activator domains (Bryant *et al*., 2000; Castillo and Kowalik, 2002; Mocarski and Courcelle, 2001; Nevels *et al*., 2004; Petrik *et al*., 2007; Song and Stinski, 2005; Stinski and Petrik, 2008). As IE proteins accumulate in the nucleus, their expression will be suppressed through the interaction between pp71 and Daxx which initiate the DNA replication (Cantrell and Bresnahan, 2005; Preston and Nicholl, 2006). The E proteins are classified as proteins β1 (E) and β2 (E-L), involved in the viral DNA synthesis, other nonstructural protein and immune response evasion (Mocarski and Courcelle, 2001). The DNA synthesis is carried in the special region of the nucleus known as nuclear replication compartments (known as nuclear domain 10, ND10) (Everett, 2006). The virus will synthesize six core proteins for replication (replication fork proteins) of viral DNA and includes UL44, UL54, UL57, UL102, UL105 and UL170 (Pari *et al*., 1993). The six core proteins along with four UL112-113 gene products and the trans activators form the replication compartment (Penfold and Mocarski, 1997). Another strand is built as fragmented strands (Okazaki fragments), where the new genome appears as concatmers. The new genome (special length) that encapsulate inside the procapsid is cut from the concatmers terminase during assembly step. One of the important proteins that require for the viral genome replication is UL84. This protein has nuclear import and export signals that allow it to shuttle easily between the nucleus and cytoplasm (Lischka *et al*., 2006; Xu *et al*., 2002). The protein was also reported to be likely a member of DExD/H box family of helicases and exhibits UTPase Activity (Colletti *et al*., 2005).

Some of the E proteins trigger the expression of late genes such as UL79, UL87 and UL95 (Isomura *et al*., 2011). The L proteins are classified as γ1 and γ2 and actually, they are structural proteins involved in the

assembly and morphogenesis of new progeny virus (Mocarski and Courcelle, 2001). Some of the true late expression genes are Ul75 (gH), UL99 (pp28) and the middle transcription start site of UL44 (Kohler *et al*., 1994; Leach and Mocarski, 1989; McWatters *et al*., 2002; Winkler *et al*., 1994).

The virus assembly starts through both the precursor (pAP, pUL80.5) and protease precursor (pPR, pUL80a). Both of them will be eliminated from the mature capsid (Gibson *et al*., 1996). As translation of the protein is in the cytoplasm, procapsid formation begins in the cytoplasm where MCP interacts with pAP in a 1:1 stoichiometric ratio (Beaudet-Miller *et al*., 1996). This complex translocates into the nucleus which is the main site for the assembly. pAP plays a main role in the oligomerization and mediates the formation of hexons and pentons (Plafker and Gibson, 1998). These larger assemblies interact with mCP and mC-BP to form the capsid precursor (Newcomb *et al*., 1999), which becomes decorated with SCP at the tips of the hexons in a process that completes the formation of capsids (Lai and Britt, 2003). pUL104 is located in one site on the capsid and it Forms a portal through which the viral DNA genome is loaded (Butcher *et al*., 1998). A new genome is detached from the concatamer through direct interaction of pUL56 and pUL89 (DNA terminase and cleavage/packaging enzyme), which bind to packaging (pac) sites at/or near the ends of replication and concatameric viral DNA to position the DNA for packaging into capsids at the protein portal (pUL104) (Thoma *et al*., 2006). Viral DNA is cleaved into unit lengths and packaged into capsids when the terminase (pUL56) arrives at the next pac site (Bogner *et al*., 1998; Scheffczik *et al*., 2002). The nucleocapsid leaves the nucleus through mechanisms well known as envelopment, de-envelopment and re-envelopment processes (dual envelopment) (Skepper *et al*., 2001). The particle will acquire the final envelope from the Golgi apparatus in special area known as viral assembly compartment (AuCoin *et al*., 2006; Das *et al*., 2007).

Latent infection was reported in the herpesviruses, where the viral genome forms a close circle DNA. This infection can appear in different types of cells (Davison *et al*., 2002; Fishman, 2013) such as bone marrow-derived myeloidprogenitor cells (Bego and St Jeor, 2006; Sinzger *et al*., 2008). Most of lytic gene expressions are shut down or downregulated through miRNA (Harris-Arnold *et al*., 2012). The reactivation of the virus was reported in people with suppression of the immune system (Dalen, 2002). The purpose of this infection is to help the virus to avoid some cellular defense mechanisms such as apoptosis of infected cells and production of alpha interferon (Ambagala and Cohen, 2007). Three possible pathways that lead to the establishment of latency have been proposed (Cheung *et al*., 2006). First is failure to express the virus gene after entry, second is interruption of virus replication and thirdly, expression of latent genes instead of productive genes, which can be reactivated to produce an infectious virus (Mocarski, 1993).

Routes of Transmission

Virus is shed in different body secretions such as blood, saliva, breast milk, semen, urine and cervical secretion, close contact with these fluids is paramountin order to get infection (AAP, 2009; Stagno and Britt, 2006). CMV cannot be transmitted through aerosol transmission (McCluskey *et al*., 1996). The virus can also be sexually transmitted (Britt, 1996; Fowler and Pass, 2006) and also through hematogenous routes (Gilbert *et al*., 1989), where other blood cells play a role in virus distribution to different organs (Ibanez *et al*., 1991; Sinzger and Jahn, 1996; Sinzger *et al*., 1996). It was reported that vascular endothelial cells can break out from blood vessel and enter the blood stream (Chen *et al*., 2003; Grefte *et al*., 1993; Nerheim *et al*., 2004; Percivalle *et al*., 1993). Moreover, the uterine micro vascular endothelial cells can Transmit infection to the infant through cytotrophoblasts (Maidji *et al*., 2002).

Complication Associated with HCMV Infection

The distribution of the virus is high in most populations (60%-100%) (Razonable and Emery, 2004; Razonable and Paya, 2003). The immune system can control the infection successfully (Huang and Kowalik, 1993) and only mononucleosis was reported in less than 7% of infected peoples (Alford *et al*., 1990; Taylor, 2003).

CMV infection is terrible in immunosuppressed transplant recipients, HIV patients and fetus of infected pregnant women (Buyck *et al*., 2010; Dollard *et al*., 2007; Freeman, 2009; Gandhi and Khanna, 2004; Steininger *et al*., 2006; Streblow *et al*., 2001; Tuthill *et al*., 2009). The most common disease cases reported in immune-competent patients are arthralgia, arthritis, ulcerative colitis, pneumonitis, hepatitis, asepticmeningitides and myocarditis (Gandhi and Khanna, 2004) fever with bone marrow suppression and tissue invasive disease (Razonable and Emery, 2004; Razonable and Paya, 2003). All these are in addition to upregulation of alloantigen's which led to acute or chronic allograft rejection (Razonable and Paya, 2005). In HIV patients, rentitis is the most common sign of CMV infection. Moreover, CMV mediates some vascularassociated diseases such atherosclerosis, restenosis and transplant vascular sclerosis (Streblow *et al*., 2001).

Congenital Infection Associated with CMV

CMV has been reported to be responsible for most birth deficits in recent time (Alford *et al*., 1990; Nassetta *et al*., 2009; Nichols and Boeckh, 2000;

Volpe, 2008). The prevalence of infection depends on the socioeconomic statuses of the mothers. Infection rate is 50-60% in the middle and high socioeconomic status pregnant women and 70-85% in low socioeconomic status pregnant women (Malm and Engman, 2007; Trincado and Rawlinson, 2001). Fetus and newborn infants can be infected with CMV through one of three routes; vertical transmission, Intra-partuminfectionand postnatally (Boppana *et al*., 2001; Fowler *et al*., 2003; Staras *et al*., 2006). Approximately 30-40% of infections are trans-placentally acquired (Malm and Engman, 2007; Stagno, 2007; Stagno and Britt, 2006; Trincado and Rawlinson, 2001). The infection is high in fetus born from a mother with a high viremia (Harrison and Myers, 1990), which validates the presence of maternal antibody IgG (Maidji *et al*., 2006). The IgG facillate the virus transmission via transcytosis for the virus-IgG complex that is mediated by neonatal Fc Receptor (FcRn) on the surface of syncytiotrophoblasts (Attard-Montalto *et al*., 1993).

Approximately, 10-30% of sero-positive women can develop congenital infection following infection with a new strain of CMV and 1-3% of this infections are transmitted to the fetus (Ahlfors *et al*., 1999; Boppana *et al*., 1999; Boppana *et al*., 2001; Kenneson and Cannon, 2007; Stagno *et al*., 1982). Reactivation of latent CMV infection during pregnancy was reported the most common source of fetus infected (Huang *et al*., 1980). However, out of 0.64%-0.70% neonates born with HCMV (Dollard *et al*., 2007; Kenneson and Cannon, 2007), only 11%-12.7% showed symptoms of infection at birth. As compared with another childhood diseases; Down syndrome, congenital infection with CMV is responsible for childhood disability. The mortality rate associated with symptomatic congenital infection is 20-30% (Bailey and Toltzis, 2011; Malm and Engman, 2007) and is related to development of hepatic dysfunction, bleeding, disseminated intravascular coagulopathy or secondary bacterial infection (Malm and Engman, 2007). Intrapartum infection usually occurs at birth during exposure to infected cervical or vaginal fluid. Around 2-28% of infected mothers shed the virus in their vaginal secretions, resulting in infection of 50% of infants (Stehel and Sánchez, 2005). It has also been shown that 9-88% of seropositive women shed virus in their milk resulting in infection rate of 50-60% among infants (Hamprecht *et al*., 2008; Stehel and Sánchez, 2005). Infection resulting from blood transfusions have also been documented (AAP, 2009; Hamprecht *et al*., 2001; Kumar *et al*., 1984; Roizman *et al*., 1981; Spreu *et al*., 2006). It was reported that the level of both humeral and cellular immunity in women played a role in transmission the infection to the fetus. The titer and avalidity of maternal IgG also plays a major role in disease transmission (Lazzarotto *et al*., 1999; Nigro *et al*., 2005). Moreover, the outcomes of congential infection depends on the time of infection, virus titer and virulence of virus strain (Bratcher *et al*., 1995; Choi and Hsiung, 1978; Griffith and Hsiung, 1980; Harrison and Myers, 1990; Kumar and Prokay, 1983). The most severe form of the disease was reported in the fetus when the infection takes place in the early stage of gestation (Barkovich and Lindan, 1994; Hayward *et al*., 1991; Twickler *et al*., 1993).

HCMV has the ability to cause congenital infection of the fetal brain during its developmental process, resulting in interference of the neocortical neuronal migration to the cortical plate (Malm *et al*., 2000; Sugita *et al*., 1991; van der Knaap *et al*., 2004), usually between the 12th and 24th week of gestation (Gressens, 2006). There is no intrapartum and postnatal infection in fully developed fetus, but in premature infants and low birth-weight new-borns, symptomatic illness including hepatitis, neutropenia and thrombocytopenia have been reported (Lombardi *et al*., 2010), as well as “sepsis-like” symptoms (Hamprecht *et al*., 2001). Another effect of CMV in newborns is Sensory Neural Hearing Defect (SNHD) (Pass, 2005), which is associated with the ability of the virus to induce labyrinthitis (Strauss, 1990). CMV enters the endolymph via the striavascularis (Bauer *et al*., 2005; Davis, 1981; Strauss, 1985; Sugiura *et al*., 2003). One third of cases of non-heredity SNHL in young children were reported during CMV infection (Adler, 2005; Fowler *et al*., 1992; Harris *et al*., 1984; Hicks *et al*., 1993; Morton and Nance, 2006; Williamson *et al*., 1990), particularly following intrauterine HCMV infection (Fowler and Pass, 2006; Morton and Nance, 2006; Ogawa *et al*., 2007). The condition can develop early at birth, where 5.2% are symptomatic or asymptomatic in neonates, or later in childhood in 15.4% of children (Dollard *et al*., 2007; Foulon *et al*., 2008; Fowler *et al*., 1997; Fowler and Pass, 2006; Isaacs and Moxon, 1999; Walter *et al*., 2008; Zhang *et al*., 2007).

Is RCMV ALL-03 a Good Model to Study CMV?

As it is well known, CMV has species specificity and HCMV cannot replicate in animals. The availability of a good model is very important to study HCMV persistence, pathogenesis and therapeutic modalities. Different non-human cytomegaloviruses were isolated in recent time (Ho, 1991). They can be divided into two groups; primates and non-primates CMV.

Primate Models for CMV

In primates CMV, the most common models are Rhesus macaque CMV (RhCMV) (Asher *et al*., 1974) and Chimpanzee CMV (CCMV). Rhseus CMV was isolated from Rhesus macaque (Alcendor *et al*., 1993;

Hansen *et al*., 2003). Its genome length of 221,459 bp is quite shorter than that of HCMV genome (230-235kbp) (Cha *et al*., 1996) and there are no isomers associated with it like in HCMV genome (Hansen *et al*., 2003). The RhCMV genome encodes for 230-260 ORF (open reading frames) (Hansen *et al*., 2003), while the HCMV encodes for 220 genes in wild type but 19 genes are missing in the laboratory strains (Cha *et al*., 1996; Mocarski and Courcelle, 2001).

It was reported that RhCMV can cross the placenta (Lockridge *et al*., 1999) and induce the same CNS abnormalities as in human infection (Barry *et al*., 2006; Tarantal *et al*., 1998). The viral DNA was detected in the brain (Chang *et al*., 2002) and interacts with immature neuronal and glial cells migrating during neurodevelopmental process (Rakic, 1988). In addition, RhCMV is the most common model used to study antiviral drugs against CMV (North *et al*., 2004). It showed the same sensitivity to gancilovir, GCV kinase, UL97, benzimidazole nucleosides likeHCMV (Serabe *et al*., 1999; Swanson *et al*., 1998), which makesit a model of choice to study antiviral drugs.

Protection from viral diseases can be through development of an effective vaccine. Study of immune response toward RhCMV has also been done. Interestingly RhCMV gpB can be neutralized by anti-HCMV antibodies which reflects the cross reactivity between both viruses. Moreover, the two encoded RhCMV pp65 have the ability to induce the same hum-oral and adaptive immune responses as in HCMV pp65 (Yue *et al*., 2006). Modification of the cellular immune response is one of important key features of the virus once in the immune system. RhCMV has three genes; Rh182, Rh183, Rh189encoding for major histocompatibility complex class I, which interacts with cellular mediated immunity (CD8+ T-cell). Similarly, RhCMV can block interferon response by expression of special gene product; Interferon Stimulated Genes (ISGs). All previous immune studies suggest RhCMV provides data for its use as a good model for HCMV vaccine development.

The CCMV resembles the second primates CMV. It has a genome with a length of 241,087 bp, which is longer than HCMV (Cha *et al*., 1996), but encodes for less number of genes (165 genes only) and also has no associated isomers (Davison *et al*., 2003; Hansen *et al*., 2003). It is very closely related to HCMV (Davison *et al*., 2003) and both primate models have been used to study the pathology and pathogenesis of HCMV especially in pregnant animals (Asher *et al*., 1974; Huff *et al*., 2003; Jones-Engel *et al*., 2006; Lockridge *et al*., 1999; Vogel *et al*., 1994).

Although both models resemble HCMV in terms of pathogenesis and infection, they are not used to study HCMV for various reasons; cost and rarity of keeping chimpanzees for experimentation since they are protected by law as endangered animals (Davison *et al*., 2003), lack of aborted Rhesus monkey fetus or neonates from congenital infection to perform histopathological studies, rarity of a seronegative Rhesus animals to perform the experimental studies (Vogel *et al*., 1994) thus making it an unused model to study congenital CMV infection (Fowler *et al*., 2003). Moreover, absence of inbred and knockout animals make this model unpractical compared with small animals (Powers and Fruh, 2008). As the rate of congential infection with CMV in rhesus is very low, this model is sutable for study of pathogenesis of the virus and not its vertical transmission (Barry *et al*., 2006).

Non Primate Models for CMV

Various small animal models for propagation of CMV have been reported in literature. Even though these models have different genome structures compared to the human genome (McGregor *et al*., 2004; Rawlinson *et al*., 1996; Vink *et al*., 2000), they are useful regarding their small size, low cost, short life span, high productivity rate and ease of handling (Loh *et al*., 2006).

The most common CMV strains used in small animal studies are Murine CMV(MCMV) (Rawlinson *et al*., 1996), rat CMV (Maastricht strain, RCMV-M and English strain, RCMV-E) (Bruggeman *et al*., 1982; Priscott and Tyrrell, 1982) and guinea pig CMV (GPCMV) (Schleiss *et al*., 2008). They all have genome lengths smaller than that of HCMV, with the lowest GC content (55%) in GPCMV and highest (61%) in RCMV-M. All CMV models showed the same pathogenesis and pathogenicity as HCMV (Bruggeman *et al*., 1983; Dix *et al*., 2003; Katzenstein *et al*., 1983; Krmpotic *et al*., 2003; Mocarski *et al*., 1996; Pass, 2001; Reddehase *et al*., 2002; Reddehase *et al*., 1985; Shanley *et al*., 1993; Stals *et al*., 1990; Zhang and Atherton, 2002) with the exception of GPCMV, which is the only model that can cross the placenta (Choi and Hsiung, 1978; Markham and Hudson, 1936).

MCMV has a genome length of 230,278 bp, with a GC content of 58.7% and an approximately 170 ORFs out of which 78 have significant homology with HCMV. Murine animals are the first choice to study CMV infection due to their small size, well characterized animals with knock out genes, short gestationperiod (19-21 d) and significantly greater litter size (10-12) of newborn pups. Unfortunately, there is no report yet about ability of MCMV to cross the placenta. Moreover, the structure of the placenta in this model is different from humans as the placenta consists of three layers which separate the fetus from the maternal circulation. This model has been used to study the brain following congenital infection by direct inoculation of the virus

into the embryo or placenta (Li and Tsutsui, 2000; Tsutsui, 1995; Tsutsui *et al*., 2005; Woolf *et al*., 2007). Although the virus cannot cross the placenta, it has shown abnormalities in the CNS and can be detected in different areas of the brain (Trgovcich *et al*., 1998), as well as the retina, where it induced retinitis (Zhang and Atherton, 2002). MCMV has been also used to study antiviral drugs such asganciclovir (Duan *et al*., 1998; Kern, 1991; Neyts *et al*., 1992; Smee *et al*., 1992; Smee *et al*., 1994) and CDV (Kern, 1991, 1999; Neyts *et al*., 1992).

RCMV is another small animal model used to study HCMV *in vivo*. Many strains of RCMV have been isolated (Bruggeman *et al*., 1982; Priscott and Tyrrell, 1982; Loh *et al*., 2003). RCMV-M has a genome size of 230,138 bp, with a 61% G+C content and single unique sequence flanked by 504-bp terminal direct repeats. High concentration of G+C contents were found in the TRs (76%) (Vink *et al*., 2000). It encode for 166 ORFs among which 133 among showed homology to HCMV and MCMV (McGregor *et al*., 2004; Rawlinson *et al*., 1996).

In contrast, the genome size of RCMV-E is 202,946 bp and it encodes for 140 ORF that showed homology to the MuHV-1, although they are almost equally divergent from both MuHV-1 and MuHV-2, 19 of them are unique and not available in other RCMV.

RCMV-M and RCM-E showed the same pathogenesis of HCMV but did not show any sign in immunocompetent rats except for death (Bruggeman *et al*., 1983; Bruggeman *et al*., 1985). Both models cannot cross the placenta and infect the fetus, hence they are not good models to study the congenital infection associated with HCMV. These models have been used to study antiviral drug (Stals *et al*., 1991; Stals *et al*., 1993) such as cidofavir (Stals *et al*., 1991; Stals *et al*., 1993) and both showed good pharmacokentics potential of the drug.

In contrast, RCMV ALL-03 resembles the last RCMV isolated and wasisolated in 2003 from the placenta and uterus of a rat (Loh *et al*., 2003). The virus can cross the Placenta just like the HCMV. The details of RCMV All-03 are discussed in next section.

GPCMV has a genome with a length of 232,678bp, excluding the terminal repeats. The G + C content of the genome is 55% and the genome sequences showed that the virus is closer to primates than rodents (Schleiss *et al*., 2008). It is the only small animal model reported to cross the placenta. Guinea Pig has a similar placental structure to humans, where the placenta is a single hemochorial made up of a single trophoblast layer separating maternal and fetal circulations (Griffith *et al*., 1985; Kaufmann and Davidoff, 1977; Leiser and Kaufmann, 1994).Guinea pig has a long gestation period (65-70 days) and can be divided in to trimesters (Bia *et al*., 1983), but this is a time consuming process as compared with other small animals such as rats which have a gestation periods 21 days. In addition, they have limited number of pups (mostly 3) when compared with other small animals such as mice or rats. GPCMV model exhibit the same pathogenesis especially in the CNS inducing Sensory Neural Hearing Loss (SNHL) as seen in human CMV (Fukuda *et al*., 1988; Griffith *et al*., 1982). Previously, this model was used in vaccine development, immune response (Bia *et al*., 1984; Chatterjee *et al*., 2001; Griffith *et al*., 1985; Harrison *et al*., 1995) and treatment of Sensory Neural Hearing Loss (SNHL) and labyrinthitis with ganciclovir (Katano *et al*., 2007; Park *et al*., 2010; Woolf *et al*., 1988). Unfortunately, there was a report of development of resistance towards GCV (Fong *et al*., 1987), which is the most common drug used in the treatment of HCMV congenital infection. In other related studies, the toxicity of antiviral compounds which cannot be reflected by *in vitro* studies was evaluated using GPCMV. *In vivo* study with CDV was done with this model and it showed renal toxicity in the tested group (Bravo *et al*., 1993; Li *et al*., 1990), which was similar to that observed in humans.

RCMV ALL-03 Model and Study of Congenital CMV Infection

In 2003, a new small animal model for CMV was isolated (Loh *et al*., 2003) and referred to as RCMV ALL-03. The virus was isolated from the uterus and placenta, thus reflecting its ability to cross the placenta as in comparison to MCMV and previous rat model (RCMV-M and RCMV-E) (Fitzgerald *et al*., 1990; Priscott and Tyrrell, 1982). The virus was detected in different organs such as the uterus, placenta, embryo, fetus, salivary gland, lung, spleen and liver as in other models (Bruggeman *et al*., 1983; Bruggeman *et al*., 1985; Loh and Hudson, 1981; Priscott and Tyrrell, 1982; Stals *et al*., 1990). The virus showed its ability to replicate in immunosuppressed group and pregnant females (Loh *et al*., 2006) as reportedin HCMV (Gould and Mims, 1980). The genome size of RCMV ALL-03 is 197,958 bp with a GC content of 46.00%. It encodes for 123 ORFs and showed close similarity (99%) to the RCMV-E (MuHV-8) (Balakrishnan *et al*., 2015).

Approximately, 123 ORFs in RCMV ALL-03 were similar to RCMV-E, 111 ORFs were similar to the MuHV-1 and 107 were similar to RCMV-M (MuHV-2). However, only 72 ORFs were found in RCMV. The highest homology of ALL-03 to RCMV was seen in a089 with RCMV-E E89, RCMV-M R89 and HCMV UL89 (DNA packaging Terminase subunit). RCMV ALL-03 showed similarity to the following ORFs; ALL-03 a025 (UL25), Ox-2 membrane glycol (immune evasion protein), ALL-03 a082 (UL82) tegument protein pp71, US family gene members; ALL-03 a139 (US22), ALL-03 a140 (US 23), ALL-03 a141 (US 24)

(Balakrishnan *et al*., 2015). The virus also showed good homology to the IE1 and IE2 intermediate early proteins, which mediate CMV gene expression and lytic cycle. Furthermore, seven conserved cytomegalovirus structural proteins and 7 conserved tegument proteins are encoded by this strain. The virus also encodes for four immune evasion proteins (ALL-03_A125, ALL-03_a138, ALL-03_a144, ALL-03_a154) which show similarity to RCMV-E.

Compared with GPCMV model, rat has a short gestation period which reduces the experimental time required for study in this animal. Additionally, the increased litter size is an added advantage in the rat unlike in the guinea pig.

Studying the ability of the CMV to spread to the brain and affect its development is very important in establishing how HCMV congenital infection progresses in the fetus during neonatal development. Although the RCMV ALL-03 was not present in the brain, heart, testes and ovary, it has the ability to replicate in brain endothelia cell line as was previously shown (Camalxaman *et al*., 2013). As it is well known, infection of the brain endothelial cells, which are the main cell of the blood brain barrier gave an insight into the mechanism of how the virus can cross the brain and cause CNS abnormalities (Fritschy *et al*., 1996; Power *et al*., 1990). Even though the previous studies on the pathogenesis of different models have not discussed the pathogenesis during pregnancy using only RCMV ALL-03, CMV infection have been shown to be reactive during pregnancy (Gould and Mims, 1980) as it is during immunosuppressive drug treatment (Loh *et al*., 2006).

Conclusion

The use of small animals as model to study HCMV has benefits as highlighted earlier due to their cost and unavailability of other animal models such as chimpanzees (Loh *et al*., 2006). Since the HCMV genome is most closely related to CCMV and RhCMV and most genes necessary for the viral replication are present in RCMV ALL-03 strain, this strain will be a good model to study the pathogenesis of HCMV especially in pregnant rats. Furthermore, since only three strains of this virus can cross the placenta (RhCMV, GPCMV and RCMV ALL-03) and most population of guinea pigs are either seropositive or resistant to GCV, RCMV (ALL-03) strain will be the best model suited for this purpose.

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Author's Contributions

Ashwaq Ahmed Abdullah: Designed, conceptualized the write up and drafted the manuscript and critically revised the manuscript.

Krishnan Nair Balakrishnan: Helped in drafting and final alignment of the Manscript.

Yusuf Abba: Edited the Manuscript and improved the grammer and structure.

Faez Firdaus Jesse Abdullah: Supervised the edited of the Manuscript and improvement of grammer and structure.

Zeenatul Allaudin Nazariah: Supervised the design and write up of the manuscript.

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Noordin Mohamed Mustapha: Supervised the design and write up of the manuscript.

Mohd-Azmi Mohd-Lila: Maked considerable contributions to conception, supervised the design of the work and write up the Manuscript.

All authors have read and approved the final manuscript.

Ethics

The authors have no conflict of interest to declare.

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