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Cytomegalovirus as an immunomodulator across the lifespan

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Abstract

Human cytomegalovirus (HCMV) is a nearly ubiquitous β -herpesvirus that establishes latent infection in the majority of the world's population. HCMV infection profoundly influences the host immune system and, perhaps more than any other human pathogen, has been shown to create a lasting imprint on human T and NK cell compartments. HCMV-seropositivity has been associated with both beneficial effects, such as increased vaccine responsiveness or heterologous protection against infections, and deleterious effects, such as pathological neurodevelopmental sequelae from congenital infection in utero and cumulative damage from chronic lifelong latency into old age. The significance of many of these associations is unclear, as studies into the causal mechanisms linking HCMV and these disease outcomes are lacking; however, HCMV-mediated changes to the immune system may play a key role. This review examines how HCMV impacts the host immune system in an age-dependent manner with important implications for human immunophenotypes and long-term disease risk.

Keywords

human cytomegalovirus; HCMV; herpesvirus; congenital CMV; adaptive NK cell; immunosenescence; vaccines; viral oncology; seroepidemiology

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Introduction

Human cytomegalovirus (HCMV) is a β -herpesvirus that has co-evolved with humans over millennia and represents an important member of the human virome, a dynamic network of commensal and pathogenic viruses analogous to the microbiome [1,2]. HCMV infects diverse cell types including endothelial, smooth muscle, and antigen-presenting immune cells, and its large genome facilitates a variety of immune evasion strategies that allow the virus to establish lifelong latency [3]. A recent estimate of the worldwide seroprevalence of HCMV was 83% overall, and as high as 96% in some countries, yet population-wide seropositivity rates differ substantially by country [4].

The clinical course of HCMV infection is widely variable and dependent on host age and immune function. Most immunocompetent individuals are asymptomatic or experience a non-specific viral prodrome upon primary infection; however, *in utero* transmission of HCMV can result in congenital infection with devastating long-term neurologic consequences [5]. Likewise, HCMV primary infection or reactivation in immunocompromised individuals, including transplant recipients and HIV/AIDS patients, can cause multi-organ damage and even death [6].

The immunologic impact of HCMV infection has garnered increased attention in recent years [7,8] as seropositivity has been linked to mortality, immunosenescence, vaccine responsiveness, cardiovascular disease, and cancer [9–13]. Importantly, many studies have reached conflicting conclusions – while some implicate HCMV in driving immunosenescence and disease risk, others suggest it enhances immune function, highlighting the need for more definitive studies [2,14,15]. A seminal study of monozygotic twins discordant for HCMV-seropositivity indicated that greater than 50% of human immune variation between individuals may be attributable to HCMV status, reflecting the significant impact HCMV has on human immunity [16]. In this review, we highlight how HCMV influences the host immune system and acts as an immunomodulator with distinct, age-related implications for health and disease (Figure 1).

HCMV infection in utero

Congenital HCMV infection affects between 0.5–2.0% of births worldwide [17] and can result from primary maternal HCMV infection, which has a placental transmission rate of 30–40%, or maternal HCMV reactivation/reinfection [17–20]. Approximately 10% of congenitally infected infants are symptomatic at birth and suffer long-term neurologic consequences [5]; another 10–15% develop neurologic sequelae after birth, namely sensorineural hearing loss. Postnatal transmission to preterm low birth weight infants via breast milk can also cause a sepsis-like illness [21].

Despite being previously considered immature, the fetal immune system responds robustly to HCMV *in utero* [22–24]. The fetal immune response to HCMV is characterized by an expansion of HCMV-specific CD8⁺ T cells and proliferation of non-specific differentiated CD28-CD8⁺ T cells [22,25,26]. Innate-like $\gamma\delta$ T cells are an important component of the fetal immune system, as they develop prior to canonical $\alpha\beta$ T cells, and HCMV infection *in*

utero induces expansion of specific V γ 9⁺ γ δ T cells (Figure 2) [27]. HCMV-induced ‘adaptive’ CD94/NKG2C⁺ NK cells (discussed below) are also increased in preterm infants with postnatal HCMV infection and children with past congenital HCMV infection, although they have not been observed in HCMV-infected infants at birth [28–31].

The long-term significance of HCMV-mediated changes in neonatal immune cell populations remains unclear, yet subsequent disease risk distinct from long-recognized neurologic sequelae is becoming increasingly apparent. A recent study implicated HCMV infection *in utero* as an etiologic agent in acute lymphoblastic leukemia (ALL), where there was a significantly increased prevalence of HCMV DNA in newborn blood spots of patients who later developed ALL compared to matched controls [32,33]. Mechanisms underlying these disease risks remain largely unexplored. There is evidence that HCMV infection also impacts maternal-fetal immune crosstalk. A recent study demonstrated that HCMV viral peptides can promote degradation of the neonatal Fc receptor (FcRn), which facilitates IgG transfer from mother to child *in utero*; disruption of IgG transfer could impact newborn immunity and predispose to infectious disease susceptibility [34]. Further characterization of the impact of HCMV on the neonatal immune system is warranted, including investigations of whether congenital HCMV infection impairs passive maternal immunity or perturbs early life NK, T and B cell development.

Immune responses to HCMV infection in early life

Over the course of human and HCMV co-evolution, most individuals were likely infected during childhood when HCMV infection is benign, with no known long-term disease risks. Full-term infants and young children who acquire HCMV postnatally generate HCMV-specific CD8⁺ T cells, but few HCMV-specific CD4⁺ T cells [35]. Despite the induction of HCMV-specific immune responses, children demonstrate prolonged mucosal viral shedding, sometimes lasting years, reflecting inadequate viral control [35–37]. Overall, the T cell compartment of seropositive children contains more differentiated (CD28⁻) and polyfunctional (CD57⁺) CD8⁺ T cells than seronegative children, mirroring CD8⁺ T cell changes seen in HCMV-seropositive adults [25,26,38]. CD94/NKG2C⁺ NK cells are also expanded in HCMV-seropositive children [37].

Despite evidence of immune activation in both T and NK cell compartments, few studies have examined whether HCMV infection in childhood impacts responses to pediatric vaccines or whether it has a positive or negative impact on immune responses to heterologous pathogens. Notably, priming of the early life immune system with the BCG vaccine has been shown to confer such protection and it is interesting to hypothesize whether HCMV infection in childhood could have similar positive implications for “trained immunity” [39]. Thus, while HCMV-infection *in utero* is deleterious, early childhood infection appears to have minimal effects on the health of infected children, though whether early life HCMV infection has beneficial impacts requires further study.

Impact of HCMV on adult T and NK cell compartments

Latent HCMV infection has a profound effect on the adult host immune system, likely resulting from an evolutionarily negotiated balance between viral persistence and immunologic control [13,14,40]. HCMV-specific T cells are immunodominant in healthy seropositive adults, accounting for nearly 10% of total CD4+ and CD8+ T cells, a phenomenon known as ‘memory inflation’ [40–42]. HCMV-seropositivity has also been associated with an overall increase in specific T cell phenotypes, including differentiated $\alpha\beta$ and $\gamma\delta$ T cells, and expansion of $V\delta 2^- \gamma\delta$ T cells (Figure 2) [43,44].

HCMV also markedly influences the adult NK cell compartment. Seropositivity is associated with expansion of ‘adaptive’ or ‘memory-like’ CD57+ NK cells (reviewed in [8]), which respond rapidly to repeat viral exposure and express the HCMV-induced activating surface receptor CD94/NKG2C [30,45]. This specialized NK cell subset has increased cytotoxicity and pro-inflammatory cytokine release [8,46,47]. Studies in mice and rhesus macaques, using MCMV and rhCMV, respectively, demonstrated that this adaptive NK memory cell response is conserved across species [48,49]. Furthermore, a recent study showed that NK cell expansion is mediated through HCMV viral peptide/HLA-E interactions, which activate the NKG2C receptor [50]. No other human pathogen is known to exert such a profound persistent effect on the host immune system as demonstrated by the T cell ‘memory inflation’ and ‘adaptive’ memory NK cell expansion seen with HCMV. The initial identification of HCMV-specific immune cell expansion led to widespread concerns that latent HCMV infection might compromise host immunity; however, accumulating evidence suggests that HCMV-seropositivity may enhance immune responses.

Heightened immune responses in HCMV-seropositive adults

Studies evaluating the impact of HCMV-seropositivity on vaccine responses and microbial challenge suggest that HCMV infection boosts immunity in early adulthood. In a study of influenza vaccine responsiveness, HCMV-seropositive young adults had higher magnitude antibody responses, cytokine levels (*e.g.*, IFN- γ), and activated CD8+ T cells following vaccination compared to HCMV-seronegative controls [11]. Following immunological challenge with staphylococcal enterotoxin B, CD8+ T cells from HCMV-seropositive young adults demonstrate polyfunctionality with increased expression of IFN- γ , TNF- α , and terminal differentiation markers (*e.g.*, CD57+) [51,52]. Similarly, studies in animal models suggest an immune-enhancing effect of latent MCMV infection wherein higher basal cytokine levels and immune activation confer protection from bacterial infection and improve vaccine responsiveness [11,53]. The NKG2C+CD57+ NK cells that expand in seropositive adults also exhibit increased proinflammatory cytokine release and antibody-dependent cellular cytotoxicity, which may prime the immune system and protect against other infections [8]. Cumulatively, these studies suggest that latent HCMV infection may be mutualistic to anti-pathogen responses, at least during early adulthood/reproductive age. Notably, it is unclear if these studies, which suggest a beneficial impact on heterologous immune responses and vaccine responses, can be generalized to other age groups.

Evidence for and against HCMV-induced immunosenescence

In the early 2000s, landmark epidemiologic studies on aging suggested that HCMV-seropositivity might accelerate normal age-associated deterioration in general immune function (*i.e.*, immunosenescence) and increase mortality in the elderly [10,15,54–56]. Additional contemporaneous studies suggested that seropositive older individuals also had a reduced response to influenza vaccination [57]. More recent follow-up studies [11,58–61] indicate that there is inconclusive evidence as to whether HCMV-seropositivity impacts elderly vaccine responses. One limitation of epidemiological studies of HCMV is that there are very few HCMV seronegative adults in old age, given >80% seroprevalence. The near ubiquity of HCMV seropositivity limits the power of association studies and introduces the caveat that individuals who remain seronegative later in life may have underlying inborn immune abnormalities rather than a lack of HCMV exposure.

Previously, it was postulated that inflation of HCMV-specific T cells due to chronic antigenic stimulation from long-term latent infection compromised T cell diversity and host immunity [15,62–66]. However, a recent study on the impact of HCMV-seropositivity on T cell receptor (TCR) diversity showed that seropositivity does not impact the elderly T cell repertoire [67]. B cell receptor (BCR) diversity is also preserved, and HCMV may even enhance memory B cell activation throughout the lifespan [68,69]. These findings that TCR and BCR repertoires are intact in HCMV-seropositive elderly adults contradict previous notions that latent infection undermines receptor breadth [67]. Thus, the mechanistic evidence for HCMV-induced immunosenescence remains significantly limited, and it is more likely that other HCMV-mediated effects contribute to the association between HCMV seropositivity and increased mortality in old age.

Lifelong HCMV-seropositivity modulates disease risk

HCMV-seropositivity has been implicated as a risk factor for cardiovascular disease (CVD), which may partially explain its association with increased mortality [12,56,70]. Vascular endothelial cells are a known reservoir for latent HCMV; increased circulating levels of IL-6 and TNF- α , perhaps due to immune activation during latent viral reactivation, may promote CVD pathogenesis [71]. Levels of IL-6 and TNF- α have been correlated with anti-HCMV IgG levels and increased CVD disease risk in HCMV-seropositive individuals [56]. A recent systematic review and meta-analysis of >35,000 individuals estimated that HCMV-seropositivity was associated with a 22% increased risk of developing CVD (RR =1.22) compared to seronegative individuals, even when controlling for known risk factors such as age, obesity, and smoking (which can increase CVD risk 2-fold) [12]. Importantly, the association between HCMV-seropositivity and CVD has only been observed in developed countries, and is not apparent in populations in the developing world [72]. Thus, the precise mechanisms underlying these associations are unclear, though one study recently implicated the accumulation of CD57+ cytotoxic T cells as a possible driver of CVD in CMV/HIV co-infection [73]. Moreover, evaluation of immune cell subpopulations in atherosclerotic plaques found a correlation between the expansion of activated effector memory T cells, HCMV DNA viral copy number, and risk of an acute coronary event [74]. More research

into possible causal mechanisms underlying the associations between HCMV infection, CVD, and immune activation is needed.

Multiple malignancies have been associated with HCMV-seropositivity [13]. In particular, HCMV and MCMV infection have been implicated in the progression of glioblastoma in humans and murine models [75,76]. It is currently unclear whether the presence of viral DNA in malignant tissue is due to viral reactivation within a locally immunosuppressed tumor microenvironment, or if the association between HCMV and malignancy reflects a broader oncomodulatory effect [71,77,78]. It is unknown if HCMV promotes tumorigenesis directly, as HCMV has not been shown to cause malignant transformation like other oncogenic herpesviruses (*e.g.*, EBV and HHV-8). Immune evasion is a more recently recognized hallmark of cancer, and it is possible that HCMV may modulate cancer susceptibility indirectly through its impact on the host immune system rather than through a direct effect via malignant transformation [3,79]. Furthermore, epidemiologic studies have not shown consistent results linking HCMV-seropositivity and cancer risk [80–82]. Memory inflation of HCMV-specific CD8⁺ T cells was previously hypothesized to be detrimental for tumor immune surveillance in later life [13]; however, it is unlikely that HCMV leads to decreased recognition of tumor neoantigens, as TCR and BCR diversity appears to remain intact in the setting of HCMV-seropositivity [67–69]. Divergent results from these studies demonstrate the need for additional definitive studies on HCMV-mediated mechanisms of cancer risk and progression.

Conclusions

Herein, we describe how the common herpesvirus HCMV profoundly shapes the host immune system and modulates disease risk across the life-course (Figure 1), with distinct age-related effects on healthy human T and NK cell compartments (Figure 2) [83]. Importantly, natural immunity to HCMV is only partially protective against reinfection or mother-to-child transmission [20,84]; work is ongoing to define immune responses that can prevent HCMV acquisition or rapidly contain viral replication to guide vaccine development [85].

The studies described above suggest that HCMV infection is deleterious at the extremes of age, but possibly advantageous in young adulthood. Notably, studies on the impact of HCMV infection in childhood and on pediatric vaccine responses remain limited. Latent HCMV infection may enhance immune responses in youth by increasing circulating proinflammatory cytokines and priming both classic adaptive immune cells such as T cells and unique adaptive NK cells to respond to infection. Interestingly, HCMV-vectored vaccines represent a promising novel vaccine platform that may leverage these benefits by eliciting strong vaccine-elicited T and NK cell responses [86–88]. Increased resistance to heterologous infections in HCMV-seropositive individuals may have conferred a past evolutionary selective advantage, helping to explain the ubiquity of HCMV in the human virome [1,14,89]. While multiple studies suggest that HCMV-seropositivity may be beneficial during reproductive-age, the virus remains an important pathogen and cause of morbidity and mortality in the immunocompromised, elderly, and prenatal populations, and is thus a vital target for vaccine development [90].

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Highlights

- Human cytomegalovirus (HCMV) infection and HCMV-seropositivity have an age-dependent impact on health and disease
- HCMV infection is associated with adverse health outcomes at the extremes of age, *in utero* and in elderly adults, but appears to boost host immunity and vaccine responsiveness in reproductive age
- HCMV causes immune activation and expansion of specific subsets of $\alpha\beta$ T cells, $\gamma\delta$ T cells, and NK cells, which creates a lifelong imprint on memory immune cell populations
- Additional mechanistic studies on how these HCMV-mediated immune changes may influence health and disease outcomes across the life course are necessary

Figure 1. Impact of HCMV on health and disease across the lifespan.

A. HCMV-infection *in utero* is associated with neurodevelopmental delay, sensorineural hearing loss, and increased cancer risk (depicted as brain/neuronal cells/inner ear and pre-leukemic clone), which may be due to the negative impact of pro-inflammatory immune responses *in utero* on development; B. HCMV-seropositivity is associated with improved influenza vaccine responsiveness and cross-pathogen protection in youth (illustrated by bacterium, vaccine syringe, and influenza virus), as immune activation and priming in the setting of HCMV infection may boost vaccine responsiveness and heterologous pathogen protection; C. HCMV-seropositivity is associated with increased mortality, cardiovascular disease, and cancer in elderly adults (left demonstrating coronary artery disease/atherosclerosis/vascular dysfunction and right depicting tumorigenesis/glioblastoma/colorectal cancer), which may be due to immune-mediated changes in the host resulting from chronic antigenic stimulation/latent HCMV reactivation. HCMV = human cytomegalovirus. Created with BioRender.

Figure 2. Imprint of HCMV on human immune cell compartments.

HCMV induces major immunophenotypic changes in three main immune cell subsets 1) “classic” αβ T cells including CD4+ and CD8+ T cells, 2) NK cells, and 3) “innate-like” γδ T cells. These phenotypic changes are characterized by immune activation and differentiation, which may modulate disease risk over the life course. HCMV = human cytomegalovirus, TCR = T cell receptor, KIR = killer cell immunoglobulin-like receptor, TEM = effector memory T cell, TEMRA = CD45RA+ effector memory T cell. Created with BioRender.