The battle between host antiviral innate immunity and immune evasion by cytomegalovirus

Shuang Li[1] · Yuanyang Xie[1] · Changyin Yu[1,2] · Chunfu Zheng[3] · Zucai Xu[1,2]

Abstract

Cytomegalovirus (CMV) has successfully established a long-lasting latent infection in humans due to its ability to counteract the host antiviral innate immune response. During coevolution with the host, the virus has evolved various evasion techniques to evade the host's innate immune surveillance. At present, there is still no vaccine available for the prevention and treatment of CMV infection, and the interaction between CMV infection and host antiviral innate immunity is still not well understood. However, ongoing studies will offer new insights into how to treat and prevent CMV infection and its related diseases. Here, we update recent studies on how CMV evades antiviral innate immunity, with a focus on how CMV proteins target and disrupt critical adaptors of antiviral innate immune signaling pathways. This review also discusses some classic intrinsic cellular defences that are crucial to the fight against viral invasion. A comprehensive review of the evasion mechanisms of antiviral innate immunity by CMV will help investigators identify new therapeutic targets and develop vaccines against CMV infection.

Keywords CMV · Innate immunity · Immune evasion · PRRs · Intrinsic cellular defences

Introduction

Based on a survey of CMV seropositivity, approximately 83% of the world's population is infected with the virus. In comparison, in developing countries, it is almost 100% [1]. It will become a lifelong chronic infection in the infected host. Most patients have no symptoms or only show mild disease status, but under immunosuppressive conditions, such as AIDS patients and transplant recipients, the virus

can be reactivated, resulting in mental retardation, seizures, and encephalitis [2, 3]. In addition to affecting nervous system diseases, it also affects the occurrence and progression of atherosclerosis, tumors, and other diseases, even endangering life [4–6]. As a result, it remains a serious public health issue.

CMV belongs to the β Herpesvirus subfamily and is a double-stranded DNA virus [7]. CMV can replicate in various cells, including epithelial cells, fibroblasts, smooth muscle cells, endothelial cells, macrophages, dendritic cells, and hepatocytes, facilitating systemic transmission, efficient proliferation, and host-to-host transmission of the virus [8, 9]. CMV relies on direct fusion or endocytic pathways to enter human cells [10]. When the viruses invade the host, the viral envelope glycoprotein trimeric complex (gH/gL/gO) binds to platelet-derived growth factor receptor α (PDGFRα), which in turn infects fibroblasts, whereas the pentameric complex (PC) (gH/gL/pUL128-pUL130-pUL131A) is required for the infection of endothelial, epithelial, and medullary-like cells [11]; in parallel, neurofibrillary protein 2, the olfactory receptor family member OR14I1, is thought to be the PC receptor that mediates viral entry into endothelial/epithelial cells [12]. After the viral envelope fuses with the cell membrane, the nucleocapsids

✉ Changyin Yu
    yuchangyin68@163.com

✉ Chunfu Zheng
    zheng.alan@hotmail.com

✉ Zucai Xu
    docxzc@126.com

1   Department of Neurology, Affiliated Hospital of Zunyi
    Medical University, Zunyi, China

2   The Collaborative Innovation Center of Tissue Damage
    Repair and Regeneration Medicine, Zunyi Medical
    University, Zunyi, China

3   Department of Microbiology, Immunology and Infectious
   Diseases, University of Calgary, Calgary, AB, Canada

are released into the cytoplasm and then transported through the microtubule system to the nucleus, where they release viral DNA [13]. The HCMV genome is expressed in a temporally sequential manner and is categorized into immediate early (IE) genes, early (E) genes, and late (L) genes. IE1 and IE2 are the earliest encoded and most abundantly expressed IE genes that can affect viral promoter activity and initiate transcription from viral E genes [14]. Typical early viral proteins include DNA polymerase (pUL54), phosphotransferase (pUL97), and terminal enzymes (pUL51, pUL52, pUL56, pUL77, pUL89, pUL93, and pUL104), which facilitate viral DNA replication and packaging processes [15]. L genes primarily encode structural proteins required for virion assembly and expulsion that make up the capsid, envelope, or tegument, such as pUL77, pUL93, pUL115, pp28, and pp150 [16]. After DNA replication is complete, it is encapsulated into a capsid, and the nucleocapsid first forms a primary envelope at the inner nuclear membrane, then crosses the nuclear membrane, subsequently unwraps at the outer nuclear membrane, and finally reaches the cytoplasm and coils in the middle compartment of the endoplasmic reticulum (ER)-Golgi apparatus, after which the viral particles are released by budding [17, 18] (Fig. 1). Viral particles can infect various tissues and organs, and in certain cell types, such as hematopoietic stem cells and undifferentiated myeloid cells, the virus can remain silent and latent [19].

The innate immune system is the first line of defence against pathogens invading the body. When viruses enter a host cell, host-pattern recognition receptors (PRRs) detect pathogen-associated molecular patterns (PAMPs), which activate intracellular signal transduction and gene expression programs, leading to the production of a series of mediators, such as inflammatory factors, cytokines, and chemokines, ultimately promoting the body's natural immune response [20, 21]. However, in the long-term coevolution process, viruses, such as herpes simplex virus-1 (HSV-1), have developed various mechanisms to evade host antiviral innate immunity, including the Toll-like receptor (TLR) signaling pathway, the retinoic acid-induced gene I-like receptor (RLR) signaling pathway, the DNA sensing signaling pathway and intrinsic cellular defences [22–27]. To date, CMV has coevolved with mammalian hosts for millions of years; the battle between them has never stopped, and multiple strategies have been developed to evade innate immunity [28].

Among PRRs, the most fully characterized are TLRs [29]. During CMV infection, viral proteins and nucleic acids, including single- or double-stranded RNA (ssRNA or dsRNA), CpG-rich genomes, and envelope glycoproteins, are the true PAMPs recognized by TLRs [30, 31]. The second subfamily comprises RLRs, including retinoic acid-inducible gene 1 (RIG-1), melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2), which can sense the viral replication intermediate dsRNA and trigger the signal cascade reaction of interferon transcription [32, 33]. The third subfamily is the nucleotide-binding and oligomerization domain (NOD)-like receptor (NLR) family, which includes NOD1, absent in melanoma 2 (AIM2), NLRP1 and NLRP3 [34]. Finally, some DNA sensors, such as stimulators of interferon genes (STING), also recognize CMV and induce an antiviral

Fig. 1 CMV life cycle. (1) CMV glycoproteins interact with specific cellular receptors, leading to (2) endocytosis and plasma membrane fusion. (3) The nucleocapsid enters the nucleus through microtubules, and linear DNA is released into the nucleus. (4) (5) Transcription and translation of viral IE genes. (6) (7) Transcription and translation of viral E genes. (8) The viral genome replicates within the nucleus. (9) (10) L proteins, mainly capsid proteins, are expressed and assembled into a new nucleocapsid (11). (12) Membrane proteins and glycoproteins are assembled in the endoplasmic reticulum and Golgi apparatus to form mature viral particles. (14) (15) The virus is released into the extracellular space by budding
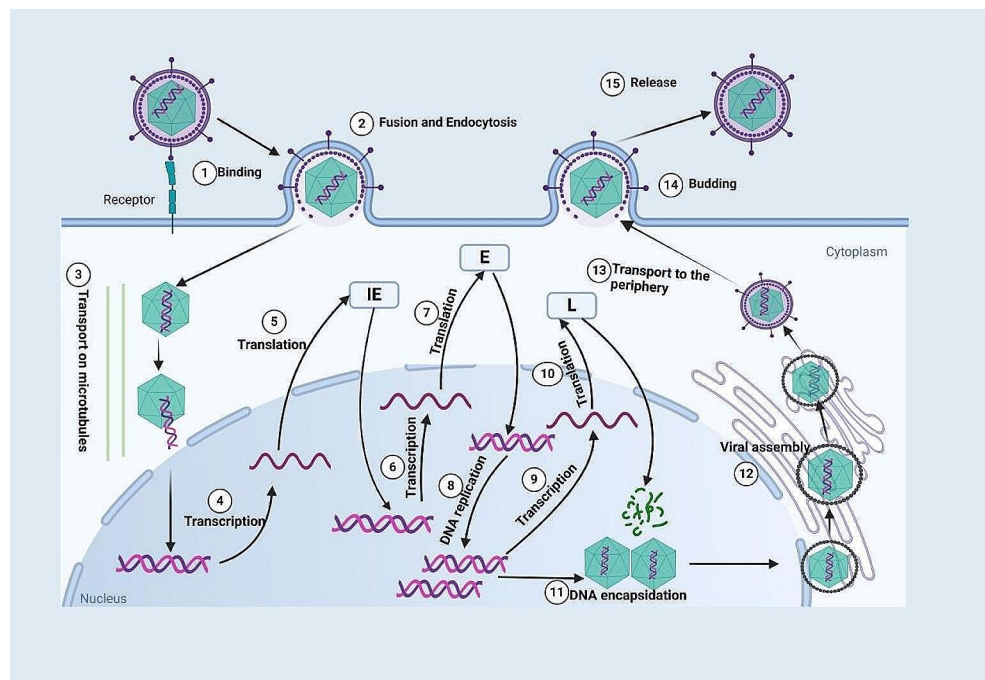
innate immune response, helping to control early CMV infection and triggering the IFN-I response, thus exerting antiviral effects [35, 36]. Accordingly, it is speculated that CMV has the opportunity to promote autoimmune evasion by blocking the above PRR-related transduction pathways.

When viruses infect the body, host cells are in a state of stress, which triggers a series of stress reactions (autophagy, apoptosis, necrosis, and ER stress), and these stress responses also act as an important part of the innate immune response process [37–39]. Therefore, it is not surprising that the cunning virus may also create intracellular environments conducive to its replication and transmission by interfering with these stress pathways [40–42].

This review summarizes and updates strategies employed by CMV to evade host innate immune surveillance, including typical PRR-mediated induction of IFN-I and its downstream interferon-stimulated genes (ISGs), as well as intrinsic cellular defences, such as apoptosis, autophagy and ER stress-mediated antiviral innate immunity. A comprehensive evaluation of the battle between host innate antiviral immunity and viral immune evasion is beneficial for familiarizing ourselves with the pathogenesis of the virus and for identifying new drug targets and potential immunotherapies to combat CMV infection-associated diseases.

CMV evades the PRR-mediated antiviral innate immune response

The innate immune system utilizes PRRs to detect the invasion of pathogenic microorganisms, thereby achieving precise recognition and immune response to harmful stimuli [43]. Once PAMPs bind to the corresponding ligands, they activate multiple adapter molecules, ultimately triggering the activation of interferon regulatory factor (IRF) and NF-κB, leading to the expression of proinflammatory cells and chemokines. Meanwhile, IFN-I also induces hundreds of ISGs, thereby endowing the host with strong innate antiviral ability [44, 45]. Nonetheless, viruses evolve various strategies to evade host antiviral innate immunity [46–48]. Here, we will summarize how CMV evades PRRs, such as TLRs, RLRs, NLRs, DNA sensors, and their downstream signaling pathways.

TLR signaling pathway

In humans, the TLR family consists of ten members [49]: TLR1, TLR2, TLR4, TLR5, and TLR6 are located on the cell surface, while TLR3, TLR7, TLR8, and TLR9 are located inside the cell [50] and contain a ligand recognition domain rich in leucine repeat sequences, a transmembrane domain, and a Toll/interleukin-1 receptor (TIR) homologous domain [51]. TLRs activate a series of innate immune

signaling pathways by recognizing PAMPs, leading to the production of interferons, proinflammatory cytokines, and chemokines, such as IL-1, IL-6, and TNFα, ultimately leading to early identification and defence against foreign pathogens [52–54].

The activation status of TLRs in the host plays a crucial role in initial virus replication and persistence [55], and TLRs are involved in almost the entire process of the virus life cycle and are able to recognize virus envelope glycoproteins to promote virus entry into host cells and recognize nucleic acid to induce the production of inflammatory factors [20, 56]. Studies have shown that TLR2 and TLR4 can recognize and participate in the detection of CMV envelope proteins such as glycoproteins gB and gH [57, 58]. Moreover, other studies have suggested that the envelope glycoproteins gB and gH interact with TLR2 and TLR1 and that TLR2/1 heterodimers are functional sensors of HCMV [59, 60]. It is believed that PRRs may initiate the innate immune response before CMV enters cells. In pregnant women with early-onset preeclampsia, the percentage of CMV IgG-positive serum significantly increases, while the expression level of TLR2/4 mRNA is upregulated [61]. During the differentiation of monocytes into macrophages, infection with HCMV promotes the expression of TLR4 and TLR5 to enhance macrophage inflammation significantly [62]. In addition, TLR3 and 9 located within cells can induce the production of IFN-I and proinflammatory cytokines by recognizing dsRNA and CpG-rich genomes [63].

Single nucleotide polymorphisms (SNPs) of TLRs can also affect the immunogenicity and disease status of CMV infection. A study suggested that TLR9 SNPs are associated with CMV reactivation and disease and that genetic polymorphisms may downregulate TLR9 signaling and lead to reduced antiviral response efficiency [64]. TLR2 and TLR7 genetic polymorphisms are also associated with CMV status in late pregnancy in women and regulate the immune response to CMV [65]. However, some studies have found no statistically significant association between SNPs in the TLR gene and congenital CMV infection or disease status [66]. Therefore, more studies are needed to determine the relationship between TLR SNPs and CMV infection.

To date, various viruses, such as HSV and hepatitis B virus, have evolved specific proteins targeting TLRs that interfere with the innate immune response [56, 67]. To respond to immune system attacks, CMV has also developed various evasion mechanisms (Fig. 2). US7 utilizes the ER-related degradation components Derlin-1 and Sect. 61 to promote the ubiquitination of TLR3 and TLR4. US8 not only disrupts the binding of TLR3-UNC93B1 but also targets TLR4 to lysosomes, leading to its rapid degradation. Therefore, US7 and US8 are considered key inhibitors of TLR3 and TLR4 in human foreskin fibroblasts (HFFs) [68].
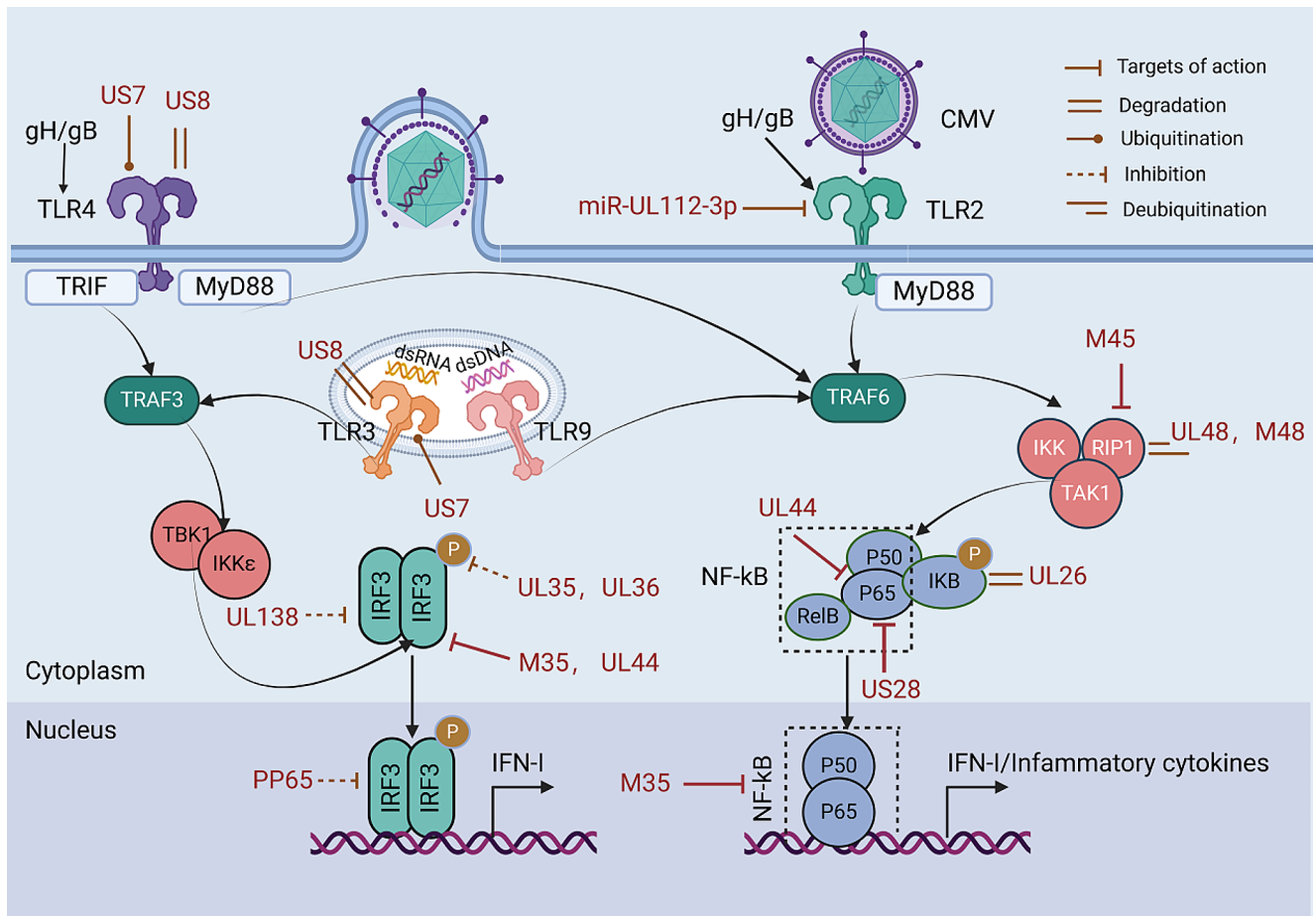
Fig. 2 The immune evasion of the TLR signaling pathway by CMV. virus-encoded products antagonizes the TLR signaling pathway to promote immune evasion. US7 promotes the ubiquitination of TLR3 and TLR4, and US8 promotes their degradation. miR-UL112-3p decreases endogenous TLR2 protein levels. CMV proteins can also interfere with multiple other steps in the TLR pathway, such as TBKI, IRF3, IKK, p65, and p50, to promote immune evasion

HCMV encodes miR-UL112-3p, which effectively inhibits endogenous TLR2 protein levels during CMV infection of normal human dermal fibroblasts (NHDFs), thereby significantly downregulating the TLR/IRAK1/NF-κB signaling pathway [69]. Currently, few studies investigated the correlation between CMV and TLRs in terms of immune evasion, and there is still a significant gap in knowledge of the mechanism by which viral protein targeting blocks the antiviral signaling pathway of TLRs. More studies on the immune evasion mechanism by which CMV targets TLRs in the future may provide new insights for disease prevention and control.

RLR signaling pathway

The three members of the RLR family are highly homologous, with the same DExD/H-box RNA helicase domain at the center and the same zinc-binding domain at the C-terminus [70]. However, LGP2 lacks a signal domain (CRAD) and needs to interact with MDA5 to play a role in viral sensing [71]. After RLRs recognize and bind to the corresponding PAMPs, their conformation changes and a pair of CRADs are released, recruiting and activating downstream mitochondrial antiviral signaling proteins (MAVSs) containing CRADs. Subsequently, the downstream protein TANK binding kinase 1/IkappaB kinase (TBK1/IKK) is recruited to activate the transcription factors IRF3/7 and nuclear factor κB (NF-κB), which produce IFN and proinflammatory cytokines [72, 73].

Undoubtedly, RLRs have become key cytoplasmic receptors for detecting RNA viruses [74]. However, it has been shown that both viral and host RNA can also act as RLR ligands during DNA virus infection [75]. In 2017, for the first time, the immunoreactivity of RIG-I, MDA5, and LGP2 in placental, chorionic, and amniotic tissues was reported and might be related to CMV sensing in pregnancy-related tissues [76]. When the placenta was infected with CMV, the secretion of IFN-β increased, further enhancing the expression of RIG-I and MDA5 at the mRNA level, and it also upregulated the expression of DDX58 and IFIH1.

This study suggested that RLRs may be involved in CMV sensing, but more studies are needed [77].

NLR signaling pathway

The NLR family consists of more than 20 members, among which NLRP3 is one of the most studied DNA sensors related to inflammasomes. Activation of the NLRP3 inflammasome by PAMPs and damage-associated molecular patterns (DAMPs) leads to the secretion of the proinflammatory cytokines IL-1β and IL-18, which play crucial roles in the antiviral innate immune response [78]. Available evidence suggests that the viral glycoprotein components of CMV, as well as increased levels of mtDNA released into the cytoplasm during CMV infection, can activate the NLRP3 inflammasome [34, 79]. NLRC5 is also upregulated in human fibroblasts after CMV infection and activates IFN-γ-mediated antiviral signaling pathways [80]. In addition, activating NOD1 also induces an IFN response and is suppressed by HCMV [81]. Due to their role in the antiviral response, these inflammasomes seem to play a protective role, but the inflammatory response is also involved in the occurrence and development of many diseases. Inhibiting the inflammatory response is a key mechanism for treating certain diseases, so it may also cause serious pathological damage to the body. For example, MCMV infection can cause neuronal death and hearing loss by activating the NLRP3 inflammasome [82]. Downregulation of NLRP3 is beneficial for hypertensive vascular and myocardial remodeling [83]. Therefore, during infection, the roles of these inflammasomes are diverse and worthy of further investigation.

AIM2 can also detect the genetic material of CMV entering the cytoplasm to promote the activation of inflammatory factors [84]. Compared to those in wild-type cells, the ability of AIM2-deficient macrophages to induce IL-1β expression and cell death is reduced, and the transcription of the viral DNA polymerase gene UL54 and the capsid protein-encoding gene UL83 is greater, which indicates that AIM2-deficient cells cannot effectively control HCMV infection [85]. In a CMV-induced sensorineural hearing loss (SNHL) mouse model, a significant increase in AIM2 levels was detected, and the expression of IL-1, IL-18, IL-6, and TNF-α increased to resist CMV infection [86]. Interestingly, the expression of AIM2 is time-dependent, with an increase in AIM2 levels in the early stages of HCMV infection and a decrease in AIM2 levels 24 h after infection. This decrease may be related to the viral immune evasion mechanism [87]. pUL83 interacts with AIM2 in the cytoplasm during the early stages of HCMV infection, thereby interfering with the activation of AIM2 [87]. Subsequently, the immediate early 86 kDa protein (IE86) of HCMV was shown to block the transcription of immature interleukin-1β and induce its degradation during the activation of AIM2 [88].

DNA-sensing signaling pathway

TLR9 was the first DNA sensor described in 2000 [89]. Since then, an increasing number of DNA sensors, including cGAS, STING, DHX9, DHX36, DDX41, IFI16, and ZBP1, have been identified [90, 91]. Among various cell types, cGAS has been identified as the only universal cytoplasmic DNA sensor [92]. When PAMPs recognize and activate cGAS, their conformation changes, which in turn catalyzes the synthesis of cGAMP and activates STING. Subsequently, STING in the ER rapidly dimerizes and undergoes typical COPII-dependent anterograde transport, passing through the ER Golgi intermediate compartment and transferring to the Golgi apparatus. STING located in the Golgi apparatus undergoes palmitoylation and recruits TBK1 for phosphorylation. Then, STING recruits and phosphorylates IRF3, which dimerizes and translocates to the nucleus to activate IFN-I, TBK1 and its homolog IKK β, which enter the nucleus to activate NF-κB signal transduction, inducing the generation of inflammatory factors and participating in antiviral immune responses [93–96].

During HCMV infection, the nucleocapsid is first delivered to the host cell through membrane fusion. Then, the nucleocapsid is transported to the nuclear pore through the cytoskeleton system, releasing viral genomes into the nucleus in a pressure-dependent manner [97–99]. A portion of the viral capsid is degraded by the ubiquitin-proteasome pathway, which then releases the viral DNA into the cytoplasm, where it is detected by a cytoplasmic DNA sensor [100]. The innate immune pathway mediated by DNA sensing has a vital impact on limiting CMV infection. Many viral proteins also counteract immune evasion from the host at the cGAS, STING, MTITA, and IFI16 levels and their downstream signaling adaptors, such as the TBK1-IRF3 axis and NF-κB (Fig. 3).

cGAS

cGAS was first discovered in 2013 as a dsDNA sensor that can activate the second messenger cGAMP, thereby activating STING to form the main pathway for perceiving nonself DNA in animals and triggering effective immune responses [25]. However, CMV likely utilizes multiple strategies to inhibit cGAS enzyme activity and interfere with host immune function. A previous study proposed that the HCMV protein pUL31 can directly interact with cGAS to inhibit the enzyme activity of cGAS, prevent DNA from cGAS sensing, and reduce the production of cGAMP and IFN-I and downstream antiviral genes [101]. The IFN levels
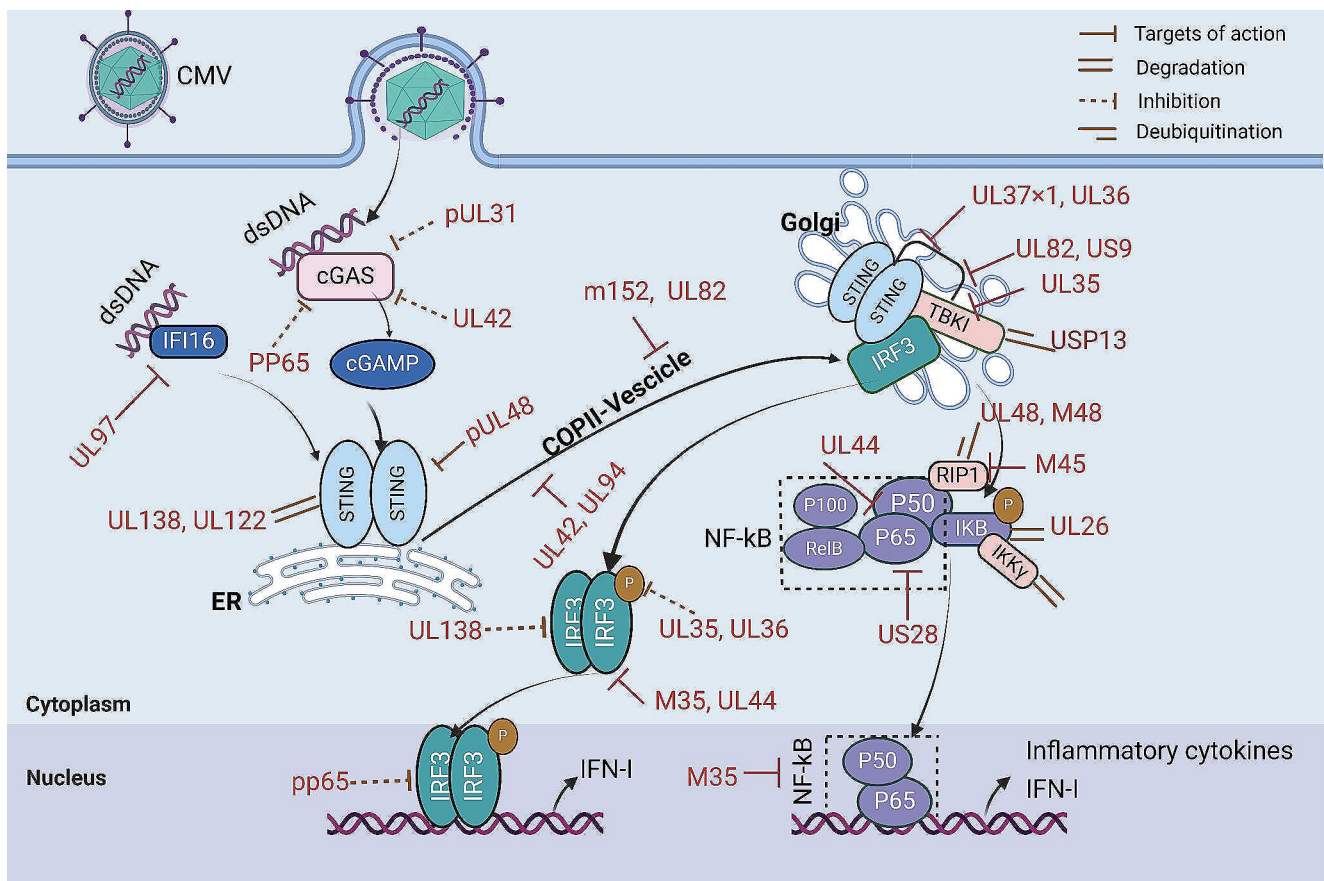
Fig. 3 The immune evasion of the DNA-sensing signaling pathway by CMV. CMV proteins can target multiple adapters and transcription factors in the DNA-sensing signaling pathway for immune evasion. UL31, UL42, and PP65 act on cGAS to inhibit cGAS activity, cGAMP synthesis or interaction with STING. UL138 and UL122 degrade STING, and pUL48 inhibits the ubiquitination of STING. UL97 binds to IFI16, causing it to detach from the nucleus. m152, UL82, UL94 and UL42 inhibit the translocation of STING from the ER to the Golgi.

USP13, UL37×1, UL36, US9, UL82 and UL35 inhibit the interaction between IRF3, TBK1 and the STING complex. UL48, M48, and M45 inhibit the ubiquitination of RIP1. UL44 binds the p65 and p50 complex, US28 inhibits the nuclear localization of p65, and UL26 prevents the degradation of IKB. UL35, UL36, UL138 and PP65 inhibit the phosphorylation of IRF3. UL44 and M35 inhibit the binding of IRF3 to the promoters of antiviral genes

produced by primary HFFs infected with mutant strains that cannot express pp65 were significantly greater than those infected with wild-type strains, indicating that pp65 may be a viral evasion protein and selectively binds to cGAS, which competitively inhibits the interaction of cGAS with STING, thereby blocking the signal transmission of the cGAS/STING/IRF3 axis [102]. In addition, another study has revealed the interaction between UL42 and cGAS through immunoprecipitation technology and further revealed that UL42 reduces the synthesis of cGAMP by inhibiting DNA binding and oligomerization of cGAS in HFFs [103].

STING

After cGAS senses dsDNA and synthesizes its second messenger, cGAMP binds to STING and initiates signal transduction. During this process, the activity of STING is regulated by its dimerization, translocation from the ER through the Golgi apparatus to the perinuclear site, and posttranslational modifications such as phosphorylation or ubiquitination [104, 105]. Investigators have shown that UL138 or UL122 could induce proteasome-mediated degradation of STING through lysosomal and proteasome-dependent pathways [106, 107]. Another study further confirmed that amino acids (aa) 136–289 in IE86 are responsible for STING degradation [108]. Additionally, UL138 colocalizes and interacts with STING and TBK1 to inhibit cGAS/STING/TBK1 signaling pathway-induced IRF3 phosphorylation and IFN-β promoter activation [106]. The UL82 gene encodes the capsid protein (pp71), and mutated viruses lacking UL82 have a reduced number of viral production after HDF infection, indicating that UL82 is crucial for HCMV replication [109]. UL82 and UL42 disrupt the process of STING translocation from the ER, resulting in the blockade of STING activation [103, 110]; in parallel, UL94 also disrupts this process by inhibiting the dimerization of STING

when HCMV infects HFFs [111]. HCMV pUL48 encodes a deubiquitinating enzyme and downregulates the ubiquitination of STING, TRAF6, TRAF3, IRAK1, and IRF7 to counteract the PRR-mediated IFN-I antiviral response in human diploid fibroblasts [112]. Another study has revealed that the MCMV protein m152 delays its transport to the Golgi compartment by binding to STING. Interestingly, m152 inhibits STING-mediated IRF signaling, but not STING-mediated NF-κB signal transduction [113]. In 2018, a study revealed that glycoprotein US9 blocks STING dimerization by binding to STING and TBK1, thereby inhibiting the interaction between STING and TBK1 [114].

IFI16

The IFI16 protein is a member of the pyrin and hin domain (PYHIN) family, which consists of one PYRIN domain and two HIN domains composed of 200 amino acids; this protein has been proven to bind to intracellular viral DNA and trigger the expression of antiviral cytokines through the STING/TBK1/IRF3 signaling pathway [115]. IFI16 binds to viral DNA in the early stages of HCMV infection in human embryonic lung fibroblasts, whereas in the late stages, IFI16 binds to pUL97, which contributes to the translocation of IFI16 from the nucleus into the cytoplasm and the integration of pUL97 into newly assembled viral particles, thereby effectively expelling IFI16 from the infected host to hijack its antiviral activity [116]. Thus, the mislocalization of IFI16 to the cytoplasm by viral proteins is critical for CMV to evade IFI16's antiviral activity [117].

TBK1-IRF3

cGAMP binds to STING to induce STING protein transformation. Subsequently, TBK1 and IRF3 are recruited to the STING complex, where TBK1 is a serine/threonine protein kinase that phosphorylates and activates IRF3, which then translocates to the nucleus and initiates type I IFN production [118]. Given that the TBK1-IRF3 axis is at the core of the antiviral innate immune response, CMV will also evolve various mechanisms to block the TBK1-IRF3 axis signal transduction.

CMV-encoded UL37 exon-1 and UL82 bind directly to TBK1 and inhibit the recruitment of TBKI and IRF3 to the STING complex to eliminate TBK1-STING-IRF3 interactions [110, 119]. One study used WT or UL35-deficient recombinant HCMV to infect primary human foreskin fibroblasts (HFF-1) and revealed that UL35 reduced the phosphorylation of TBK1, STING, IRF3, and STAT1 [120]. USP13 can uncouple multiubiquitin chains connected to K27, thereby reducing the recruitment of TBK1 and its downstream signaling [121]. These findings emphasize the importance of viral protein to evade innate immune sensor TBKI.

UL44 inhibits the binding of IRF3 to downstream antiviral gene promoters, and its overexpression also inhibits the activation of the interferon-stimulated response element (ISRE) induced by IRF3 in HFFs [122]. Investigators have shown that UL36 and UL138 can directly interact on TBK1 or IRF3 to inhibit the phosphorylation of IRF3 induced by the cGAS/STING/TBK1 pathway when HCMV is transfected into 293T cells or HFFs [73, 106]. pp65 is distributed between the nucleus and the cytoplasm and is important for producing viral particles and inducing dense bodies [123]. This protein regulates the IFN-I response by inhibiting the accumulation of IRF-3 in the nucleus and reducing its phosphorylation [124]. The reduction of antiviral activity by M35 during MCMV infection is dependent on its dimerization, where its homodimer binds directly to specific DNA sequences in the Ifnb1 promoter, thereby antagonizing the recruitment of IRF3 to the promoter of antiviral genes [125].

NF-κB

NF-κB plays a crucial regulatory role in the innate immune response and includes a series of important nuclear transcription factors. The NF-κB family in mammals consists of five members: p65/RelA, RelB, p105/p50/NF-κB1, p100/p52/NF-κB2, and c-Rel [126]. Although the p50, p52, and Rel proteins can form multiple homologs and heterodimers, the main form of NF-κB is the heterodimer of p65 and p50 [127]. In a resting state, NF-κB in the cytoplasm combines with the inhibitory factor IκB to form the trimeric p50-p65-IκB. When IκB kinase (IKK) is activated, it catalyzes the phosphorylation of two conserved serine residues of IκB and degrades them through the ubiquitin-proteasome pathway connected by K48, and activated NF-κB translocates into the nucleus and binds to its corresponding DNA sequence to induce target gene transcription, leading to the production of IFN and inflammatory factors [128–130].

The results revealed that both HCMV and MCMV regulate NF-κB activity in a time-dependent manner, activating NF-κB in the first few hours of infection but inhibiting its activation afterward, and the potential molecular mechanisms are yet to be determined [131]. In vitro cell experiments confirmed the interaction between the HCMV proteins pUL44 and p65 or p50, thereby inhibiting the activation of NF-κB induced by IKKβ and p65 overexpression, as well as inhibiting the binding of p65 to the promoter of CXCL2 [122]. HCMV UL26 blocks the nuclear translocation of NF-κB, phosphorylation of the IKK complex and degradation of IκB in MRC5 fibroblasts [132]. US31 may act as an E3-like ubiquitin ligase that promotes the ubiquitination of phosphorylated p100, thereby activating the

NF-κB2 pathway [133]. Compared to infection with the mutant virus lacking pp65, infection with the wild-type virus downregulates IL-1β levels by inhibiting NF-κB activity [134]. HCMV US28 expression in undifferentiated monocytic THP-1 cells inhibits the nuclear translocalization of p65, attenuating the NF-κB pathway to facilitate viral entry into latency [135]. Later, it was revealed that MCMV M35 shuttles to the nucleus before p65 translocation and inhibits type I IFN transcription regulated by NF-κB [136].

NF-κB activation requires the ubiquitination of receptor-interacting protein 1 (RIP1) and NF-κB essential modulator (NEMO) [137]. Moreover, the M45 protein also targets NEMO to autophagosomes for degradation in lysosomes in mouse embryonic fibroblasts infected with MCMV [138]. M45 also blocks the ubiquitination of RIP1, thereby counteracting the innate immune signaling pathway [139]. CMV-encoded UL48 and M48 interact with RIP1 and rely on its deubiquitinating enzyme activity to cleave K48- and K63-linked polyubiquitin chains to inhibit NF-κB activation [140, 141].

The IFNAR-JAK-STAT signaling pathway and its downstream ISGs

IFNAR-JAK-STAT signaling pathway

IFN occupies an absolute core position in antiviral innate immunity, and IFN-I binds to IFNAR1 and IFNAR2 to promote downstream signaling cascades [142]. When IFN binds to IFNAR1 and IFNAR2, it recruits and phosphorylates tyrosine kinase 2 (TYK2) and JAK1, followed by further phosphorylation and activation of STAT1/STAT2 [143, 144]. Activated STAT1 and STAT2 form heterodimers and bind to IRF9 in the cytoplasm, forming heterotrimeric complexes of IFN-stimulating gene factor 3 (ISGF3) [145]. Furthermore, the complex undergoes nuclear translocation and binds to the ISG promoter to initiate the expression of ISGs [146].

In patients with chronic HCV infection, by comparing the transcriptional levels of JAK-STAT pathway mediators between the CMV-positive and CMV-negative groups, it was found that the expression of STAT2 and IRF7 in the CMV-positive group was downregulated, and it was speculated that the elevated risk of CMV in liver cirrhosis patients after HCV infection may be related to dysfunction of the JAK-STAT pathway, which weakens the antiviral effect [147].

Viral proteins reducing ISG expression and evading innate immune system attacks by manipulating the IFNAR-JAK-STAT signaling pathway are shown in Fig. 4. Promoting the degradation of STAT1/STAT2 and interfering with the tyrosine phosphorylation of STAT1/STAT2 are two major evasion mechanisms [148]. The replication of the M27 deletion virus is highly reduced, and its virulence is weakened in mice, indicating that pM27 is a key protein affecting CMV replication and virulence [149]. pM27 binds and downregulates STAT2 in mouse embryonic fibroblasts, while IFN-γ induces an increase in STAT2 tyrosine phosphorylation in M27(-) MCMV-infected cells, which means that pM27 expression also downregulates STAT2 tyrosine phosphorylation [150]. Moreover, pM27 recruits DDB1-containing ubiquitin ligase complexes and directly induces the ubiquitination and degradation of STAT2 through the ubiquitin-proteasome pathway [151]. Similar to pM27, both isoforms of the pUL145 protein (pUL145-Long, pUL145-Short) were found to recruit DDB1-containing ubiquitin ligases to ubiquitinate and degrade STAT2 in HCMV-infected U251 cells [152]. There is conclusive evidence that HCMV UL23 directly interacts with human N-myc-interacting factor (Nmi) or blocks STAT1 phosphorylation in U251 cells to inhibit the nuclear translocation and expression of STAT1 and attenuate the antiviral effects of IFN [153, 154]. UL26 was recently found to form complexes with several STAT family members and various PIAS proteins (repressor proteins that activate STAT transcriptional activity) to block STAT phosphorylation in MRC5 cells infected with HCMV [155]. CMV encodes miR-US33as-5p, which inhibits the phosphorylation of STAT1, STAT2, Tyk2, and Jak1 by binding to the 3′-UTR of IFNAR1, resulting in inactivation of the JAK-STAT signaling pathway and decreasing the expression of ISGs (Mx1, RSAD2, DDX58, BST2, IFIT2, and ISG20) [156].

ISGs

ISGs can be induced in an interferon-dependent or interferon-independent manner to limit viral infection and replication after CMV infection of HFFs, and as a result, elevated expression of IFIT1, IFIT2, IFIT3, Mx1, Mx2, CXCL10, and ISG15 has been detected [157, 158]. In response to these viral defences, CMV has also evolved a series of immune evasion strategies against ISGs.

ISG15

ISG15 belongs to the ubiquitin-like protein family, and its protein modification (ISGylation) is closely related to innate immunity, which can inhibit viral replication [159]. Viral dsDNA could bind to specific receptors to increase ISG15 protein. When HCMV infects primary human fibroblasts, IE1 downregulates ISG15 by inhibiting dsDNA-induced ISGylation [160]. The expression of HCMV UL26 restricts the expression of ISG15 and protein ISGylation in MRC5
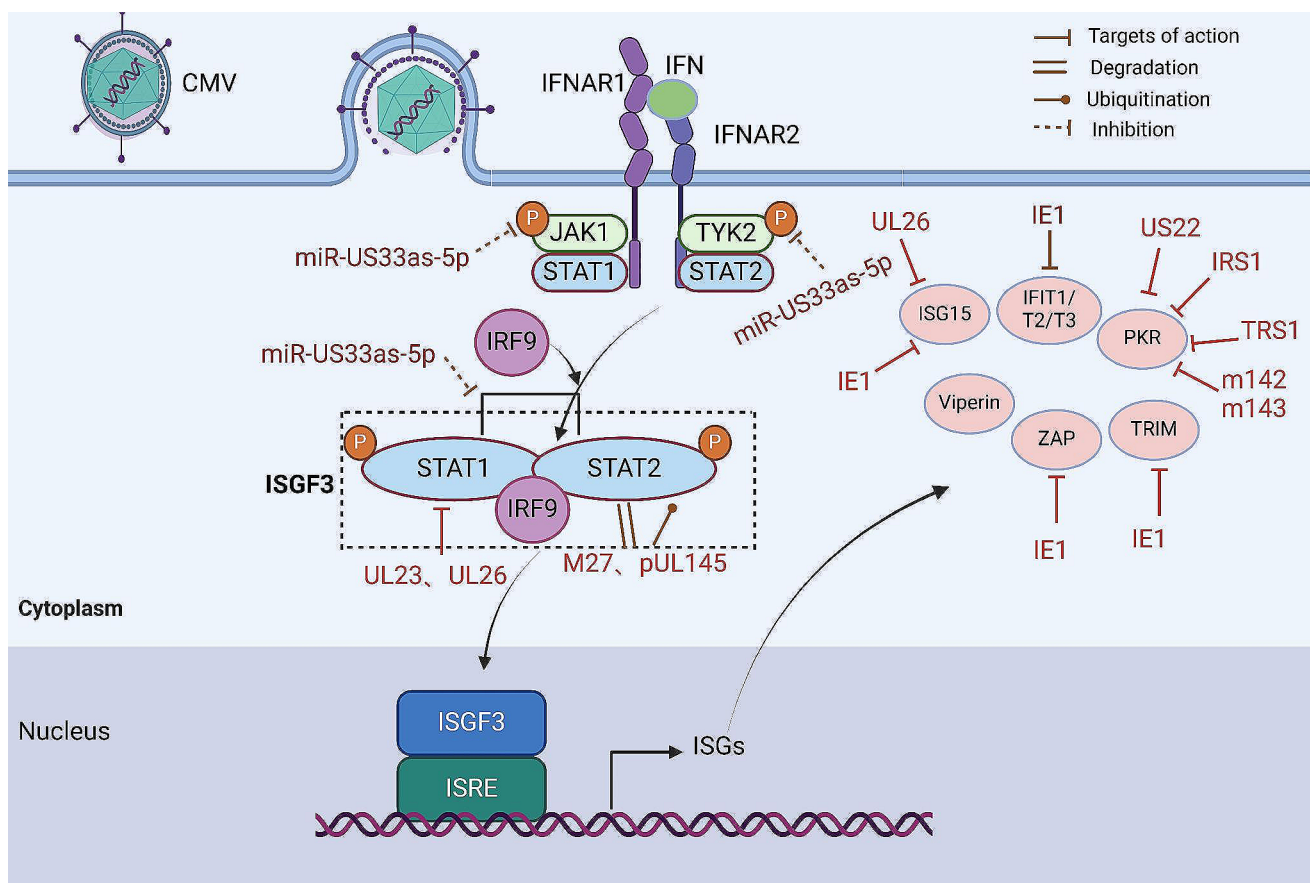
Fig. 4 The immune evasion of the IFNAR-JAK-STAT signaling pathway by CMV. CMV has evolved multiple tricks to evade immune killing via the IFNAR-JAK-STAT signaling pathway. pM27 and pUL145 induce the ubiquitination and degradation of STAT2. UL23 and UL26 block the phosphorylation of STAT1. MiR-US33as-5p inhibits the phosphorylation of STAT1, STAT2, Tyk2, and Jak1. IE1 and UL26 downregulate the levels of ISG15. IE1 induces the citrullination of IFIT1, IFIT2 and IFIT3. TRS1, IRS1, m142, m143, and US22 blocks PKR to exert antiviral effects, and IE1 induces TRIM desumoylation

fibroblasts [161]. Other studies have shown that UL26 interacts with ISG15 and evades ISG15-related antiviral immune responses by inhibiting ISGylation [162]. Additionally, pUL50 could inhibit protein ISGylation by proteasomal degradation of UBE1L, an E1-activating enzyme for ISGylation [163].

ZAP

Zinc-finger antiviral protein (ZAP) is an effective antiviral protein. The expression of ZAP may disrupt the transcription of UL4-UL6, reducing viral mRNA and protein [164]. Moreover, ZAP's antiviral activity exhibits HCMV strain-dependent differences [165]. However, one study revealed that HCMV can evade the antiviral activity of ZAP by inhibiting CpG dinucleotides in the IE1 gene [166].

IFIT1 and ITIT3

Investigators discovered that virally infected astrocytes markedly reduce viral titers in IFITI-overexpressing cells and increase viral titers in IFITI-knockdown cells, suggesting that IFIT1 has crucial antiviral functions [167]. IFIT3 knockout mice showed increased susceptibility to CMV infection, further indicating that IFIT3 plays an important antiviral role during CMV infection [168]. Upon HCMV infection of primary human fibroblasts, IE1 induces the expression of the protein arginine deiminase gene (PAD), which contributes to the significant citrullination of certain ISGs, such as IFIT1, IFIT2, IFIT3, and Mx1, to evade host immune defences [169].

Viperin

Viperin is an antiviral protein that can inhibit the replication of various DNA and RNA viruses. HCMV infection directly induces the expression of Viperin [170]. Viperin

is transmitted to the ER, mitochondria, and viral assembly chambers and exhibits antiviral activity when located in the ER, which enhances TLR7- and TLR9-mediated IFN production to combat CMV infection [171, 172]. However, another study found that HCMV infection does not interfere with viperin mRNA and protein and viperin promotes HCMV infection in human trophoblast cells [173]. These contradictory results indicate that viperin plays an extremely complicated role in CMV infection, and more studies are needed to investigate the potential underlying mechanisms.

PKR

PKR first binds to CMV dsRNA, which then dimerizes and activates autophosphorylation. Activated PKR, in turn, inhibits mRNA translation by phosphorylating its substrate eukaryotic initiation factor 2α (eIF2α), thereby hindering virus translation initiation and replication [174]. Studies have shown that viral proteins TRS1 and IRS1 can bind to both dsRNA and PKR simultaneously, blocking PKR kinase activity and inhibiting eIF2α phosphorylation by binding to conserved amino acids in the PKR-eIF2α binding site [175–178]. In mouse embryonic fibroblasts, MCMV m142 and m143 also effectively selectively antagonize PKR by binding to dsRNA, blocking the phosphorylation of PKR and eIF2α, and relocating PKR to the nucleus and insoluble cytoplasmic compartments [179, 180]. In addition, some investigators have attempted to identify a PKR antagonist encoded by GPCMV and ultimately found that gp145, a member of the US22 protein family, can target dsRNA to block the PKR pathway [181].

TRIMs

The TRIM protein family is a large class of E3 ubiquitin ligases that primarily play an antiviral role by promoting the ubiquitination of key protein molecules [182]. Promyelocytic leukemia-nuclear body (PML-NB), also known as TRIM19-NB, is a key mediator of intrinsic immunity against pathogens, and HCMV IE1 is composed of a spherical core (IE1CORE) region and an inherently disordered region on both sides. Studies have shown that IE1CORE effectively binds to the coiled-coil domain of TRIM19, selectively preventing SUMOylation at specific lysine residues, such as K160, thus inducing deSUMOylation of TRIM to counteract the intrinsic immunity of TRIM-NB [183, 184]. Interestingly, the core area of IE1 is integrated not only with TRIM19 but also with TRIM5α [184]. In 2013, a study identified cellular proteins that interact with IE1 and revealed that IE1 also interacts with TRIM33 [185]. Therefore, given the interaction between IE1 and TRIM5α

or TRIM33, IE1 might also antagonize the antiviral effects of TRIM5α and TRIM33.

CMV evades apoptosis/necrosis, autophagy, and ER stress

When CMV infects the host, viral proteins or nucleic acids effectively induce a series of cellular stress responses, including apoptosis, necrosis, autophagy, and ER stress, to kill and clear the virus and maintain cellular homeostasis (Fig. 5).

Apoptosis/Necrosis

Apoptosis is usually considered an innate cellular response to invading pathogens that can clear cells infected by pathogens and limit and resist pathogen invasion [186]. Apoptosis can be initiated through internal or external pathways, which include three main pathways: the mitochondrial pathway, cell death receptor pathways (such as the Fas/FasL pathway), and the ER stress pathway [187]. When exogenous and endogenous cell apoptosis pathways converge, they cleave and activate Caspase family proteases such as Caspase 3, Caspase 8, and Caspase 9, subsequently activating or inhibiting substrates that promote morphological changes related to cell apoptosis, such as chromatin concentration, cell contraction, and nuclear and plasma membrane foaming [96, 188]. In addition to cell apoptosis, necrosis, characterized by swelling of cytoplasmic organelles, moderate chromatin condensation, loss of membrane integrity, and leakage of cellular components into intercellular spaces, has also received increasing attention [189]. Necrosis is also considered a strategy for host cells to resist the invasion of pathogenic microorganisms such as viruses and bacteria [190].

Host cells can directly or indirectly activate multiple cell death pathways by detecting CMV components or by activating stress pathways through viral replication [191], but CMV also encodes various inhibitors of cell apoptosis and necrosis to ensure the persistence of infection. The interfering function of UL36 in apoptosis or necrosis has been fully studied. Notably, UL36 or M36 is a multifunctional inhibitor of apoptosis and necrosis and promotes viral growth, and the growth of MCMV deficient in M36 is severely attenuated both in macrophages and in vivo [192]. UL36 targets the degradation of mixed lineage kinase domain-like (MLKL), a key protein involved in cell necrosis, and inhibits the apoptotic program in HCMV-infected primary human fetal foreskin fibroblasts [193]. However, UL36 does not inhibit apoptosis in mouse cells, suggesting that the inhibition of apoptosis by this protein is species-specific
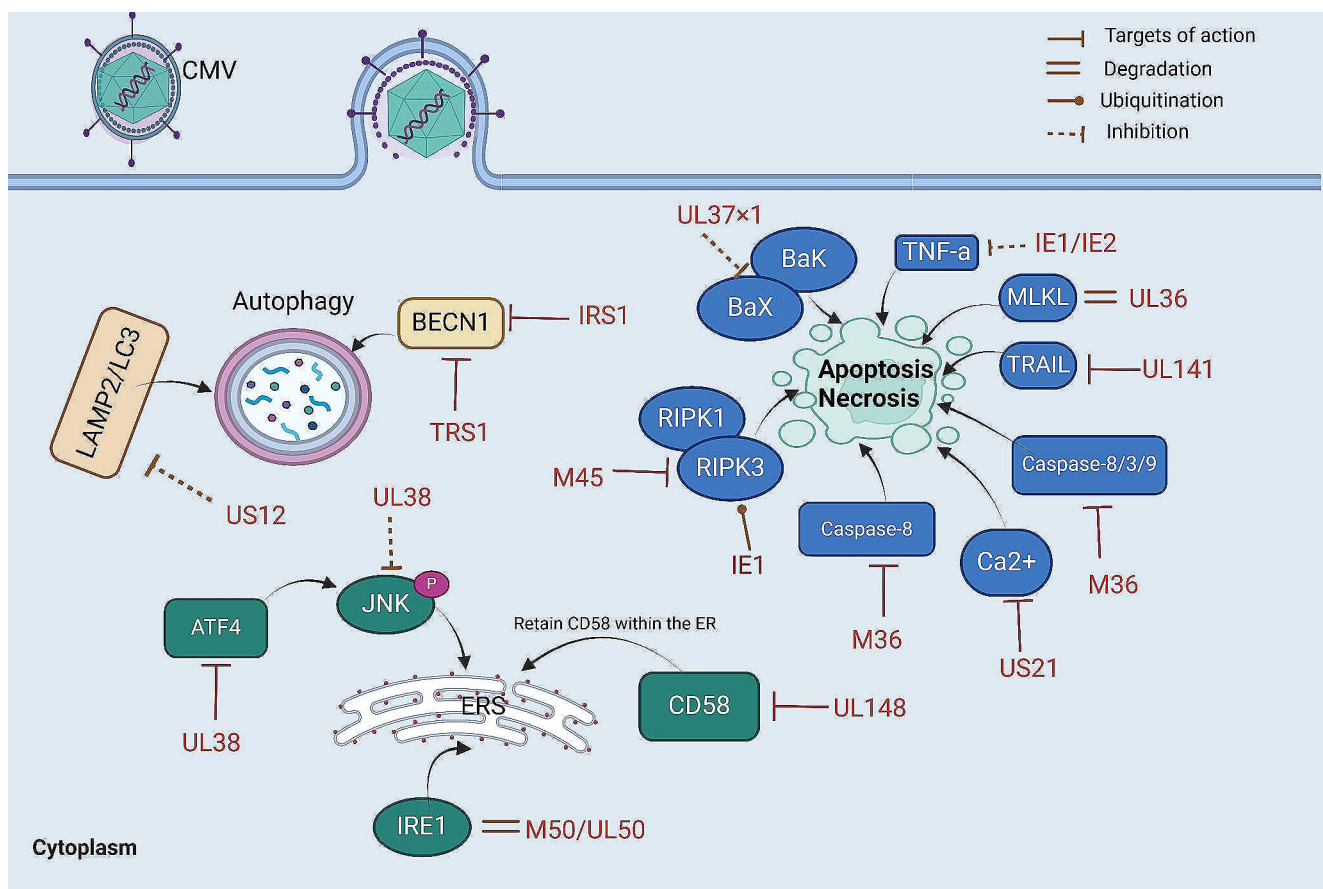
Fig. 5 The immune evasion of ER stress, autophagy, and cell apoptosis by CMV. CMV counteracts stress responses such as ER stress, apoptosis and autophagy to increase survival. Inhibition of apoptosis/necrosis: UL36 degrades MLKL; M36 inhibits CASP8, CASP3, and UL37×1 binding and inhibits Bak and Bax; UL141 binds to TRAIL death receptors; M45 inhibits the RIPK3-dependent necrosis pathway; and IE1 and IE2 inhibit TNF-α-induced apoptosis. IE1 induces the ubiquitination of RIPK3, and US21 regulates the intracellular Ca^{2+} balance. Inhibition of autophagy: TRS1 and IRS1 bind to BECN1 to inhibit autophagy. US12 upregulates ULK1 phosphorylation and LC3-II conversion. Inhibition of ER stress: UL38 induces the accumulation of ATF4 and limits the phosphorylation of JNK. UL148 retains CD58 in the ER, and UL50 and M50 significantly decrease the IRE1 protein level

[194]. Consistent with these results, MCMV M36 encodes an apoptosis inhibitor that binds to caspase-8 and blocks the death receptor pathway in macrophages [195]. Bak and Bax are core regulatory factors for the intrinsic pathways of cell apoptosis [196]. The protein product of HCMV UL37×1 can target mitochondria and inhibit cell death by binding and inhibiting Bak and Bax [197]. HCMV UL141 encodes a glycoprotein that can bind to proteins such as TRAIL death receptors, downregulate the cell surface expression of members of the tumor necrosis factor receptor superfamily (TNFRSF), and thus resist host defence [198].

Receptor-interacting protein kinase-1 and −3 (RIPK1 and RIPK3) are key mediators of necrosis and strictly regulate the process of necrosis. The MCMV protein M45 contains the RIP homologous interaction motif (RHIM), which is sufficient to protect infected cells from necrotic cell death [199]. Recently, M45 was shown to inhibit the RIPK3-dependent necrosis pathway through Z-DNA

binding protein 1 (ZBP1)-dependent (in non-myeloid cells) and ZBP1-independent (in macrophages) pathways. M36 suppresses the TNF signaling-dependent CASP8-CASP3 activation axis, as well as CASP8-independent cleavage activation of CASP9 and CASP3 [200]. Therefore, MCMV proteins ensure their adaptability by blocking different host proteins involved in programmed cell death pathways. IE1 and IE2 are early characterized antiapoptotic proteins that are crucial for regulating host cell death to ensure HCMV replication [201], and the relevant mechanisms include inhibiting TNF-α-induced cell apoptosis and inhibiting cell apoptosis by activating phosphatidylinositol kinase (PI3K) to promote survival pathways [202]. A recent study demonstrated that IE1 interacts with RIPK3 in an RHIM domain-independent manner in HFFs, resulting in substantial upregulation of posttranslational modifications of RIPK3, particularly ubiquitination, to prevent apoptosis [203]. The US21 protein is an ion channel encoded by viruses that

regulates intracellular Ca^{2+} homeostasis and protects cells from apoptosis [204].

Autophagy

Viral infections usually result in autophagy, which is an inherent cellular defence mechanism [40]. Autophagy typically controls infection by delivering viral particles to lysosomes for degradation and further coupling with PRR signaling pathways to induce interferon-mediated viral clearance [205, 206]. Currently, little is known about the interaction between CMV and autophagy. It is generally believed that inducing autophagy can damage viral DNA replication and interfere with viral particle release through different mechanisms [207]. Some autophagy inducers, such as trehalose and SMER28, can induce autophagy to reduce the accumulation of viral proteins in HFFs and HAECs, interfere with viral particle transport pathways, redirect viral particles to acidification compartments for degradation, and delay viral genome replication [208, 209]. However, knocking out autophagy-related genes and inhibiting the activity of autophagy-related proteins can downregulate the replication of HCMV, indicating that autophagy-related factors are required for effective HCMV replication and induced autophagy will enhance viral replication [210, 211]. The sharp contrast in autophagy may be due to the fine requirement and balance of autophagy during its replication cycle.

Not surprisingly, various strategies have been developed to block the autophagy process in CMV. The binding of the viral protein TRS1 to BECN1 could inhibit autophagy [212], which could be completely inhibited 24 h after HCMV infection in human primary fibroblasts. IRS1, homologous to TRS1, can also bind to BECN1 and inhibit autophagy. When these two proteins are expressed simultaneously, they hinder the development of autophagosomes, but when they are expressed separately, they block the onset of autophagy [211]. US12 interacts with regulatory proteins necessary for inducing autophagy, thereby upregulating the phosphorylation of the autophagy initiation protein ULK1 and the transformation of LC3-II to induce and accelerate autophagic flux [213]. However, additional studies are needed to determine whether US12 increases viral replication through autophagy.

ER stress

The ER is a crucial organelle involved in physiological processes such as protein processing and the regulation of Ca^{2+} homeostasis [214]. The synthesis and folding of proteins are precisely regulated and sensitive to changes in ER homeostasis. When the ER is subjected to stress, such as Ca^{2+} depletion, hypoxia, and viral infections, it produces a large amount of unfolded proteins [215]. The ER enters a stress state once its folding capacity is exceeded or when there is an excessive accumulation of misfolded proteins. These proteins are generally detected by three ER-resident sensor molecules, activating transcription factor 6 (ATF6), inositol-requiring enzyme 1α (IRE1α) and protein kinase R-like ER kinase (PERK), which further activate the unfolded protein response (UPR). Moreover, the phosphorylation of the PERK translation initiation factor eIF2α reduces protein translation [216]. Eventually, ER homeostasis is restored by increasing protein folding ability and reducing protein load.

Some studies have shown that HCMV can manipulate the UPR to promote infection. HCMV with a mutated UL38 has severe growth defects, but its growth is restored in HF cells expressing wild-type pUL38, possibly because pUL38 protects cells from ER stress during HCMV infection by inducing the accumulation of activated transcription factor 4 (ATF4) and limiting c-Jun N-terminal kinase (JNK) phosphorylation [217]. HCMV UL148 retains CD58 within the ER, preventing it from reaching the cell surface to weaken the CD58-mediated antiviral response. However, UL148 also promotes the activation of PERK and IER1 and reshapes the ER, but these two effects can be separated as the virus mutates and evolves [218, 219].

RE1/X box binding protein 1 (XBP1) is an important component of unfolded protein response elements. The expression of M50 in MCMV-infected NIH-3T3 cells leads to a significant decrease of IRE1 protein, while mRNA splicing and the expression of XBP1 are also inhibited in infected cells. Similarly, the homolog of M50, HCMV UL50, also degrades IRE1 [220]. Another study further revealed that the M50 protein inhibits the IRE1 branch of the UPR by associating IRE1 with SEL1L, thereby promoting its degradation via the ER-related degradation (ERAD) mechanism [221].

Conclusion

CMV is ubiquitous and can establish lifelong infection in the host. It can cause serious complications in individuals with a suppressed or dampened immune system and is also the most common cause of congenital viral infections. CMV infection can trigger a wide range of defence mechanisms, among which the innate immune defence mechanism is the first line of defence against viral invasion, mainly limiting virus infection and transmission by producing IFN-I and ISGs. In the long-term struggle between the virus and the host, CMV has developed various strategies to evade innate immune attacks and facilitate its growth and reproduction. Multiple viral proteins are involved, especially some envelope proteins, IE proteins, and other functional proteins that

target key adapters to antagonize antiviral signaling pathways, such as TLR2/4, cGAS, STING, NF-KB, TBKI, and IRF3. Moreover, some viral proteins can also interfere with intracellular processes, such as apoptosis, necrosis, autophagy, and ER stress pathways, to evade the innate immune system and result in persistent infections.

Accumulating evidence suggests that TLR agonists have great potential as antibacterial, anticancer, and vaccine adjuvants and are also of great significance for vaccine development and immunotherapy against HSV, HBV, HIV, and other viruses [222–224]. Moreover, TLR antagonists have also been developed as reagents and drugs to suppress immune responses [225]. Therefore, this article reviews the immune evasion mechanism by CMV to target PRRs and various cellular processes, which may also provide great insights into developing vaccines and antiviral drugs.

Declarations

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