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CONFERENCE PROCEEDINGS

How does cytomegalovirus factor into diseases of aging and vaccine responses, and by what mechanisms?

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Abstract Cytomegalovirus (CMV) is an important pathogen for both clinical and population settings. There is a growing body of research implicating CMV in multiple health outcomes across the life course. At the same time, there is mounting evidence that individuals living in poverty are more likely to be exposed to CMV and more likely to experience many of the chronic conditions for which CMV has been implicated. Further research on the causal role of CMV for health and well-being is needed. However, the strong evidence implicating CMV in type 2 diabetes, autoimmunity, cancer, cardiovascular disease, vaccination, and age-related alterations in immune function warrants clinical and public health action. This imperative is even higher among individuals living in socioeconomically disadvantaged settings and those exposed to high levels of chronic psychosocial stress.

Keywords CMV · Chronic disease · Vaccination · Socioeconomic · Immunity · Aging

Abbreviations

CAD	Coronary artery disease
CVD	Cardiovascular disease
GrB	Granzyme B
NHANES	National Health and Nutrition Examination Survey
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
T1D	Type 1 diabetes
T2D	Type 2 diabetes
WHAS	Women's Health and Aging Studies

CMV and pathologies of aging

Aging is characterized by a low-grade chronic inflammatory state, also called "inflammaging" (Franceschi et al. 2000), which represents a significant risk factor for morbidity and mortality of elderly individuals as it is implicated in the pathogenesis of several disabling diseases of the elderly, including type 2 diabetes, osteoporosis, Alzheimer's disease, rheumatoid arthritis, and coronary heart disease (Holmes et al. 2009; Isaacs 2009; Lindholm et al. 2008; Mundy 2007; Sarzi-Puttini et al. 2005). Circulating inflammatory mediators

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such as cytokines and acute phase proteins are markers of inflammaging. Among these, elevated serum levels of IL-6 (2.6 pg/dL) and C-reactive protein (3.1–10 mg/L) have been shown to predict 3-year mortality in the elderly by the Invecchiare in Chianti study (Alley et al. 2007). The ways in which inflammaging contributes to adverse health outcomes is still unclear, and therefore, the identification of pathways controlling inflammaging across multiple systems is important to understand, so that interventions can be tailored to reduce inflammaging potentially improving the health of elderly individuals.

One of the driving forces of inflammaging is believed to be chronic stimulation of immune cells with cytomegalovirus (CMV). CMV mainly infects fibroblasts; epithelial, endothelial, and stromal cells; smooth muscle cells (Haspot et al. 2012); and adipocytes (Bouwman et al. 2008), which are believed to present CMV antigens in the context of MHC class I. The inflammatory response initiated by CMV-stimulated cells elicits the release of pro-inflammatory cytokines secreted from cells of the immune system and generates a vicious cycle, leading to immune system remodeling. Briefly, CMV induces the production of a variety of pro-inflammatory mediators which in turn induce CMV reactivation (Freeman 2009). In particular, in vitro studies have shown that CMV induces NF-kB activation in HeLa cells, promoting the production of TNF-α which leads to further activation of latent CMV and additional upregulation of the inflammatory response (Prosch et al. 1995).

Several studies have shown clonal expansion of CMV-specific T cells in seropositive elderly individuals as well as associations of CMV seropositivity (or absolute titers) with frailty, disability, and mortality. However, conflicting reports exist in the literature, probably due to the fact that anti-CMV IgG serology is a measure that makes no distinction between recent and long-established persistent infection. Moreover, there is also evidence that high IgG levels are correlated with virus reactivation and/or increased activity of the virus.

CMV and type 2 diabetes

Type 2 diabetes (T2D) is one of the most prevalent chronic inflammatory diseases of the elderly. T2D in the elderly represents 50% of total T2D cases and prevalence of T2D peaks at 15% in individuals 75 years of age and older, suggesting that complications of T2D increase with age (Smith-Palmer et al. 2014). Immunosenescence and inflammaging are implicated in the pathogenesis of T2D which in turn also alters the immune response, and therefore, T2D elderly patients are more susceptible to infections as compared with healthy age-matched controls.

Association of CMV seropositivity with pathogenesis of T2D was demonstrated in a cohort of individuals 85 years of age and older (Chen et al. 2012). Results showed that CMV-seropositive individuals were at higher risk of developing T2D, and had a higher level of HbA1c and non-fasting glucose than CMV-seronegative individuals, suggesting for the first time a role for CMV infection in the pathogenesis of T2D in very elderly but not in young individuals. This can be explained by the fact that the direct deleterious effects of CMV on pancreatic cells might have become significant after a long period of CMV infection. Moreover, hyperglycemia has been shown to impair host defenses and responses to infection, which may lead to higher seroprevalence of CMV in T2D patients (Geerlings and Hoepelman 1999). Thus, higher prevalence of CMV would be a result, not a cause, of disease. The fact that CMV DNA can be detected in samples of pancreatic tissue from patients with T2D strongly supports the association of CMV with T2D (Lohr and Oldstone 1990). Human pancreatic β-cells have also been shown to be susceptible to in vitro infection with CMV (Smelt et al. 2012).

Retrospective studies have shown that CMV is one of the most important causes of post-transplant morbidity and mortality, due to increased allograft rejection, predisposition to opportunistic infections, and also development of post-transplant diabetes (Hjelmesaeth et al. 1997). An association between late-onset CMV infection and the development of post-transplant diabetes has been shown (Leung Ki et al. 2008), and several mechanisms by which CMV may damage the pancreas have been proposed, including (1) CMV-induced cytopathic effects of β-cells and induction of apoptosis; (2) cytotoxic effects by infiltrating leukocytes; (3) induction of pro-inflammatory cytokines caused by infection of β-cells, neighboring pancreatic cells or infiltrating leukocytes leading to altered β-cell function or apoptosis; and (4) CMV-induced T cells crossreacting with β-cell autoantigens and consequent killing of the β-cells (Hjelmesaeth et al. 2005). The induction of pro-inflammatory cytokines, together with the infiltration of immune cells, is likely to provoke a strong and

destructive immune response against the β-cells, although experimental evidence still needs to be provided.

CMV and atherosclerotic cardiovascular complications

The association between CMV infection and atherosclerotic cardiovascular disease (CVD) is well-known from the literature (Blankenberg et al. 2001; Gkrania-Klotsas et al. 2012; Muhlestein et al. 2000; Roberts et al. 2010; Simanek et al. 2009, 2011; Spyridopoulos et al. 2016). Since immunological processes are key features of atherosclerosis, it has been postulated that CMV infection increases cardiovascular mortality via immunological mechanisms. In fact, CMV induces dramatic changes in the human immune system, especially the T lymphocyte compartment, which exhibit many accelerated aging-related changes in CMV-seropositive individuals (Chidrawar et al. 2009; Wertheimer et al. 2014). CMV has been identified in more than half of atherosclerotic plaques, and CMV-positive plaques are associated with increased numbers of macrophages and CD3+ T cells (Yaiw et al. 2013). In addition, CMV drives both CD4+ and CD8+ T cell expansion toward terminal differentiation such as CD4+CD28null cells and CD8+CCR7 −CD45RA+ T_{EMRA} cells. These cells are highly cytotoxic and high in granzyme and perforin expression but could simultaneously express high level of pro-inflammatory cytokines including IFN-γ and TNF-α (Chiu et al. 2016). Production of pro-inflammatory cytokines in turn activates p38 in T cells, inhibits T cell telomerase activity, and promotes loss of CD28 and T cell differentiation, further creating a vicious cycle of immunosenescence (Macaulay et al. 2013). CMV-specific T cells are found to express high levels of CX3CR1, which binds to injuried vascular endothelium-expressing fractalkine, and the β2-adrenergic receptor, which permits rapid response toward stress (Pachnio et al. 2016; van de Berg et al. 2012). It is important to note that not all persistent virus infections result in terminally differentiated T cells. For example, in CMV-seronegative individuals, herpes simplex virus infection does not affect T cell subset homeostasis significantly (Derhovanessian et al. 2011). At the present, it is hypothesized that this difference is due to the higher intensity and/or broad anatomical location of sites from which CMV reactivates and/or generates antigens for T cell stimulation, but that remains to be experimentally addressed.

CMV seropositivity and elevated CRP, especially when in combination, are strong predictors of mortality in patients with coronary artery disease (CAD) (Muhlestein et al. 2000). The association of CMV infection with death is probably partially mediated by chronic systemic inflammation. In a population-based study involving 1468 participants, a composite measure of TNF-α and IL-6 mediated a substantial proportion of the association between CMV and all-cause (18.9%, $P < 0.001$) and cardiovascular (29.0%, $P = 0.02$) mortality (Roberts et al. 2010). A meta-analysis based on 9000 CMV-infected individuals and 8.608 controls from six prospective studies and 49 retrospective case-control studies showed that CMV infection overall has an odds ratio of 1.67 for CAD risk (Ji et al. 2012). The European Prospective Investigation into Cancer (EPIC) study identified an association between higher levels of CMV-IgG and ischemic heart disease (with a hazard ratio of 1.4 when compared to seronegativity). Simanek et al. reported significant associations between CMV infection and both CVD and CVD-related mortality in the US population (Simanek et al. 2009, 2011). Similarly, Roberts et al. showed that CMV was associated with CVD mortality in a predominantly Latino population living in the US and that these associations were partly mediated by IL-6 (Roberts et al. 2010). Our preliminary data among end-stage renal disease patients showed also the level of CMV-specific IgG correlates with CVD in CMV-seropositive individuals. In a multivariate model using CMV-IgG quintile to predict existence of CAD, we found that CMV-IgG quintile independently associates with concurrent CAD (with an odds ratio of 2.1 when compared to the lowest quintile). Obviously, different levels of immune response toward CMV may pose higher levels of risk for CMV-infected individuals.

CMV and autoimmune diseases

A link between CMV and autoimmune diseases is suggested by several published data. A general point of view is that CMV infection could cause and/or promote autoimmune diseases, and CMV replication may enhance tissue damage caused by autoimmune pathologies. On the other hand, autoimmunity-driven inflammatory processes are believed to support productive infection rather than prevent viral reactivation and growth.

Rheumatoid arthritis Latent CMV infection influences the clinical course and outcome of rheumatoid arthritis (RA) (Davis et al. 2012; Pierer et al. 2012), and CMV has been associated with more severe joint disease in patients with RA (Rothe et al. 2016). Specific immunopathogenic mechanisms through which CMV could contribute to aggravation of joint damage in RA patients include the expansion of CMV-specific CD4+ CD28− (Pawlik et al. 2003) and CD8+CD28− (Rothe et al. 2016) T cells, which directly contribute to tissue lesions.

The presence of miR-UL112-3p, the only circulating CMV micro-RNA (miR), has been shown in the plasma of patients with RA (Mohammad et al. 2014). This miR inhibits the translation of the CMV's trans-activator IE72, which impacts on active infection and might favor maintenance of latency (Murphy et al. 2008). This miR also targets cellular mechanisms involved in IL-32-mediated TNF-α release, which may also affect the establishment and maintenance of viral latency and persistence (Huang et al. 2013).

Systemic lupus erythematosus Patients with systemic lupus erythematosus (SLE) have higher frequencies of CMV infection (Esen et al. 2012) as well as higher CMV-specific IgG (Barzilai et al. 2007), and in those SLE patients with higher CMV-specific IgG, higher amounts of serum autoantibodies were detected (Palafox Sanchez et al. 2009). In this last study, it was also found that anti-CMV IgM positivity was associated with lower levels of autoantibodies specific for U1RNP/Sm and U1-70 k as compared to anti-CMV IgG positivity, suggesting a role for CMV reactivation in the regulation of autoantibodies. Contrasting results have also been reported with higher CMV-specific IgM, but similar IgG, correlated with more severe disease activity and autoantibodies in SLE patients (Su et al. 2007).

SLE patients often require immunosuppression to induce remission of active disease symptoms, and these patients are at higher risk of opportunistic infections. It has indeed been shown that CMV seropositivity complicated the course of SLE patients treated for disease activity (Berman and Belmont 2017). These results suggest that SLE patients undergoing aggressive immunosuppressive treatments should be tested for IgG CMV. A universal prophylaxis intervention management approach to decrease the risk of developing this potentially life-threatening infection should be considered for highest-risk patients.

Type 1 diabetes CMV DNA has been detected in PBMCs of type-1 diabetes (T1D) patients, and a strong correlation between CMV DNA and islet cell-specific autoantibodies has been shown, suggesting that persistent CMV infections may be relevant to the pathogenesis of T1D (Pak et al. 1988). The disease may be the result of an immune response to chronic exposure to either viral antigens or cell-specific antigens in the context of MHC class I and II overexpression (Bottazzo et al. 1985). Association of CMV seropositivity with recurrence of humoral and cellular autoimmunity to islet autoantigens has also been shown in a T1D patient receiving a pancreas allograft (Zanone et al. 2010). Conversely, no association between CMV and onset of T1D was found in young children (Aarnisalo et al. 2008).

CMV and cancer CMV is not an oncogenic virus. However, CMV infection has been implicated in different malignant diseases and the term "oncomodulation" has been conied to better explain that CMV infects tumor cells and increases their malignancies (Michaelis et al. 2009). Detection of CMV DNA, mRNA, and/or antigens in tumor tissues suggested a role of CMV infection in the etiology of several human malignancies. Molecular mechanisms of CMV-induced oncomodulation are multiple and are summarized below.

CMV infection increases the ability of cancer cells to evade immune surveillance. It has been reported that the CMV proteins US2, US3, US6, and US11 decrease expression of MHC class I on immune cells. Through this mechanism, infected cancer cells avoid adaptive immune response, in particular cytotoxic T cell responses (Lee et al. 2000). Also, the CMV-encoded proteins UL16 and miR-UL112 downregulate MHC class I expression. MHC class I-related UL16 proteins are cellular ligands for the activating receptor NKG2D, which is expressed on cytotoxic NK cells, γδ T cells, and CD8+ cells (Wilkinson et al. 2008). Immune evasion may also occur through production of immunosuppressive cytokines. The CMV-encoded viral IL-10 homolog (UL111a; cmvIL-10) is a potent immunosuppressive molecule, similar to human IL-10 (Kotenko et al. 2000).

CMV infection also increases the proliferative capacity of cancer cells, and several CMV proteins, such as the CMV-encoded chemokine receptor US28, have been shown to promote cell cycle progression and cyclin D1 expression in tumor cells (Maussang et al. 2006). The CMV IE1 protein, which is detected in >90% of

human malignant gliomas, increases phosphatidylinositol 3-kinase/AKT activity (needed for cell proliferation) and at the same time inactivates the tumor suppressors Rb and p53 (promoting entry into S phase of the cell cycle) (Cobbs et al. 2008).

Resistance to apoptosis is a common feature of cancer cells and represents a relevant mechanism of protection of cancer cells during chemotherapy (Hanahan and Weinberg 2000; Pucci et al. 2000). CMV protects tumor cells from apoptosis through the induction of several intracellular signaling pathways such as AKT, mitogen-activated protein kinase, and c-Jun NH2-terminal kinase, following binding of CMV glycoproteins to PDGFR or virus coreceptors [reviewed in (Cinatl et al. 2004; Michaelis et al. 2009)].

CMV also alters cancer cell invasion, migration, and adhesion to the endothelium. CMV-infected neuroblastoma cells express increased adhesion to human endothelial cells, occurring because CMV downregulates neural cell adhesion molecule receptors in infected neuroblastoma cells, contributing to higher tumor cell adhesion (Blaheta et al. 2004). Increased adhesion to the endothelium has also been shown in human prostate cancer cells (Blaheta et al. 2006). CMV is able to induce interleukin 8 (IL-8), a promoter of tumor angiogenesis, in leukemia and glioma cells, through NF-κB/AP-1-mediated transactivation of the IL-8 promoter (Murayama et al. 2000). CMV also suppresses the expression of angiogenesis inhibitors (thrombospondins) in glioma cells (Cinatl et al. 1999).

CMV and frailty

Frailty, which is characterized by a state of decreased physical activity and poor endurance, has been associated with clinical CVD (Bellumkonda et al. 2017). As a result, it is possible that CMV infection also results in frailty via chronic inflammation and/or CVD. Indeed, CMV seropositivity was found to be associated with frailty. In the Women's Health and Aging Studies (WHAS) (Wang et al. 2010), researchers found, after having adjusted for age, history of smoking, BMI, DM, and heart failure, that the odds ratio for frailty in persons with CMV infection was 3.2. Furthermore, in persons with high IL-6 level (>4.2 pg/mL), the adjusted odds ratio for frailty in persons with CMV infection increased to 20.3. Interestingly, in the BELFRAIL cohort, neither CMV seropositivity nor CMV IgG titer was associated with frailty in individuals aged 80 and older. The observation might be due to survival effect because the participants were only 70–79 years old in the WHAS study and the BELFRAIL cohort recruited only people older than 80. Another explanation could be the severity of inflammation. A study performed in breast cancer patients showed the IL-6 level significantly associated with frailty, but the CMV status was not reported (Brouwers et al. 2015). In long-term care geriatric patients, higher baseline hs-CRP and IL-6 levels were associated with worse physical performance and gait speed at 12 months independent of age and comorbidity (Langmann et al. 2017). As a result, CMV infection might only result in frailty or other deleterious health conditions in individuals with high level of inflammation, but obviously further studies are needed to establish the solid link between CMV and frailty.

CMV, infectious diseases, and vaccine responses

Results on the effect of CMV seropositivity on influenza vaccine responses are controversial with most of the studies showing a negative effect of CMV (Derhovanessian et al. 2013b, 2014; Frasca et al. 2015; Trzonkowski et al. 2003) and others showing no effect (den Elzen et al. 2011; Furman et al. 2015). The negative effects of CMV seropositivity have been associated in both elderly (Derhovanessian et al. 2013b; Frasca et al. 2015) and young (Frasca et al. 2015) individuals with the presence of late differentiated/exhausted T cells (CD27−CD28−CCR7−CD45RA+ or with CD28−CD57+), which produce pro-inflammatory cytokines and have therefore a significant role in age-related immune pathologies, suggesting that this virus may underlie rudimentary aspects of immunosenescence even in chronologically young individuals (Turner et al. 2014). Results from a recently published study have demonstrated that CMV seropositivity negatively affects antibody response to the influenza vaccine to a greater extent than inflammatory markers, such as β2-microglobulin and IL-6, in older adults (Reed et al. 2017). Conversely, the positive effects of CMV seropositivity on the response to the influenza vaccine have been shown only in young individuals (Furman et al. 2015). In particular, it has been shown that CMV-seropositive young individuals exhibited enhanced in vivo antibody responses, Th1 and Th2 responses, and cytotoxic T cell responses, as compared with CMV-seronegative individuals, suggesting that CMV can boost the immune response of young

individuals and therefore shows features of a mutualistic agent conferring benefits to the host.

When memory T cell responses to influenza antigens were investigated, it was found that 40% of CMV-seropositive elderly, and 80% of the CMV-seronegative elderly, had an influenza-specific CD4 T cell response (Derhovanessian et al. 2014). The proportion of young individuals mounting specific CD4 T cell responses was comparable between seropositive and seronegative individuals, suggesting that the effects of CMV may be only seen in the elderly because they have been exposed to the virus for longer periods of time (Derhovanessian et al. 2014). Moreover, the percentage of individuals with CD8 T cell responses to influenza antigens was lower than those with CD4, and this response was not influenced by whether the subjects were seropositive or seronegative. CMV-seropositive responders had significantly higher frequencies of late-differentiated CD4 T cells (CD45RA+CCR7−CD27−CD28−), as compared with CMV-infected non-responders (Derhovanessian et al. 2014). These late-differentiated memory T cells, which are expanded in elderly individuals, are specific for previously encountered CMV antigens (pp65 and IE1), and their presence correlates with the ability to mount robust pro-inflammatory responses against major CMV antigens (TNF-α, IFN-γ, IL-17), suggesting that these cells are positively associated with longer survival in elderly individuals, and are at least partially functional and necessary for further protection to subsequent infection (Derhovanessian et al. 2013a).

CMV serostatus has been shown to be a key determinant of the Granzyme B (GrB) response to influenza challenge; CMV-seropositive subjects had low levels of inducible GrB activity in response to influenza challenge (Haq et al. 2016), suggesting that CMV seropositivity associated with a decline in GrB responses to influenza may predict increased susceptibility to influenza in older adults. CMV seropositivity has also been shown to induce the expansion of polyfunctional CD8+ T cells (CD8+CD57+) secreting multiple cytokines (IFN-γ, TNF-α), which can degranulate in response to stimulation, and are therefore crucial for the generation of optimal responses to infections and vaccines (Pera et al. 2014). The authors of this study have suggested that CMV seropositivity may provide protection against some pathogens by keeping the immune system in a state of alert. This could also explain its high prevalence in humans.

CMV also impairs B cell responses to the influenza vaccine, and a negative association between CMV seropositivity and the B cell predictive biomarkers of optimal vaccine responses has been reported (Frasca et al. 2015). In this cohort, CMV seropositivity has also been associated with increased levels of systemic and B cell-intrinsic inflammation, suggesting an additional mechanism by which CMV downregulates the B cell antibody response.

T2D is one of the chronic diseases where influenza vaccination is recommended, and older adults with T2D are less prone to influenza-induced clinical complications once vaccinated (Wang et al. 2013). The influenza vaccine response was measured in T2D elderly individuals and compared to healthy age-matched controls (McElhaney et al. 2015). Results showed no differences between T2D elderly and healthy elderly in the antibody response to the vaccine. In this cohort, CMV did not determine per se any functional alteration in clinical and functional parameters of participating elderly individuals. In the same study (McElhaney et al. 2015), the antibody response to the vaccine was compared between CMV-seropositive and CMV-seronegative elderly participants. Results showed that both healthy and T2D CMV-seropositive individuals had a significant higher response, which was unexpected, suggesting that in addition to age and diabetic status, immunological history such as CMV status should be taken into account.

Social and economic determinants that influence CMV epidemiology and transmission

CMV infection has been considered a disease of poverty and continues to be strongly patterned by socioeconomic status in the US and globally (Hotez 2008; Manicklal et al. 2013). Indeed, there is a substantial body of evidence suggesting that CMV is socioeconomically (e.g., educational attainment and income) patterned across the life course. For example, in 2009 Simanek et al. showed that educational attainment was significantly associated with seropositivity for CMV and that CMV infection was associated with CVD using data from the NHANES for individuals ages 45 years and older (Simanek et al. 2009). In 2009 and 2012, Dowd et al. reported that CMV seropositivity was higher among adults and children with lower household income and educational levels (using parental data on socioeconomic indicators

for the children) (Dowd et al. 2009, 2012). More recently, using data from the Sacramento Area Latino study of Aging, Meier et al. found that early-life socioeconomic status influences adult probability of CMV infection and that this association was mediated by measures of midlife socioeconomic status (Meier et al. 2016). In addition, using data from NHANES, Feinstein et al. observed that socioeconomic disparities in all-cause mortality in the US were associated with CMV infection and that this pathway was strongest among older individuals (Feinstein et al. 2016). Further support for a role for CMV in socioeconomic differentials in immunity was demonstrated in a study by Aiello et al., where CMV was found to be a significant mediator of the impact of income on T cell markers of aging (Aiello et al. 2016). Specifically, Aiello et al. showed that for every 10,000 decrease in income, there was a correspondingly significant decrease in effector to naïve T cell ratio for both CD4 and CD8 cells and that the observed socioeconomic differential in immunity was partially accounted for by CMV seropositivity (Aiello et al. 2016). Of note, reductions in the proportion of naïve cells were associated with lower income independent of effector cell proportions, suggesting that these findings are not only explained by an overall increase in effector cells. Nonetheless, further research should include the total counts of each cell type and subsets to examine whether income is associated with absolute quantity of naïve and effector cell types.

The reasons why significant socioeconomic patterning of CMV exists have not been fully elucidated. The associations may reflect increased exposure to CMV among individuals who are living in disadvantaged settings, which may be more likely to be characterized by overcrowding, lack of access to hygiene and sanitation resources, and increased use of daycare at earlier ages, which have all been implicated in increased transmission of CMV as well as many other infectious diseases (Hotez 2008; Manicklal et al. 2013). At the same time, there is evidence that individuals of lower socioeconomic status are burdened by a higher force of CMV infection at earlier ages, measured by the instantaneous per capita rate of CMV acquisition by age (Colugnati et al. 2007). Taken together, individuals experiencing greater socioeconomic disadvantage not only have greater exposure to CMV but also tend to experience significantly higher rates of transmission of CMV and are infected at an earlier age compared to individuals of higher socioeconomic status.

There is also a growing body of literature demonstrating consistent associations between socioeconomic disadvantage and other psychosocial stressors and CMV antibody levels (Aiello et al. 2010). In response to exposure to stressors, human immunity may be altered, providing an opportunity for CMV to replicate and circulate, in turn inducing production of CMV-specific IgG antibodies (Rector et al. 2014). For these reasons, higher CMV IgG antibody levels have been used as a surrogate measure of stress-related altered cell-mediated immunity in several studies (Segerstrom and Miller 2004). For example, higher CMV antibody levels have been noted in response to exam stress, space flight, and loneliness (Jaremka et al. 2013, 2014; Mehta et al. 2000; Sarid et al. 2001). Other studies have identified associations between socioeconomic status and CMV IgG antibody levels. In 2008, Dowd et al. showed that lower educational attainment was associated with significantly higher antibody response to CMV among older Latinos in the US (Dowd et al. 2008). Using data from NHANES, Dowd et al. demonstrated an association between lower income and education with higher CMV IgG antibody levels in the US population (Dowd and Aiello 2009). These findings also held for children living in US households with income below the poverty line (Dowd et al. 2012).

Aiello et al. used data from the Multi-Ethnic Study of Atherosclerosis and showed that chronic exposure to stressors resulted in a higher antibody response to CMV along with several other persistent pathogens, suggesting that exposure to stressors might influence not only CMV but also other persistent pathogens, including other herpesviruses and chronic bacterial species (Aiello et al. 2009). In 2014, Rector et al. reported associations between measures of psychological well-being (depression, vital exhaustion, and poorer mental health) with higher CMV antibodies in an occupational cohort in Germany, and these associations were shown to be more robust among those of lower socioeconomic status (Rector et al. 2014). Together, these studies indicate that socioeconomic status and other psychosocial stressors may modify CMV IgG antibody response in humans. Further research regarding the extent to which CMV IgG antibody levels rise and persist in response to stressors is needed. Moreover, research exploring the variability in CMV IgG immune response to acute versus chronic exposure to stressors is warranted. Finally, there is little research on the age-related

differences in CMV IgG antibody response to stressors, making it difficult to identify whether exposure to stressors at certain age periods are more or less detrimental to CMV immunity and age-related alterations in immune function.

Future needs and avenues

This review identified multiple clinical and epidemiological studies supporting associations between CMV and chronic conditions, including T2D, autoimmune conditions, CVD, frailty, vaccination response, and age-related alterations in immune function and inflammation. At the same time, there is a growing body of research suggesting that socioeconomic status and other psychosocial stressors influence CMV infection and IgG antibody response. Together, this work indicates that CMV may have pleiotropic influences on health that vary by age and socioeconomic status. Further work integrating both the social and clinical patterning of CMV is needed. Moreover, there is a need to better understand how factors such as timing of CMV infection, infectious dose, and reactivation of CMV over time influence health and well-being. Research examining methods for dampening CMV immune response in aging populations is needed to better define the associations between CMV and vaccination efficacy. The causal link to the many exposures and outcomes that we have reviewed here is still debatable. Nonetheless, the body of evidence suggests that CMV is an important culprit for many critical exposures and health outcomes, warranting a more urgent clinical and public health response to research and intervention studies that can clarify the role and extent to which removing CMV infection and altering its influence on age-related immunity may protect and reduce the burden of many diseases that are common and increasing in the population. Future studies should consider research on vaccinations and interventions to cut down on the transmission of CMV in human populations, especially among individuals living in lower socioeconomic settings and early in life when CMV infection is common.

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