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Cracking the Human Cytomegalovirus Code: Trinary Challenges of Latency, Immune Evasion, and Correlates of Protection

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ABSTRACT

Human cytomegalovirus (HCMV) poses a significant challenge to vaccine development due to its complex biology characterized by latency, immune evasion strategies, and undefined correlates of protection (CoPs). HCMV latency allows the virus to evade immune surveillance by remaining in a quiescent state in host cells, with the risk of reactivation triggered by immune damage or cell differentiation. In addition, HCMV employs an arsenal of immune evasion strategies, including modulating MHC expression, inhibiting natural killer (NK) cell activity, and subverting antibody-mediated responses, so these mechanisms further complicate vaccine design. Despite these obstacles, advances in basic research in immunology and vaccine technologies offer new opportunities. Strategies such as targeting latency-associated mechanisms, using memory inflation of CMV-specific T cells to induce long-term tissue-resident immunity, and developing immunogens that antagonize viral immunoevasins are promising approaches. New platforms, including mRNA and vector-based vaccines, show the potential to elicit robust humoral and cellular responses against key viral antigens such as glycoprotein B, pentamer complex, and pp65. In addition, adjuvants that restore impaired NK and T cell function could improve vaccine effectiveness. This review examines the molecular and immunological barriers to HCMV vaccine development and highlights innovative approaches to address these challenges. By addressing the complexities of latency, immune evasion, and CoPs, we propose a roadmap for developing a multimodal vaccine that can provide effective and durable protection against HCMV infections.

Keywords: Human cytomegalovirus; Immune evasion; Latency; Memory inflation; mRNA vaccines; Vaccine development

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INTRODUCTION

Cytomegalovirus (CMV) is an enveloped DNA virus that belongs to the herpesvirus family. After the initial infection, the virus remains latent in body tissues for life.[1] In healthy individuals, heterophile-negative infectious mononucleosis is the most common complication of CMV infection in most populations.[2] However, organ transplant recipients, acquired immunodeficiency syndrome patients, premature infants, and patients with various malignancies sometimes experience viral reactivation or reinfection with a different strain of CMV. This infection is called a recurrent infection.[3] Women who become infected with CMV during pregnancy can transmit the infection to their fetus, resulting in permanent disabilities such as hearing loss, vision loss, and intellectual disability in the child.[4] CMV infection is found to be common in organ transplant recipients and has the potential to result in severe symptoms such as pneumonia, hepatitis, chorioretinitis, and even death. In addition, although antiviral therapies (ganciclovir and foscarnet) are available for the treatment of CMV infections in immunocompromised patients, there is a need for new treatment options with fewer side effects.[5,6]

Developing an effective vaccine against CMV could be very effective in combating this virus.[7] In the 1960s and 1970s, studies of the CMV virus began, and in these years, CMV was recognized as an important cause of infections and congenital diseases.[8] Development of the CMV vaccine began in the 1970s with attenuated strains, and in the 1980s, one of its strains was shown to be safe and effective in kidney transplant patients.[9] Many vaccines have been tested since 2000. For example, targeting specific proteins such as glycoprotein B (gB) has been considered. According to studies, antibodies against gB may be a good option for a CMV vaccine since it plays a role in the virus' fusion with the host cell surface. This is because antibodies against gB may neutralize CMV infection in fibroblast cells.[10,11] Studies have shown that the gB vaccine, when administered with the MF59 adjuvant, sparks antibodies against the antigen domain that controls cell-to-cell spread.[11] Further studies have shown that pp65 in CMV vaccines is a main point of attack for cellular immune responses.[12] The subsequent discovery of the pentameric protein complex (PC) that produces most neutralizing antibodies led to efforts to incorporate this complex into vaccines. Studies have shown that neutralizing antibodies specific to PC are much more effective than antibodies against gB in neutralizing infections in epithelial cells, endothelial cells, and monocytes.[13] Furthermore, the presence of maternal antibodies to PC early in pregnancy has been associated with a reduced risk of HCMV transmission to the fetus.[14]

Today, vaccines against CMV have been developed with different platforms, including live attenuated viral proteins, recombinant viral proteins, dense bodies, vector vaccine subunits, or synthetic peptide epitopes. These vaccines have been extensively evaluated using various animal models and have shown promising immunogenicity and protective efficacy.[15-20] Some vaccines have also entered clinical trials.[21-33] Among the most recent vaccines against CMV are with new technologies, such as the mRNA vaccine, which uses the gB-PP65-PC antigens in its structure and has shown promising results.[34] Despite all the studies that have been conducted, the development of a suitable vaccine against CMV is considered problematic work due to several reasons, such as the complex immunobiology of the virus, its ability to cause latent infection.[35] and the ability to evade the immune system in various ways, and the lack of a clear correlate of protection (CoP) for HCMV.[36] This review examines some of the issues that give rise to challenges in developing a vaccine against CMV.

CMV Latency

A significant hurdle to developing a successful vaccine is CMV latency.[37,38] During latency, the CMV genome persists in certain cells without producing new viruses.[37,39] As a result, the immune system stops recognizing the virus and it improves resistance to antiviral medications that target viruses that are actively replicating.[38] This phenomenon causes a challenge for vaccine development because the primary target of vaccines is to induce recognition and elimination of actively replicating viruses by the immune system. In individuals with compromised immune systems or transplant recipients, latent viruses can reactivate and cause medical conditions.[38,40] Given that current antiviral therapies only put a damper on the replication of active CMV and not latent viruses, it raises significant red flags.[38,41] The effectiveness of a CMV vaccine depends on its ability to target latently infected cells and end their reactivation in addition to preventing the

occurrence of primary infection.[38] A deeper insight into the mechanisms underlying CMV latency emergence, viral reactivation triggers, and immune responses to latent infection is necessary to bring about this herculean challenge.

The Mechanisms of CMV Latency

CMV latency is described as a complex process involving viral and host factors that suppress viral replication and let go of the viral genome in a quiescent state. This gives the opportunity for the virus to remain throughout the host's lifetime without being recognized and eliminated by the immune system. A hallmark of latency is the restricted expression of viral genes essential for active replication.[37] During latency, key viral genes that drive replication are turned off, particularly the major immediate-early (*MIE*) gene locus, which is crucial for viral activation.[42] To control its expression during latency, the MIEP region (MIE enhancer/promoter) is specifically regulated in a variety of ways (Figure 1A).[42] Chromatin remodeling creates a tightly packed structure around the *MIE* gene, preventing the virus from becoming active. For example, MIEP-associated histones at H3K9 and H3K27 become trimethylated (me3) during latency.[43,44] These changes are related to gene silencing and produce a repressive environment. Cellular repressor proteins such as heterochromatin protein 1 (HP1), epidermal growth factor receptor-related factor (ERF), Ying Yang 1 (YY1), and KRAB-associated protein 1 (KAP1), also interact with MIEP or adjacent regions and on top of that, contribute to transcriptional repression.[43-48]

The virus also gives rise to factors that play a role in maintaining latency. For example, viral long non-coding RNA 4.9 has been shown to become associated with MIEP and recruit the polycomb repressive complex 2 (PRC2) repressor complex.[49] Moreover, HCMV encodes microRNAs that target and bring under control host cell factors involved in various processes, including cell signaling pathways.[50,51] Some HCMV microRNAs directly coordinate viral transcripts to dampen lytic gene expression.[50] HCMV can manipulate cell signaling pathways to form a favorable environment for latency. Viral proteins, including pp71, a viral transactivator critical for lytic infection, are taken out of the nucleus of latently infected cells, preventing initiation of lytic gene expression.[52,53] Some studies also give evidence of the role of cell signaling in suppressing *MIE* gene expression.[54-56] However, the specific signaling processes and pathways involved are not well understood. Cell differentiation affects HCMV latency as a dynamic process. Though their precise function in CMV pathogenesis is not well understood, other cell types have the potential to harbor latent viruses, even though latency is mainly studied in hematopoietic progenitor cells (HPCs), including $CD34^+$ cells and $CD14^+$ monocytes.[57-60] The differentiation of HPCs into mature myeloid cells, including dendritic cells and macrophages, has a strong correlation with the shift from quiescence to reactivation. This differentiation process can spark changes in cell signaling and chromatin structure that promote virus reactivation.[43,44,58,61]

According to most investigations, CMV latency is a sophisticated tactic the virus has developed to stay in the host. The virus takes a multifaceted approach that includes limiting viral gene expression, manipulating host cell signaling, and exploiting cellular differentiation processes to create an environment that favors latency. This complexity poses significant challenges for developing vaccines and therapies to eliminate the latent CMV reservoir.

Factors Triggering CMV Reactivation

Several elements, such as cell differentiation, inflammatory signals, and cell signaling pathways, play a role in the reactivation of latent CMV.[37,50,62] These elements provide the opportunity for the virus to re-enter the lytic replication cycle by upsetting the fragile state that maintains viral latency. Primary in CMV reactivation is the differentiation of latently infected HPCs, particularly $CD34^+$ cells and $CD14^+$ monocytes, into mature myeloid cells like dendritic cells and macrophages.[44,59,60,63,64] Alterations in the cellular environment, such as modifications to signaling pathways, chromatin structure, and gene expression, arise during the transition from a progenitor to a differentiated state.[42] These modifications are likely to make the environment more conducive to the virus's reactivation. For instance, repressors can be eliminated, and transcriptional activators can interact more efficiently when differentiation-dependent chromatin remodeling occurs around the *MIE* locus, particularly in the MIEP region.[65-67] Furthermore, signaling pathways and differentiation-specific transcription factors (dsTFs) have the potential to be triggered, which would facilitate the process of the start of viral gene expression.[68,69]

CMV reactivation is strongly tied to immune activation and inflammatory signals.[70] Interferon

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gamma (IFN-γ), tumor necrosis factor (TNF), and interleukin 6 (IL-6) are examples of proinflammatory cytokines that have a positive effect on myeloid cell maturation and have a hand in the CMV reactivation process.[71-73] These cytokines, often secreted in response to stress, infection, or tissue damage, can activate signaling pathways that disrupt latency and promote viral gene expression.[40] They can, for instance, trigger the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, a crucial modulator of immunological responses and inflammation, which can attach to MIEP directly and initiate its activation.[70] It is crucial to remember that immunosuppression can indirectly aid in CMV reactivation, despite its apparent paradox. Reduced NK immune surveillance in immunocompromised people can result in inflammatory diseases or other opportunistic infections that can release proinflammatory cytokines and, eventually, CMV reactivation.[74-76]

Shifts in cell signaling pathways are of utmost importance for checking the ratio of reactivation to quiescence. Several factors, including cytokines, growth factors, and cellular stress, can influence these interconnected signaling pathways.[77] Mitogen-activated protein kinase (MAPK) signaling, phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mechanistic target of rapamycin (mTOR) signaling, and other signaling pathways are central to CMV reactivation.[77] In certain cell types, the MAPK pathway – particularly the ERK-MAPK branch – has been found to be a critical mediator of CMV reactivation.[44,78] Stimulation of this pathway can lead to phosphorylation and activation of transcription factors such as cAMP response element-binding protein (CREB), which binds to MIEP and initiates the expression of viral genes.[79] It is important to remember that MAPK signaling appears to play a cell type-specific role in reactivation and that blocking this pathway may even promote reactivation in various situations.[44,80] Another important signaling cascade tied to reactivation is PI3K/Akt/mTOR signaling. For example, growth factors, such as epidermal growth factor (EGF), are prone to spark this pathway, increasing cell survival and proliferation, and potentially resulting in reactivation.[81-83] Mechanistically, KRAB-associated protein 1 (KAP1), a cellular suppressor protein that binds to MIEP, can also be phosphorylated by mTOR activation.[84] This phosphorylation event impairs the ability of KAP1 to repress and could be a factor in its reactivation.[85,86] The function of PI3K/Akt/mTOR signaling in reactivation is likely to be complex and context-dependent, similar to the MAPK signaling pathway. Although their precise functions are unclear, some additional signaling pathways have been suggested to play a role in CMV reactivation. These contain stress-activated kinase pathways, G protein-coupled receptor signaling, and the cAMP/PKA pathway (Figure 1C).[79,87-90] Further investigation is required to fully understand how these different signaling pathways interact and how they contribute to CMV reactivation.

It is possible that other factors, such as allogeneic stimulation, stress, and viral factors, contribute to CMV reactivation.[37,91-93] Contact of latently infected cells with allogeneic cells, for example, during a transplant, tends to result in CMV reactivation.[91] The mechanism behind this phenomenon is not yet fully understood, but it is probably based on the activation of immune reactions and inflammatory signals.[91] Furthermore, a variety of stress factors, such as hypoxia, nutrient deficiency, and DNA damage, can induce CMV reactivation.[94-97] These stressors frequently initiate cellular signaling routes that disturb latency and result in viral gene expression. Specific viral proteins have demonstrated an ability to aid in reactivating. An example is the viral protein US28, which is similar to a chemokine receptor and has been shown to influence cell signaling pathways and play a role in reactivation. However, how it works exactly is still a topic of debate (Figure 1B).[37]

It is crucial to understand that these factors often interact synergistically and that multiple signals may be required to overcome the barriers to maintaining viral latency. The specific combination of factors that trigger reactivation can vary depending on the type of host cell, the immune status of the individual, and the CMV strain. Further investigation is necessary to unravel the intricate relationship between these factors.

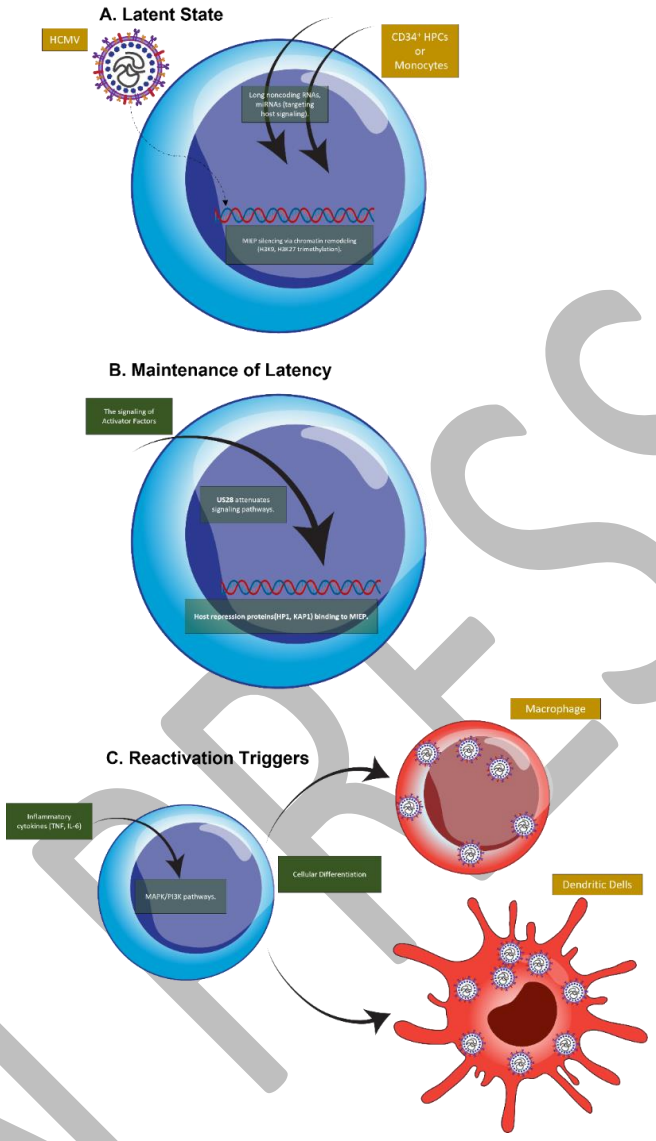

Figure 1. Key mechanisms of cytomegalovirus (CMV) latency and reactivation in CD34⁺ hematopoietic progenitor cells (HPCs) and monocytes: The figure illustrates the intricate molecular and cellular processes underlying CMV latency establishment, maintenance, and eventual reactivation within CD34⁺ hematopoietic progenitor cells (HPCs) and monocytes. There are three critical steps: A. Establishment of Latency: Upon CMV infection, the viral genome enters the host nucleus where latency is initiated. Long noncoding RNAs and microRNAs encoded by CMV target host signaling pathways, resulting in the silencing of the major immediate-early promoter (MIEP) through chromatin remodeling. This involves histone modifications such as H3K9 trimethylation and H3K27 trimethylation, preventing transcription of lytic genes and establishing a latent state. B. Maintenance of Latency: During latency, host-derived repression proteins such as heterochromatin protein 1 (HP1) and KRAB-associated protein 1 (KAP1) bind to the MIEP, further stabilizing its silenced state. The viral-encoded US28 protein actively attenuates host signaling pathways, reinforcing latency by preventing immune recognition and minimizing cellular activation. C. Reactivation of CMV: Reactivation is triggered by external stimuli, including inflammatory cytokines (e.g., tumor necrosis factor [TNF], interleukin 6 [IL-6]) and cellular differentiation into macrophages or dendritic cells. These signals activate the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways, which disrupt chromatin remodeling and reactivate the MIEP. This allows for the production of viral proteins and eventual viral replication in differentiated cells.

The Immune System and Latent CMV

CMV infection comes to pass in three stages (i.e., lytic, persistent, and latent), with each stage exerting an influence on the immune response uniquely. CMV latency, hand in hand with the viral reactivation, gives rise to three specific immune responses against latent CMV. These responses comprise CMV-specific T cell responses, memory inflation, and natural killer-like CD8 T cells.[98] Following CMV infection, CMV-specific T cells undergo a phenotypic transition from effector cells to memory cells, encompassing effector memory (TEM), central memory (TCM), and tissue-resident memory (TRM) subsets.[99] Within TCM cells, a limited group of inflationary memory $CD8^+$ T cells, found mainly in lymph nodes with small numbers in the spleen, are the most important TCM cell subset in response to latent CMV infection.[98]

Essential subsets of TEM cells that elicit a significant functional response against latent CMV infection comprise CD8 effector memory cells re-expressing CD45RA (TEMRA), CD4 TEMRA, and Cytotoxic CD4 T cells (CTL). TEMRA CD8 cells exhibit lower proliferation compared to effector cells, but they have the capacity to generate significant amounts of IFN-γ. Depending on the CD57 expression, these cells are subdivided into two types: $CD57^+$ TEMRA, which are in the terminal expansion phase of the immune response, and $CD57^-$ TEMRA, which have a higher proliferation capacity and are more flexible in differentiation.[99,100] CD4 TEMRA cell subsets are fewer in number than CD8 TEMRA cells. These cells comprise under 10% of all CMV-specific IFN-γ^+ CD4 T cells and provide a clue to CD57, viewed as a marker of polyfunctionality, particularly in CMV-positive individuals.[101-103] A subset of the T cells ($CD57^+CD27^-CD28^-CD244^+$) is cytotoxic and shows TCR oligoclonality. Studies have shown specific stages of CD4 CTL differentiation marked by CCL3, CCL4, and CCL5 proteins and supported by common TCR complexes.[104,105] CD4 CTLs are found more frequently in specific organs (like the spleen and liver) and are not present in others, including salivary glands (SGs).[106,107] TRM cells generate tissue-specific responses in tissues affected by CMV infection in both mice and humans. These cells are categorized into two subtypes: CD8 TRM cells, characterized by CD103 and CD69 markers, and CD4 TRM cells, identified by CD11a and CD69 markers.[108-110]

Memory inflation, a distinctive feature of CMV-specific CD8 T cells, is characterized by continued expansion during the latent phase of CMV infection, rather than the typical cycle of expansion and contraction. These cells achieve sustained levels in different tissues and continue their functional and often memory-like phenotype over time.[111] Protease processing, antigen avidity for MHC and TCR, $Tcf1^+$ cells, and the reactivation of latent infection in lymphatic endothelial cells are some contributing elements that play a role in memory inflation. Sporadic reactivation of CMV in latently infected lymphatic endothelial cells sparks CMV-specific T cells, leading to their expansion.[112,113] A subset of $Tcf1^+$ cells promotes the maintenance of the inflationary T cell pool in response to cytokines such as IL-12 and type I interferons.[114] Only certain peptides that are processed by the constitutive proteasome in infected cells (not the immunoproteasome) are permitted to give rise to inflammatory responses.[115] A significant factor in raising memory inflation is the location and avidity binding of peptide antigens to MHC molecules.[116] CMV-specific inflationary T cells are characterized by distinctive features such as phenotypic markers and tissue distribution that facilitate their identification. These cells express markers of effector memory (such as CD45RA for TEMRA cells), markers of T cell maturation, and sometimes conventional markers of natural killer (NK) cells. High frequencies of inflammatory cells are found in the spleen, blood circulation, and various peripheral tissues.[111] Memory inflation plays a protective role by enabling CMV-specific T cells to incessantly "scan" the body for reactivation of the virus. This surveillance prevents viral relapse and contributes to long-term control of CMV in infected individuals. The number of these inflationary T cells directly correlates with their ability to protect against CMV reactivation.[98] Understanding memory inflation is valuable for CMV vaccine strategies because vaccines can be designed to induce long-lasting, inflationary T cells that provide robust and sustained immune surveillance against CMV. On the other hand, it is possible that mimicking the inflationary response in vaccine design will give rise to vaccines that have wide tissue distribution and a strong cytotoxic response against CMV-infected cells.

CMV-specific T cells upregulate NK cell markers, including CD57, KIRs, LIRs, and CX3CR1, associated

with NK cell molecules that distinguish these cells from conventional T cells. These cells produce high levels of inflammatory cytokines and have the potential to become degranulated in CMV-positive individuals, as shown by the CD107a marker on the plasma membrane.[117] NKG2C, in combination with other NK cell markers such as CD56 and KIR, are upregulated in CD8 T cells during the course of HCMV infection. These cells are oligoclonal and do not express PD-1 despite the fact that they are stimulated over a long duration. These $NKG2C^+$ CD8 T cells demonstrate robust effector functions against HCMV-infected fibroblasts through the interaction of NKG2C and TCR. Transcriptional analysis shows that BCL11B, a transcription factor in these $NKG2C^+$ CD8 T cells, plays a role in their developmental fate. Deletion of BCL11B in normal CD8 T cells gives rise to an innate-like population ($CD56^+CD94^+DAP12^+NKG2C^+CD45RA^+CCR7^-PD^{-/low}$) capable of targeting $HLA\text{-}E^+$ cells.[118] Terminally differentiated CMV-specific CD8 T cells usually express high levels of NKG2C.[119] NKG2C specifically recognizes CMV UL40 protein peptides presented in the HLA-E context and promotes adaptive NK cell expansion. CD94/NKG2C is also involved in alternative activation pathways for CD8 T cells.[120,121]

The intricate molecular details surrounding HCMV latency provide important foundations for developing innovative vaccines. These findings may transform vaccine design by addressing challenges specific to the life cycle of HCMV and its interactions with the host immune system. Latency represents a significant hurdle in vaccine development because latent HCMV is invisible to immune surveillance.[76] Innovative vaccine strategies could focus on disrupting latency-maintaining mechanisms, such as chromatin remodeling at the MIE promoter, or on viral factors, such as long noncoding RNAs and microRNAs that regulate latency. Vaccines could aim to activate latent viruses in a controlled manner to expose them to immune-mediated clearance.[122-124] The expansion of CMV-specific T cells with unique properties, such as inflationary memory $CD8^+$ T cells, has the potential to provide a natural model for vaccine development. Vaccines could aim to mimic this memory inflation phenomenon to generate long-lived, tissue-resident T cells capable of monitoring latent reservoirs and controlling reactivation. HCMV-specific T cells expressing NK markers (e.g., NKG2C, CD57) exhibit potent antiviral effects.[125] Vaccines that promote the development of such T/NK hybrid populations could represent an effective tool to combat HCMV. Incorporation of adjuvants that stimulate signaling pathways involved in maintaining or reactivating latency could improve vaccine efficacy. For example, targeting KAP1/TRIM28 or other chromatin-modulating factors could promote immune responses against latent cells.[48,126,127]

Immune Evasion

A significant portion of HCMV's genetic elements is evolved to evade host defenses (Table 1). Of the approximately 170 open reading frames, most genes (70%) are dispensable for viral replication in vitro,[128] and many have been suggested to modulate host immunity.[129-131] All major viral gene classes, including immediate-early, early, late, and latency-associated proteins, as well as noncoding RNAs, are part of this evasion strategy. The CMV-encoded immunoevasin families include the UL18 family, the US region gene cluster, the RL11 family, and the US12 family.[132]The UL18 ORF, an MHC class I homolog, encodes a glycoprotein that comes together to form complexes with β2-microglobulin and peptides. This glycoprotein is exposed to post-translational modifications that lead to the expression of a mature form, gpUL18, in the latter stages of HCMV infection and appears to play a role in modulating NK responses.[133] The US region gene cluster encompasses 2 gene families, US2 and US6, which are involved in regulating MHC-I cell surface expression.[134,135] The RL11 family embraces several members (e.g., RL5A, RL6, RL11-13, UL1,4-11), some of which, such as RL11-13, prevent the activation of the Fc receptor (FcR) by binding to the Fc region of the IgG molecule.[129,136] The US12 family consists of a tandem array of US12-21, which are engaged in regulating the expression of NK ligands, adhesion molecules, and cytokine receptors.[131,137] HCMV resorts to a multifaceted strategy to evade host immunity. These strategies involve modulating the infected cell's antiviral mechanisms, the innate immune response, and the adaptive immune response.

Table 1. Summary of key immunoevasins of human cytomegalovirus

Immunoevasin	Target	Mechanism of Action	Reference
UL18	NK cells (LIR1 receptor)	Mimics MHC-I to bind LIR1 on NK cells, reducing cytotoxicity.	134
US2, US6	MHC-I molecules	Downregulate MHC-I expression by targeting heavy chains for proteasomal degradation (US2) and blocking peptide transport (US6).	135,136
RL11	IgG molecules	Prevents Fc receptor activation by binding to the Fc region of IgG.	130,137
US12 Family	NK ligands, adhesion molecules	Modulates ligand expression, reducing NK cell recognition and adhesion molecule signaling.	132,138
LUNA, IE72, pp77	Intracellular immune sensors (e.g., cGAS-STING pathway)	Modulates intracellular antiviral signaling pathways and disrupts nuclear domains to facilitate immune evasion.	138,143
vMIA (pUL37x1)	Apoptosis pathways	Inhibits mitochondrial apoptosis by binding to ANT and preventing membrane permeability changes.	152
UL40	HLA-E molecules	Mimics MHC signal peptides, stabilizing HLA-E to inhibit NK cells through their inhibitory receptors.	173,176
UL142, UL16	NKG2D ligands (e.g., MIC-A, ULBP1)	Induces degradation or retention of NKG2D ligands in Golgi to escape NK cell detection.	177,180
gp68, gp34 (RL11 family)	Fc region of IgG	Prevents antibody-mediated NK cell activation by masking IgG Fc regions.	189,193
pp65	DNA sensors like cGAS	Inactivates cGAS to reduce interferon production.	147
UL111A (cmvIL-10)	Immune suppressor pathways	Upregulates host IL-10, enhancing immunosuppressive effects.	223
US3	Peptide loading complex (TAP)	Inhibits TAP and tapasin, preventing MHC-I peptide loading and expression.	219,220
UL141	TRAIL death receptors	Binds and retains TRAIL death receptors intracellularly, preventing TRAIL-mediated NK killing.	195

ANT: adenine nucleotide translocator; cGAS: cyclic GMP-AMP synthase; Fc: fragment crystallizable region; HLA-E: human leukocyte antigen E; IL-10: interleukin 10; IgG: immunoglobulin G; LIR1: leukocyte immunoglobulin-like receptor 1; MHC-I: major histocompatibility complex class I; MICA: MHC class I chain-related protein A; NK: natural killer cells; NKG2D: natural killer group 2D; UL18: human cytomegalovirus (HCMV) immune evasion protein; ULBP1: ULBP1 protein; US2: unknown signal protein 2; US6: unknown signal protein 6; TRAIL: tumor necrosis factor-related apoptosis-inducing ligand.

Modulation of the Antiviral Mechanism of Infected Cells

When HCMV infects the host cell, it generates factors that either put the brakes on the antiviral responses within the infected cell or curb the production of cytokines such as IFN-I from the infected cell to spark an antiviral response. One of HCMV's strategies to modulate the immune response is to restrain intracellular sensors involved in virus recognition. These sensors include the DN10:Sp100:hDaXX complex, which hinders the process of the viral genome integrating into the host by disrupting nuclear domains, the factors GAL9 and SPOC1 involved in the antiviral response, ZBP1, a sensor of viral transcribed RNA, and the cGAS-STING pathway and IFI16, which are involved in the recognition of viral DNA.[137-142] Through the production of factors such as LUNA, IE72, and pp77/UL35, HCMV results in host epigenetic regulation that can impact viral replication, latency, and reactivation.[143-145] Another strategy of HCMV to modulate the antiviral mechanisms is to target signaling pathways such as NF-κB, IRF-3, and signaling pathways stimulated in response to IFN-I. By expressing factors such as PP65, UL23, UL44, and LncRNA1.2, this virus can suppress these signaling pathways.[146-149] Human CMV can also neutralize the antiviral effects of IFN-I. MxB falls into the category of interferon-inducible protein with potential antiviral activity that interferes with protein translation and cell cycle initiation. pUL69 can induce initiation and prevent cell cycle progression by impairing MxB function.[150] IFN-I impacts the expression of IFN-stimulated genes (ISGs), which influence an antiviral response, by operating on the Interferon-sensitive response element (ISRE). By expressing UL23, HCMV obstructs STAT1 phosphorylation, which is necessary for IFN-I signaling, and ultimately throws a spanner in the works of the IFN-I response after infection.[149]

On top of that, the HCMV virus can prevent the clearing away of the infected cell source by suppressing programmed cell death through factors such as IE1-p72, vICA, and vMIA, ultimately leading to immune system evasion. Human cytomegalovirus (HCMV) encodes a protein called viral mitochondria-localized apoptosis inhibitor (vMIA) or pUL37x1, which acts as a potent apoptosis inhibitor. This protein, which results from the expression of the immediate-early gene UL37, accumulates mainly in the mitochondria of infected cells. There is evidence that vMIA binds to the outer mitochondrial membrane by forming a complex with the Adenine Nucleotide Translocator (ANT) and halts the progression of the apoptotic process by preventing the permeability of this membrane. This protective mechanism allows the virus to resist a variety of apoptotic stimuli, including signaling from cell death receptors, cytotoxic agents, and secondary infections with other viruses such as adenovirus.[151] Human CMV has demonstrated the unique ability to inhibit multiple necroptosis pathways. By targeting the downstream steps of RHIM signaling, particularly after RIP3-dependent phosphorylation of MLKL, this virus inhibits both the TNF-α receptor (TNFR1) and M45mutRHIM-induced necroptosis. The crucial role of viral protein E1 in suppressing TNFR1-dependent necroptosis was confirmed. Furthermore, the IE1 p72 isoform plays an important role in creating an environment resistant to necroptosis by influencing host cell response and modulating interferon activation. The IE1 mutant virus results also highlight that IE1-p72 is necessary to protect cells from TNFR1-dependent signaling and plays a key role in creating this protective environment.[152]

Modulation of Innate Immune Responses

The evasion of innate immunity by CMV is evidence of its evolutionary complexity and gives rise to challenges for the control of this virus. Efforts to address these evasion strategies are critical to address the significant health burden of CMV, particularly in high-risk populations. Human cytomegalovirus (HCMV) has developed several strategies to evade the innate immune response. Specifically, HCMV circumvents this response by interfering with chemokine function (inhibiting the chemokines themselves, their receptors, or their signaling pathways) and bypassing NK cells. UL22A is a chemokine modulator expressed by HCMV that leads to a decline in leukocyte infiltration into the area of infection by attenuating CC chemokines and specifically inhibiting RNATES.[153,154] Additionally, the virus has the ability to impair the patrolling function of Leukocytes in the bloodstream by upregulating US28, which acts as a receptor for CX3CL1. As a further point, US28 counteracts the effects of some CC chemokines targeted by UL22.[155] Viral chemokines, like vCXCL1 (encoded by UL146), may also be produced by human CMV. These chemokines attract cells with CXCR1/2 receptors to the environment, such as neutrophils, and attach to these receptors to adapt them into carriers that help spread the virus to uninfected cells.[156,157] Additionally, vCXCL1 increases PD-L1 protein levels

in liver cells, which increases the resistance of these cells to CD8 T cell killing.[158] HCMV encodes four 7-transmembrane membrane proteins (7TM), including US28, US27, UL33 and UL78. These proteins share significant sequence homology with human chemokine receptors. The combination of two different 7TM proteins may reveal new functional properties. For example, UL33 and UL78 form heterodimers with the human chemokine receptors CCR5 and CXCR4, causing a decrease in cell surface expression, a decrease in ligand-induced internalization, disruption of signaling, and changes in the migratory functions of CCR5 and CXCR4.[159]

Natural killer (NK) cells are vital for combating HCMV as they eliminate infected cells without prior immunization.[160-162] NK cells eradicate HCMV-infected cells and induce apoptosis by releasing perforin and granzymes.[163,164] They secrete interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which enhance antiviral defense and recruit other immune cells.[165,166] NK cells recognize cells with reduced MHC class I molecules, a common strategy of HCMV to evade cytotoxic T cells.[167] Certain NK cell subsets (e.g., $NKG2C^+$ cells) exhibit memory-like responses and improve long-term HCMV control.[168] The ability of HCMV to evade NK cell-mediated immunity is crucial to its survival and pathogenesis. The human CMV virus resorts to multiple strategies to evade NK cells. The most important include missing-self-recognition evasion, in which cells downregulate MHC-I molecules, and induced-self recognition evasion, in which cells express ligands that increase NK cell activation, IgG targeting, and Fc receptor inhibition, which leads to blocking of the antibody-dependent cellular cytotoxicity (ADCC) process in NK cells and targets adhesion molecules and, or other molecules involved in NK functions. These strategies lead to the disarmament of NK cells, thereby impairing their executive functions. HCMV can evade missing-self recognition by upregulating 2 factors, UL18 and UL40. By forming a complex with beta-2 microglobulin (β2M), the UL18 factor functions as an MHC-I homologue, reducing the cytotoxicity of $LIR1^+$ NK cells through high-affinity binding to the inhibitory receptor LIR1.[169-171] Furthermore, the peptides encoded by UL40 mimic the signal peptide sequence of the MHC molecule, which, by binding to HLA-E, increases the expression of this NK cell inhibitory ligand on the infected cell surface.[172-175]

Stressed cells such as HCMV-infected cells express ligands for NK-activating receptors (such as NKG2D, 2B4, and NCRs), which promote induced-self recognition. By expressing factors such as UL142, UL148A, US9, US18, and US20, HCMV targets the NKG2D ligand called MIC-A and causes lysosomal degradation or retention in the Golgi network.[131,176-178] Another NKG2D ligand, MIC-B, is targeted by the UL16 and miR-UL112 factors expressed by HCMV.[179-183] Combined, UL16 is empowered to target other NK cell-activating ligands such as ULBP1, ULBP2, and ULBP6.[184,185] UL142 is an MHC-like factor that maintains MICA and ULBP3 in the cell and prevents their access to NK-activating receptors.[179] Natural cytotoxicity receptors (NCRs) are a family of activating receptors expressed on natural killer (NK) cells and include NKp30, NKp44, and NKp46. They play an important role in activating NK cells and the subsequent elimination of target cells. The pp65 factor expressed by HCMV can directly target NKp30.[186] In addition, the expression of the NKp30 ligand (B7-H6) on the surface of infected cells is reduced by the factors US18 and US20.[131,187]

NK cells have the potential to bind to virus-infected and IgG-coated cells via the FcγRIIIa receptor (CD16a), leading to antibody-dependent cellular cytotoxicity (ADCC). However, HCMV leads to reinfection in the presence of different types of protective IgG, suggesting that HCMV can effectively neutralize the functions of antibodies. HCMV has the RL11 gene cluster, which encodes factors such as gp34, gpRL13, and gp95, and the gene region between UL118-UL119, which encodes the gp68 factor. The factors gp68 and gp34, which can bind to the Fc of all IgG isotypes, place their Fc region beyond the reach of CD16, leading to ADCC inhibition. The factors gp35 and gpRL13 are specific only for IgG1,2 and remove it from the reach of NK cells through the internalization of antibodies.[188-192] CMV can target ligands and adhesion molecules of NK cells through the upregulation of distinct factors. CMV expresses other factors such as US2, UL11, and UL141, each of which leads to evasion of NK responses through different mechanisms. US2 activity affects NK functions, such as suppression of integrin signaling and suppression of cell adhesion and migration.[193] The CMV UL141 glycoprotein, despite its lack of homology to TNF family cytokines, can bind to the ectodomains of TRAIL-DRs, leading to its retention in the cell, thereby

protecting the infected cell from TRAIL-dependent NK cell-mediated killing.[194]

Modulation of Acquired Immune Responses

The acquired immune response plays an important role in the control of HCMV infection. The acquired immune response, particularly $CD8^+$ T cells, is crucial for controlling primary HCMV infection. These T cells target the infected cells and prevent the virus from replicating and disseminating.[125,195-198] After primary infection, HCMV develops a latent state in certain cell types.[199] The acquired immune response helps maintain this latency by controlling the virus.[200] In immunocompromised individuals or during phases of immunosuppression, HCMV can reactivate from latency.[201] The adaptive immune response, particularly memory T cells, is crucial in preventing or limiting such reactivation. The acquired immune response provides long-lasting immunity against HCMV but does not eliminate the virus.[202,203] This immunity helps prevent reinfection and serious illness in most people.[203] However, HCMV has evolved mechanisms to evade the acquired immune response. HCMV can reduce the expression of MHC class I molecules on infected cells, reducing the likelihood that they will be recognized by $CD8^+$ T cells.[204,205] HCMV can also affect various functional aspects of the acquired immune response.[85,203]

HCMV can reduce antigen presentation to T lymphocytes through various strategies, such as reducing the expression of MHC molecules or interfering with peptide loading mechanisms on MHC molecules.[206,207] The products of the US6 gene family (including US2, US3, US6, and US11), as well as the tegument factors pp65 and pp71, have the potential to reduce MHC-I expression in myeloid dendritic cells and Langerhans cells.[208-213] The US2 and US11 subgroups target allomorphic HLA-I molecules.[214] The cytoplasmic tail of the US2 in interaction with the Sec61 complex leads to the translocation of the HLA-I heavy chain from the endoplasmic reticulum and its proteasomal degradation in the cytosol.[215] US11 interacts with HLA-I using the Derlin1 factor and a glutamine residue in its transmembrane domain, leading to its transfer to the cytosol.[216,217] HCMV also has a US10 gene that targets the HLA-G molecule through an unknown mechanism and can sometimes delay the maturation of HLA-I in infected cells.[218,219] The HCMV pp65 protein downregulates HLA-DR molecules by mediating the accumulation of HLA-II class molecules in lysosomes, leading to degradation of the HLA-DR α chain.[220] Expression of the UL82 gene leads to the production of a factor called pp71, which plays a role in protein trafficking within the cell. Studies have shown that this factor plays an important role in limiting the transfer of HLA-I to the cell surface and its accumulation within the cell.[221] HCMV can also interfere with peptide loading through the expression of factors US3 and glycoprotein US6, leading to a reduction in its expression since MHC is not very stable without peptides. In the endoplasmic reticulum, the US3 factor inhibits its function by binding to tapasin, and HLA-I remains in the endoplasmic reticulum. The glycoprotein US6 prevents peptides produced by the proteasome from entering the endoplasmic reticulum by inhibiting TAP1/2. The UL111A gene encodes CMV-encoded human interleukin 10 (cmvIL-10), which potentiates its immunosuppressive effects by upregulating hIL-10 and directly modulating the function of acquired immune cells.[222] pUL11 can bind to CD45 on the surface of T cells and differentiate them into an anti-inflammatory phenotype that produces IL-10.[223]

Immune Response to HCMV Evasion

Viruses have evolved to mimic host molecules and bind effectively to inhibitory receptors, subverting the immune response.[224] To counteract this, the host has evolved activating receptors that specifically recognize viral proteins.[224] These activated receptors often lack inhibitory signaling motifs, allowing them to trigger an immune response without viral interference. Evolution has favored a relatively simple solution to this complex problem: modification of existing inhibitory receptors.[225-227] By removing inhibitory signaling motifs and adding a charged amino acid, the host can convert these receptors into potent activating receptors.[228] This strategy proved effective and efficient across various species that independently adopted it.[229]

HCMV has developed mechanisms to evade immune detection, including expression of the UL40 protein. UL40 interacts with HLA-E and alters its distribution at the cell surface. This manipulation could prevent NK cells from recognizing infected cells.[230,231] However, NK cells expanded with the CD94-NKG2C receptor can recognize these altered HLA-E complexes thanks to their specific sensitivity to UL40-induced changes. The proliferation and differentiation of these specialized NK

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cells is significantly influenced by the inflammatory environment. An inflammatory milieu, possibly created by the viral infection itself, provides the necessary signals for the proliferation and maturation of these cells. The CD94-NKG2C receptors on these NK cells are remarkably sensitive to even minor changes in the HLA-E binding sequence. This novel sensitivity allows them to detect subtle changes caused by the UL40 protein and identify infected cells.[232,233] No identified immunoevasins to date have been reported to target killer cell-like immunoglobulin-like receptors (KIRs), which constitute a major class of MHC-I-binding receptors in humans. The lack of KIR-targeting immunoevasins may be an evolutionary blind spot for CMV.[234] Understanding the role of KIR in viral infections can lead to developing new therapeutic strategies. Epidemiological studies have linked specific KIR alleles to the outcome of various viral infections, including CMV, hepatitis C, and HIV.[235,236] This suggests that targeting KIRs can enhance immune responses against CMV and other viral infections.

The detailed investigation of the immune evasion mechanisms of HCMV provides valuable insights that can significantly advance the development of innovative vaccines. These mechanisms, which target multiple arms of the immune system, reveal critical vulnerabilities that can be exploited for therapeutic interventions. The viral proteins such as UL18, UL40, and RL11 family members, which mimic or disrupt host immune functions, could be integrated as targets in subunit or peptide-based vaccination strategies. By developing immunogens that elicit robust responses specifically against these immunoevasins, vaccines can improve immune recognition and neutralize these evasion pathways. Modulation of the innate immune system by HCMV via pathways such as NK cell inhibition (e.g., UL18 and UL40 interactions) and chemokine dysregulation provides opportunities for adjuvant design. Vaccines could contain adjuvants that mimic natural NK cell activators or restore chemokine functions to enhance early antiviral responses.[237-240] Understanding how HCMV downregulates the expression of MHC molecules via the US2 and US11 proteins provides a blueprint for vaccines aimed at restoring or bypassing these antigen presentation pathways. For example, peptide-based vaccines could use modified epitopes designed to resist degradation or improve T cell recognition. The virus' strategies to avoid antibody-mediated cytotoxicity through Fc-binding proteins (e.g., gp68, gp34) suggest that monoclonal antibodies designed to avoid these viral traps will complement vaccination efforts and provide both preventive and therapeutic benefits could offer. Adaptive development of activating receptors to combat viral mimicry, such as NK receptors sensitive to UL40-modified HLA-E, could inspire novel vaccine platforms. These could include engineered NK cells or receptor-based therapies that, in combination with vaccines, provide improved immunity. Strategies targeting viral factors that influence latency (e.g., IE1-p72) and reactivation (e.g., pp71) could be essential components of vaccine formulations to effectively control both acute and latent phases of infection. Overall, a deep understanding of HCMV's immune evasion tactics underscores the necessity of developing multi-pronged vaccines that target both innate and adaptive immune responses. Combining these insights with advanced immunological tools such as mRNA platforms and vector-based vaccines can lead to transformative breakthroughs in the prevention and control of HCMV infections.

Correlate of Protection

Correlates of protection (CoPs) are measurable immune responses or markers that are statistically associated with protection against clinical disease. These markers help identify the immune mechanisms that prevent infection or reduce disease severity, serving as critical benchmarks in vaccine development.[241] In HCMV vaccine research, CoPs are essential for identifying the immune responses needed to protect against HCMV. For instance, antibodies targeting viral glycoproteins such as gB and the PC and cellular responses involving $CD8^+$ T cells are considered potential CoPs.[242] However, the lack of understanding of these markers has led to several challenges in developing effective vaccines. Despite significant progress in HCMV vaccine development, significant uncertainties remain. For example, the precise role of antibodies in innate protection against HCMV is not fully understood. There is evidence that antibodies can inhibit the growth of cells against viruses, but this role requires further study.[13,243-245] Studies suggest that antibodies and $CD8^+$ cells are the most important protective factors against HCMV. Consequently, new technologies in production and excision should focus on stimulating humoral (antibodies) and cellular immune responses.[123] HCMV has glycoproteins that bind to cell

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surface receptors and enter cells in a manner that depends on the type of virus entering the cell. For example, in fibroblasts, the combination of glycoproteins gH, gL, and gO binds to the PDGFRα receptor and promotes the fusion of gB with the cell membrane at neutral pH. On the other hand, in epithelial and endothelial cells, the pentameric complex (consisting of UL128, UL130, UL131A, gH, and gL) binds to neuropilin 2 and activates pH-dependent endocytosis.[246]

During vaccine development, different antigens can be targeted using multiple platforms, such as nucleotide-based platforms, to achieve the desired CoPs. Antibodies to gB neutralize infection of fibroblast cells, and gB is considered an important target for virus-neutralizing vaccines.[10,11] Antibodies against the PC inhibit infection of endothelial, epithelial, and myeloid cells and are considered key candidates for vaccine development.[13,14] Antigens such as PP65 and IE1 are effective triggers of cellular immune responses.[12,247] The main goal of developing a vaccine against HCMV should be to enhance the host's immune response and disrupt the function of the virus at various stages of infection, including acquisition, systemic replication, and pathogenesis, as well as inhibit its reactivation to reduce the burden of illness. Because the stages of HCMV infection occur at different anatomical sites, the immune properties associated with each site may be different. For example, an immune agent that facilitates viral clearance in the mucosa may not affect reducing HCMV viremia in the patient's blood, which is one of the major challenges in vaccine development. Advances in identifying CoPs and understanding their mechanisms, coupled with the development of vaccines that can fully stimulate humoral and cellular immunity, will pave the way for more effective vaccines against HCMV.[248]

Conclusions and Perspectives

The development of an effective vaccine against HCMV faces major challenges based on the complex biology of the virus, including latency, immune evasion, and the lack of a clear CoP.[249-251] However, these obstacles provide opportunities for innovative strategies that could redefine vaccine development against HCMV and other persistent viruses. The ability of the virus to establish latency represents a significant obstacle as it allows HCMV to evade immune recognition and persist in host cells indefinitely. Future vaccines could exploit insights into the molecular mechanisms of latency, such as chromatin remodeling at the major early promoter (MIEP) and the regulatory roles of viral long non-coding RNAs and microRNAs. Vaccine formulations containing components that target these latency-maintaining pathways could activate the virus in a controlled manner and enable immune defense.[252] Alternatively, by mimicking the phenomenon of natural memory inflation, vaccines can generate long-lived tissue-resident T cells capable of effectively monitoring and controlling latent reservoirs.

The complex mechanisms of HCMV immune evasion, such as modulation of MHC expression, inhibition of NK cell responses, and impairment of antibody-mediated cytotoxicity, complicate vaccine development efforts.[253,254] These evasion strategies can be counteracted by designing vaccines that elicit robust immune responses that can neutralize immunoevasins, such as UL18 and UL40, which mimic host molecules. New vaccine platforms may also utilize adjuvants that restore chemokine function or increase NK cell activity, thereby enhancing primary antiviral responses.[255,256] Furthermore, incorporating epitopes that resist viral destruction mechanisms and enhance T cell recognition could improve vaccine efficacy. The lack of definitive CoPs for HCMV complicates vaccine development.[251] Advances in understanding immune responses to HCMV suggest that vaccines should simultaneously stimulate strong humoral and cellular immunity. Antibodies against gB and PC are effective in neutralizing HCMV infections in various cell types, making them prime candidates for inclusion in vaccine formulations.[251] Furthermore, cellular immune responses targeting antigens such as pp65 and IE1 are crucial for controlling active and latent infections, [34] Using these insights, vaccine platforms such as mRNA-based vaccines or viral vector-based vaccines could deliver a comprehensive immune response.[34]

Innovative vaccine technologies, including mRNA platforms, provide unprecedented flexibility in targeting multiple HCMV antigens. mRNA vaccines encoding gB, pp65, and PC antigens have shown promise in inducing strong humoral and cellular immunity.[257] Such platforms also enable rapid adaptation to emerging HCMV strains, increasing the long-term benefits of these vaccines.[257] As an illustration, Moderna's mRNA-1647 vaccine, developed using an mRNA-based platform and incorporating the gB, pp65, and PC antigens, has advanced successfully to Phase III clinical trials.[258] Given the complex nature of HCMV interactions with the host

immune system, future vaccine designs should adopt a multifaceted approach. For example, future vaccines should focus on viral proteins that are critical for latency and reactivation, such as IE1-p72 and pp71. These vaccines should also promote the development of hybrid T/NK cell populations that express markers such as NKG2C and CD57, known for their potent antiviral effects.[259,260] Future vaccines should preferably contain multiple antigens that trigger both humoral and cellular immune responses, ensuring protection at different anatomical sites and stages of infection.[34,257] In addition, they should use adjuvants that increase the activity of immune cells impaired by HCMV evasion mechanisms, such as NK and T cells. By turning the challenges of latency, immune evasion, and CoPs into opportunities, the development of an effective HCMV vaccine becomes a tangible goal. Integrating advanced immunological tools and novel vaccine platforms will be crucial to overcome this complexity and achieve sustainable control of HCMV infections.

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