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Partners in Crime: The Role of CMV in Immune Dysregulation and Clinical Outcome During HIV Infection

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Abstract

In the current era of combination antiretroviral therapy (ART), human immunodeficiency virus (HIV)-infected individuals are living longer and healthier lives. Nevertheless, HIV-infected persons are at greater risk for age-related disorders, which have been linked to residual immune dysfunction and inflammation. HIV-infected individuals are almost universally co-infected with cytomegalovirus (CMV) and both viruses are associated with inflammation-related morbidities. Therefore, a detailed investigation of the relationship between CMV and aging-related morbidities emerging during chronic HIV infection is warranted. Here, we review the literature on how CMV co-infection affects HIV infection and host immunity and we discuss the gaps in our knowledge that need elucidation.

Keywords

CMV infection; HIV infection; Inflammation; Aging; Immune response

Introduction

Antiretroviral therapy (ART) can control HIV replication indefinitely in most HIV-infected individuals who adhere to their medications [1]. Nevertheless, and depending on timing of ART initiation, HIV-infected persons may experience greater morbidity and mortality than the HIV-uninfected do. These morbidities include non-AIDS defining disorders such as cardiovascular disease, a spectrum of malignancies, frailty, and neurocognitive impairment that are also seen as people age [2]. This increased morbidity and mortality has been associated with residual immune dysfunction which persists in some individuals despite long term suppressive ART [3]. The mechanisms of residual immune dysfunction are incompletely understood and most likely multifactorial in origin. Persistent co-infections

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with other pathogens are common in HIV infection, and likely contribute to overall immune dysfunction during HIV disease [4, 5]. For example, HIV-infected individuals are nearly universally co-infected with cytomegalovirus (CMV), and both HIV and CMV infections are independently associated with increased inflammation and inflammation-related morbidities [6]. Therefore, a detailed investigation of the relationship between CMV and aging-related morbidities emerging during chronic HIV infection is warranted.

Epidemiology, Life Cycle, and Pathogenesis of CMV Infection

Cytomegalovirus (CMV, also known as human herpesvirus 5 or HHV-5) is a widespread β-herpesvirus that causes persistent infection and is often acquired during childhood or during sexual debut. CMV seroprevalence can vary from 40 to 100 % in the adult population depending on age, socioeconomic status, and geographical region [7–9]. Primary CMV infection in immunocompetent hosts is often asymptomatic or minimally symptomatic, but morbidity and mortality dramatically increase during immunodeficiency (particularly among transplant recipients and HIV-infected people) [7, 8]. After primary infection, the virus establishes episomal latency in pluripotent CD34+ hematopoietic stem cells in the bone marrow [10]. As these cells differentiate along the myeloid lineage to monocytes and macrophages, latent CMV can reactivate and be released in response to different (often inflammatory) stimuli to infect new cellular targets. Other non-hematopoietic sites of latency have been suggested, particularly in epithelial cells, but this is still controversial since most in vivo studies failed to distinguish between true latency (no productive infection) and persistence (low-level productive infection in the absence of cytopathic effects) [10]. In fact, episodic bursts of asymptomatic CMV reactivation are frequently documented (particularly among HIV-infected persons) and are rapidly controlled by cell-mediated immune-surveillance [11]. One very common site of CMV shedding is the genital tract. The frequency of CMV shedding in genital secretions varies substantially across different studies and is strongly dependent on the geographical location, cohort characteristics, and detection methods used [9]. When an infected person has a compromised immune system, shedding of CMV increases dramatically. For example, in Southern California, almost half of HIV-infected men who have sex with men asymptomatically shed CMV in their genital tract, regardless of CD4+ T cell count or use of ART [12–14]. Less is known about the frequency of CMV shedding in the genital tract of HIV-infected women. Two studies of HIV-infected women conducted in the USA with partial uptake of ART found that CMV DNA was detected infrequently (3–7 %) in cervicovaginal lavage [15, 16]. In a study of HIV-infected Kenyan women not on ART, CMV was detected in 59 % of provider-collected cervical swabs [17]. Another recent study quantified vaginal shedding of CMV DNA longitudinally among 96 HIV-infected women starting ART in Rakai, Uganda. Vaginal CMV was detected in 75 of 96 women (78.0 %) and in 379 of 1080 individual visits (35.1 %). Compared to shedding pre-ART, CMV shedding increased, peaking from month two to four after ART initiation, suggesting a possible immune reconstitution inflammatory syndrome (IRIS). Other sites of CMV reactivation are the following: oral mucosa (where CMV may be found in 15–30 % of HIV-infected persons) [18, 19], peripheral blood mononuclear cells (PBMC) (where CMV may be found in 13–20 % of HIV-infected persons), urine (where CMV may be found in 10–30 % of HIV-infected persons), stool, and breast milk [20–22]. Such

asymptomatic shedding at different mucosal sites is likely important for the natural history and transmission dynamics of CMV itself, and also for the interplay of CMV with other co-infecting viruses (e.g., HIV) and with the host immune environment.

CMV Infection and the Host Immune Environment

CMV has established a powerful interaction with the immune system, having infected humans since our species arose [9]. In a complex host-virus relationship, CMV elicits and maintains a high frequency of virus-specific T cells that engage in a lifelong effort to restrain CMV replication and prevent life-threatening disease [23]. In HIV-uninfected individuals, approximately 10 % of both CD4 and CD8 memory T cells in the circulation target CMV antigens, and these frequencies can increase to about one third of CD4+ T cells and nearly half of CD8+ T cells in older persons [23, 24]. In HIV-infected adults, CMV-specific CD8 and CD4 T cell numbers are further elevated, similar to proportions observed in the HIV-uninfected elderly, and remain high even after ART-mediated suppression of HIV replication [25, 26]. With a large 230-kB genome, CMV is one of the largest viruses to infect humans. A recent study using ribosomal profiling to determine the protein-coding capacity of CMV showed that as many as 751 CMV open-reading frames are translated into CMV proteins in virus-infected cells [27•], suggesting that the CMV proteome is far more complex than hitherto recognized. Interestingly, many of these proteins were not essential for CMV replication and are thought to allow the virus to avoid immune recognition, protecting reactivating cells from attack and destruction by host defenses. Since CMV replication is enhanced by inflammatory stimuli, it is not surprising that the virus also developed ingenious strategies to induce and augment inflammation [28]. In fact, CMV is able to directly upregulate the expression of several cytokines and inflammatory mediators in host cells, including IL-1β, IL-6, and type I interferon, thereby exacerbating the inflammatory response [29–32]. CMV infection has also recently been shown to be associated with an increase of IL-15 in plasma [33]. Although there is little evidence of direct upregulation of IL-15 by CMV, other herpesviruses have been shown to directly induce IL-15 production [34]. The elicitation of IL-15 and other common γ-chain cytokines (including IL-2 and IL-7) is of particular interest, as these cytokines can drive antigen non-specific activation, proliferation, and expansion of naïve and memory CD4 and CD8 T cells [35]. In addition, CMV encodes its own cytokines and chemokine homologs as well as cytokine receptor homologs that can further modulate levels of human cytokines, chemokines, and growth factors [29, 36, 37]. While regulating inflammatory responses to benefit its own replication, CMV has also developed mechanisms to avoid immune recognition and protect infected cells from attack by host defenses. For example, CMV impairs antigen presentation by inhibiting the expression of HLA class I and class II molecules; CMV can also induce immune-inhibitory pathways (for example PD-1 and IL-10) and can inhibit activation of natural killer (NK) cells by virus-encoded HLA class I homologs and NK cell immune evasion proteins, thereby impairing destruction of infected cells [36–41]. Strategies of immune evasion and immune subversion by CMV are summarized in Table 1.

CMV Infection Drives CD8 T Cell Expansion

As noted above, CMV reactive T cells comprise a substantial proportion of the effector memory T cell repertoire and this appears to increase with age [25, 26]. Since CMV replication tends to occur in effector tissues rather than in inductive lymphoid tissues, the exact anatomical sites of interaction between immune cells and CMV (for both CMV-antigen specific and nonspecific interactions) are not well defined. One possibility is that many of these events occur in the draining lymph nodes, as many cytokines (including IL-1β, IL-2, and IL-15) are increased in lymph tissue or are elicited from lymph node histocultures of HIV-infected persons [42, 43]. In support of this hypothesis, recent evidence in mouse models suggests that murine (m)CMV can directly infect macrophages and non-hematopoietic cells in lymph nodes [44], selectively inducing proliferation of CD8 T cells [45, 46]. This so-called "$CD8^+$ T cell memory inflation" is characterized by the accumulation of high-frequency functional antigen-specific $CD8^+$ T cells with an effector-memory phenotype, which are typically enriched in peripheral organs. Although persistence of antigens is considered essential, the mechanism of this inflation is not completely understood, and it is not clear if similar mechanisms play a role also in the setting of human CMV infection [47]. One recent study investigated the clonal and phenotypic relations between T cells obtained from peripheral blood and lymph nodes during primary and latent human CMV infection to understand what cells sustain the circulating CMV-specific effector pool [48]. Interestingly, new clones that appear after primary CMV infection or during CMV reactivation seldom originated from peripheral blood or lymph nodes, suggesting that the precursors of the new CMV-specific clones are probably located elsewhere (e.g., in other secondary lymphoid tissues) or are recruited directly from the naïve CD8+ T cell pool.

Does "Occupancy" of the T Cell Repertoire by CMV-Reactive Cells have Impact on Immune Potential?

As CMV-infected persons age, an increasing proportion of their T cell repertoire becomes CMV-reactive and these cells are characteristically more differentiated (presumably as a result of repeated exposure to CMV peptides) and have a phenotype characteristic of replicative exhaustion and senescence [49]. The expansion of the T cell repertoire committed to CMV may compromise the ability to respond de novo to antigens by decreasing the diversity of the remaining naïve T cells or out-competing the naïve T cells for resources [50–53]. Other studies, however, found that the entrance of CMV-specific CD8+ T cells expanded the antigen-primed $CD8^+$ T cell pool rather than competing for space with pre-existing memory T cells specific for persistent or cleared viruses [54, 55]. Furthermore, as predicted by their maturation phenotype, CMV-specific $CD8^+$ T cells are negligibly present in the lymph nodes and thus do not limit immunologic "space" at sites where immune reactions are initiated [55]. These different findings might reflect the variability among humans in the magnitude of CMV-specific T cell responses that in turn reflect differences in CMV dosage, antigen exposure during shedding, and/or the immune competence of the host [56]. In support of this model, there is reason to suspect more profound influence of CMV infection on the immune repertoire in thymectomized individuals where the naïve T cell

repertoire is already diminished due to reduced thymic output, [57] and perhaps too in the elderly who have survived decades of thymic involution [58].

CMV Infection in the Young and the Old

Because the prevalence of CMV infection increases with age and also varies according to socio-economic factors [59], it has been difficult to distinguish the effects of CMV infection on aging-related complications from the effect of other confounding variables. To assess the relative contribution of heritable versus non-heritable factors, Brodin, et al. performed an elegant system-level analysis of 210 healthy monozygotic twins between 8 and 82 years of age [60•], measuring over 200 different immunologic indices, including cell population frequencies, cytokine responses, and serum proteins. The authors found that over three quarters (77 %) of these parameters were dominated and over half (58 %) were almost completely determined by non-heritable influences. Interestingly, in twins discordant for CMV serostatus, more than half of all these indices were affected, providing strong evidence that CMV co-infection has a profound effect on the immune system in healthy individuals. Large population studies in Scandinavia demonstrated that infection with CMV makes a significant contribution to the so-called immune risk profile (IRP), which is predictive of an increased mortality in very old individuals [61]. This immune risk profile (including expansion of CD8+ CD28 T cells and inverted CD4/CD8 T cell ratio) was rarely seen in Swedes who survived into their eleventh decade [62]. Other epidemiological studies in the USA suggested that CMV infection itself might have a negative impact on survival [63, 64], and higher levels of anti-CMV antibody were correlated to poor survival in older adults with stable cardiovascular disease [65, 66]. What different antibody titers actually reflect is however unclear and one recent study found that high CMV IgG levels were associated with less CMV replication [67], suggesting that CMV IgG levels are not simply a correlate of replication burden.

In summary, there is increasing evidence that CMV has a broad impact on human immunity: in older adults, it might exacerbate the aging processes contributing to the development of age-related morbidities that have been linked to immune senescence, such as frailty, cancer, neurocognitive impairment, and cardiovascular disease [2, 61, 68]. The effects of CMV infection on host immunity, however, are not always deleterious, and a recent study suggested that CMV might even have a beneficial effect on the immune system in younger healthy people, which could help to explain why humans and many other species tolerate the very high prevalence of this infection [69•].

Bidirectional Interaction Between HIV and CMV Replication

As described above, CMV is able to maintain an inflammatory environment that is beneficial for its own replication and survival and it has concurrently developed numerous strategies to control immune function so that CMV-reactive immune cells and other effectors are less able to eradicate virus-infected cells. It is reasonable to hypothesize that other co-infecting pathogens (for example HIV) could take advantage of this particular immune environment to protect their own persistence and replication.

Several studies have suggested that both direct and indirect interactions between CMV and HIV could influence their replication and the resulting disease pathogenesis. Several mechanisms could play a role including the following: (i) direct interaction between CMV-encoded regulatory proteins and the HIV long terminal repeat (LTR) region resulting in transactivation of viral gene expression [70, 71], (ii) enhanced HIV replication stimulated through a release of CMV-induced inflammatory cytokines and chemokines [72], (iii) upregulation of CCR5 expression in central memory T cells, which has been recently described in cord blood mononuclear cells exposed in vitro [73] and might be mediated by enhanced (CMV-induced) interferon production [74], and (iv) clonal expansion of HIV-infected T cells through CMV-induced inflammatory cytokines and chemokines [75]. This relationship between CMV and HIV has been widely documented in the genital tract, where presence of detectable CMV DNA has been repeatedly associated with increased genital shedding of HIV RNA [12, 13, 76–79] and with increased HIV transmission [11, 14, 76]. Additionally, presence of detectable CMV DNA was also associated with increased levels of HIV DNA in peripheral blood cells in both treated and untreated HIV infected individuals [20, 21, 75].

Impact of CMV Co-infection on the Course of HIV Infection

In the setting of underlying immune deficiency, CMV is associated with a wide range of serious clinical diseases, such as retinitis, pneumonitis, colitis, and other end organ disease [9], as well as with indication of more rapid HIV disease progression and increased occurrence of AIDS-related events [80, 81]. The incidence of these life-threatening conditions has decreased dramatically with the advent of ART. These changes are likely the consequence of a restoration of CMV-specific immune responses that result in diminished CMV expression and viremia [82]. While the clinical importance of CMV co-infection in the setting of ART-treated HIV infection is less clear, emerging evidence links CMV to determinants of both clinical risk [59] and immune pathogenesis [19, 75] during well-controlled HIV infection. Indeed, CMV co-infection is linked to a more inflammatory profile [83], including increased circulating levels of Interferon gamma-induced protein (IP)-10 and D-dimer, and to a profound expansion of circulating CD8 T cells and a reduced CD4/CD8 ratio that characterize treated HIV infection, [83, 84] and that is linked to an increased morbidity and mortality [85, 86].

Even in the setting of ART-treated HIV infection, asymptomatic shedding of CMV was linked to increased levels of T cell activation, proliferation, and exhaustion [19, 75]. In HIV/CMV co-infected individuals, more CD8 T cells express the marker of cellular senescence CD57 and fewer express the co-stimulatory molecule CD28, compared to CD8 T cells of age-matched monoinfected persons [84, 86]. As discussed above, one of the main hallmarks of CMV infection is a demonstrable expansion of CD8 T cells (referred to as “memory T cell inflation”) [23, 87–90], which is particularly prominent and appears at younger age within the HIV co-infected populations [84, 91]. This ongoing recruitment, activation, and apparent dysfunction of virus-specific CD8 T cells fails to eliminate or effectively control CMV replication and results in an expanded pool of effector CD8 T cells, and consequently a low CD4:CD8 ratio that is associated with an increased risk of non-AIDS morbidity and mortality [85, 86]. Since both aging and CMV contribute to immune

senescence [52, 92], it is not surprising that the importance of CMV co-infection becomes increasingly recognized as co-morbid conditions complicate the extended lifespan of the ART-treated HIV-infected population. A proposed simplified summary of the interactions between HIV infection, CMV replication, CD4, and CD8 T cells is shown in Fig. 1.

Recent epidemiological studies suggest a direct connection between CMV infection (or the magnitude of CMV-antibody response) and non-AIDS associated morbidities during ART-treated HIV infection, including neurocognitive impairment, cancer, and cardiovascular disease [59, 93]. The most frequent association is between CMV and cardiovascular disease, which has been described in the setting of post-transplant atherosclerosis [94, 95] and HIV infection [66, 96]. Both CMV replication itself and the immune response against CMV can promote changes in endothelial cells that might contribute to the pathogenesis of atherosclerosis [97, 98]. Possible mechanisms include the secretion of pro-angiogenic factors through CMV-infected endothelial cells (e.g., IL-6, GM-CSF) and direct endothelial damage through CMV-induced inflammation. Additionally, immune cells responding to CMV infection can activate immune cascades resulting in endothelial damage and aggravating the effect of CMV replication. For example, there is increasing evidence to support a key role for fractalkine-fractalkine receptor (CX3CR1) interactions in the host inflammatory response leading to vascular injury [98, 99]. Interestingly, the expression of the host chemokine fractalkine (a key marker of inflammation in endothelial cells) is strongly upregulated in the presence of PBMCs from donors with a high frequency of CMV-specific T cells [99]. The fractalkine-CX3CR1 interaction results in recruitment of natural killer cells, monocytes and possibly also CX3CR1+ CD8+ T cells [100] that may participate in driving vascular inflammation, coagulation, and the formation of atheromas. The cardiovascular complications associated with CMV infection are most likely multifactorial, and include consequences of direct effect of CMV replication driving activation of immune cells and cytokine/chemokine-mediated effects as an additional risk factor for development of chronic inflammation and endothelial cell injury.

Conclusions

Through millions of years of co-existence, CMV has developed a number of strategies to adapt and synergistically coexist with the human immune system. A detailed knowledge of the interactions among CMV, HIV, and host immune responses is necessary to understand the complex mechanisms underlying aging-related complications during HIV infection and to develop new strategies to prevent the premature occurrence of end-organ diseases that may be linked to CMV infection. For example, it will be important to understand the directional relationships among CMV reactivation, inflation of the CMV-specific T cell response, and immune dysregulation to determine where intervention should be targeted to affect these outcomes. Newer less toxic drugs with activity against CMV (e.g., Brincidofovir [101] and Letermovir [102]) could be applied in clinical trials to evaluate first the effects of CMV suppression on immune activation and inflammation. As these agents will not eradicate CMV, prolonged courses of therapy may be needed, particularly when effects on clinical outcomes are the endpoints. It remains to be seen if attenuation of CMV expression will be sufficient to reverse the inflammatory process initiated by CMV infection.

Conceivably, HIV co-infected individuals with the most brisk CMV-specific immune response are at greater risk for morbid outcomes while persons with less robust CMV-specific T-cell responses are not. Additional analyses stratified on the basis of the quantity and quality of the CMV response and in relation to markers of CMV replication will be needed to explore this issue. These analyses should not only include the T-cell compartment but should also encompass other immune defenses affected by CMV infection such as B cells and NK cells. Another intriguing open question is why CMV, uniquely among all human herpes viruses, is able to drive such dramatic expansion of virus specific T cells, while other common persistent viruses such as EBV do not.

In this regard, it is not clear whether strategies to enhance CMV-specific immune responses such as via therapeutic immunization will decrease viral expression and provide indication of benefit or on the other hand, might further enhance the CD8 T cell expansion and inflammation that have been linked to non-AIDS-related co-morbidities during HIV infection.

Carefully designed clinical trials targeting CMV replication and immune responsiveness may help to understand the complex interrelationships between CMV and HIV pathogenesis and also may direct the design of interventional strategies that will have a positive effect on HIV disease progression and aging-related complications.

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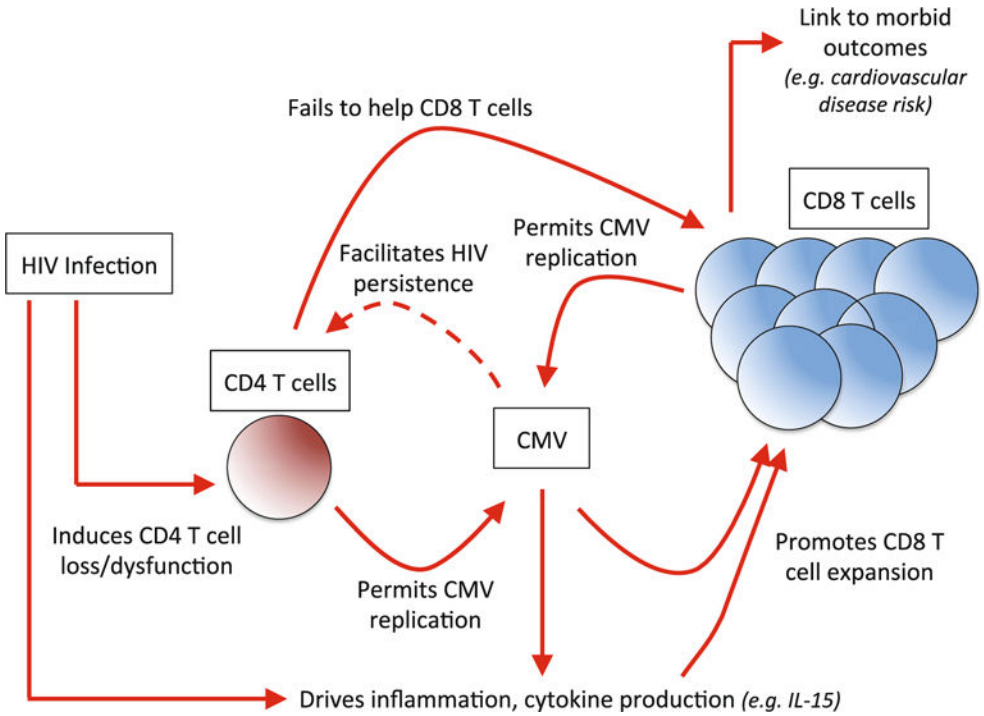

Fig. 1.

Proposed model connecting CMV, HIV, CD4 T cell dysfunction, and CD8 T cell expansion. We propose a model where HIV infection itself drives inflammation and cytokine production (for example IL-15) promoting $CD8^+$ T cell expansion. HIV infection also induces $CD4^+$ T cell loss and dysfunction, thereby failing to provide help to $CD8^+$ T cells and permitting more CMV replication, which contributes to inflammation and further promotes the expansion of $CD8^+$ T cells. Signals from CMV infection may also promote HIV persistence in $CD4^+$ T cells (dotted line). Expanded $CD8^+$ T cells are unable to control CMV replication, contributing to the vicious cycle. In addition, $CD8^+$ T cell expansion, coupled with a loss of $CD4^+$ T cells (leading to a lower CD4/CD8 T cell ratio) are linked to morbid outcomes of CMV and HIV infections, including cardiovascular risk (and other non AIDS events)

Table 1

Summary of strategies of immune evasion and immune subversion/hijacking by CMV

Category	Strategy	Function	CMV protein/gene	References
Immune evasion	MHC class I inhibition	Destabilizes heavy chains	US2	[103]
		Impairs heavy chain transport and maturation	US3	[104]
		Inhibits peptide translocation by TAP	US6	[105, 106]
		Downregulates MHC-I heavy chains	US11	[107]
		Downregulates nonclassical HLA-G surface expression	US10	[108]
	MHC class II inhibition	Induces degradation of HLA-DR and HLA-DM	US2	[109]
		Reduces peptide-loaded MHC-II complexes	US3	[110]
	Interruption of interferon signaling	Blocks multiple levels of IFNα signal transduction	UL83	[111]
		Inhibits Stat2 signaling	IE1	[112]
		Inhibits NFκB binding to DNA	IE2	[113]
	NK cell evasion	MHC-I homolog	UL18	[114]
		Prevents surface expression of NKG2D	UL16	[115]
		Downregulates MICA, leading to NKG2D reduction	UL142	[116]
		Downregulates MICB, leading to NKG2D reduction	miR UL112	[117]
		Downregulates NK cell activating ligand CD155	UL141	[118]
		Inhibits NKp30 activating receptor	UL83 (pp65)	[119]
		Promotes lysosomal degradation of MICA	US18	[120]
		Promotes lysosomal degradation of MICA	US20	[120]
		Encodes an MHC-like protein	UL37	[121]
Immune Hijacking	Interferon stimulation	Mimics IFNγ-mediated host gene expression	IE1	[122]
	Cytokine and chemokine homologs	IL-10 homolog	UL111A	[37]
		CXCL1 homolog	UL146	[123]
		CXCL2 homolog	UL147	[124]
		CC chemokine receptor homolog	US28	[125]
		TNFR homolog	UL144	[126]
	Blocks apoptosis of infected Cells	Prevents apoptosis	IE1	[127]
		Upregulates antiapoptotic molecule c-FLIP	IE2	[128]
		Inhibitor of caspase-8 mediated apoptosis	UL36	[129]
		Mitochondria-localized inhibitor of apoptosis	UL37	[130]
		Downregulates TRAILR1 and TRAILR2	UL141	[131]
		Stabilizes mitochondrial membrane potential	RNA 2.7	[132]
	Host cytokine induction	IL-6, IL-1β	IE genes	[32, 133]
		TNFα, IFNγ, IL-15	Unknown	[33, 134]

MHC major histocompatibility complex, *NK cells* natural killer cells, *IFN* Interferon