Immunity to Cytomegalovirus

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Abstract

Cytomegalovirus is one of the most immunodominant antigens that are encountered by the human immune system. The human cytomegalovirus (HCMV) exhibits a broad cellular tropism and can infect most major organ systems and cell types. Immunologic control of HCMV replication includes several distinct categories of effector cells: natural killer cells, macrophages, B cells and T cells however virus-specific CD8+ and CD4+ T cells appear to play a pivotal role. The importance of cell mediated immunity against CMV is exemplified by the occurrence of severe and prolonged HCMV infection in immunocompromised individuals, including transplant recipients, late stage HIV patients, congenitally infected newborns, elderly subjects and/septic patients. Severely impaired T-cell function leads to viral reactivation and consequences are widely variable, ranging from asymptomatic infections to life-threatening situations.

Monitoring of protective HCMV-specific immune response may serve as an early predictive marker for identifying individuals at high risk for HCMV disease prior to the detection of increased viremia. The identification of patients who are at high risk of CMV is a more complex challenge for the laboratory. Mainly HCMV specific T cell immunity, resp. enumeration of CD8+ HCMV specific T cells would be expected to correlate with the incidence of HCMV disease. Recently, it has become possible to enumerate antigen-specific CD8+ T cells by using tetramers. HCMV-specific cellular immunity by evaluating the activation capacity of CD8+ T cells to a mitogenic stimulus or whole HCMV antigen or HCMV peptides assessed by IFNy ELISPOT or ELISA seem to be promising in the assessment of HCMV-specific function/immunity. However the clinical utility of these assays will need to be evaluated.

Keywords: HCMV; Immune system; Cellular immunity; T cells; Cytokines

Introduction

Human cytomegalovirus (HCMV), a member of Herpesviridae family, is a ubiquitous opportunistic pathogen. Compared to other human herpesviruses, HCMV is the largest, with a genome of approximately 235 kb. HCMV genome contains a number of accessory genes; most of them are engaged in immune evasion or inhibition of cell death. HCMV infection usually peaks first during childhood. The next peak occurs in young adults, mostly by sexual transmission [1,2]. Primary HCMV infection in healthy hosts is usually a clinically silent event with few symptoms like fever, myalgia, cervical lymphadenopathy etc. After an initial primary infection, HCMV can remain latent throughout the lifetime of the host and sporadic reactivation events, if they occur, are generally well controlled by immunosurveillance. Viral latency is defined as the persistence of viral genome in the absence of production of infection virions [3,4].

Transplacental transmission during pregnancy or neonatal infection can lead to neurological damage, manifesting itself as deafness or learning disability in early life [4,5].

Infection with HCMV occurs as result of exposure of mucosal surfaces of the upper respiratory tract or the genital tract. Although the cellular target of HCMV infection remains incompletely defined, the widespread expression of putative cell surface receptors including proteoglykans, integrins and epidermal growth factor receptor suggest that the tropism of virus is not limited to specific cell types on the mucosal surfaces. After mucosal infection with HCMV, local and initial viremia leads to infection of visceral structures such as the liver and spleen. Infection of these organs is then followed by a secondary viremia that leads to more generalized infection [6].

HCMV exhibits a broad cellular tropism and can infect a remarkably broad cell range within its host. Epithelial cells, endothelial cells, fibroblasts and smooth muscle cells are the predominant targets for virus replication [7,8]. Infectivity in the blood compartment is most frequently associated with peripheral blood leukocytes and endothelial cell. Endothelial cells also appear to be crucial for infection of various tissues during HCMV dissemination. Even though the polymorphonuclear leukocytes cannot support virus replication, they have been shown to carry virus and viral gene products. Other cells of peripheral blood cells that enable HCMV resistance and transmit infectious virus include monocytes, resp. macrophages [9,10,11]. Moreover, it appeared that HCMV infection of host cells, including monocytes and endothelial cells, could induce expression of variety mediators of the inflammatory response including adhesion molecules, chemokines, cytokines, and pro-inflammatory enzymes such as COX-2 [6].

The outcome of HCMV infection typically correlates with the immune status of the host. HCMV infection is well controlled in immunocompetent hosts and infection of healthy individuals is often asymptomatic. In contrast, infection of immunocompromised hosts, especially organ and stem cell transplantant recipients and AIDS patients can be devastating.

Immune response to HCMV infection

HCMV, like other herperviruses, broadly influences the magnitude and quality of both innate and adaptive immune response. Cells
infected with HCMV exhibit profound reprogramming of gene expression. Antiviral genes belonging to the interferon-stimulated gene family and inflammatory genes such as those for TNF-α, IL-1, IL-6, IL-8, IL-12, IL-18 and cyclooxygenase 2 (COXX-2) are hallmarks of innate immunity that contribute significantly to control infection [1,12,13].

Infection with HCMV is followed both humoral and cellular immune responses. Antibody-mediated complement lysis is an important mechanism for elimination of virus-infected cells. HCMV have evolved mechanisms limiting complement activity and it is able to inactivate the complement cascade, increasing virus replication and survival [14,15].

Humoral immunity is established early and immunoglobulin G (IgG) antibody remains the standard assay for determining infection history but the protection value of this response is unclear [16].

It is widely believed that the cellular immune response is the major mechanism by which HCMV replication is controlled. The presence of protective anti-HCMV cellular immunity is hypothesized to prevent HCMV disease regardless of the anti-CMV status [17]. The crucial role of cell-mediated immunity against HCMV demonstrates the fact that severe and prolonged HCMV infections occur in individuals with congenital, iatrogenic, or acquired immunodeficiencies. Infection in most individuals with primary B cell disorders usually is not severe [18].

Immune control of HCMV replication includes several distinct categories of cells: natural killer (NK) cells, macrophages, B cells, αβ and γδ T cells but particularly T cells seem to play a key role in this process. Mostly T lymphocytes are of major importance in the initiation and maintenance immunity against viral infection. Both virus-specific CD8+ and CD4+ T cells seem important in the control of active as well as persistent infection. The main function of cytotoxic CD 8 T cells resides in the specific lysis of virus-infected target cells, CD4 T cells are critical for the induction and regulation of immune responsiveness. This function is mediated by the specific activation of dendritic cells, which present antigenic peptides in the context of MHC class I molecules to induce virus-specific cytotoxic CD8 cells. Furthermore, CD4 T cells provide help for B cells to secrete virus-specific antibodies. Both CD4 and CD8 T cells secrete cytokines, such as interferon-γ (IFN-γ) or tumor necrosis factor α (TNF-α), that may have direct antiviral effects [19,20,21].

Secretion of cytokines and chemokines has both local and systemic effect, whereas lysis of infected cells by components of CD8+ T cell cytotoxic granules depends on cell-cell contact. Upon resolution of the viral expansion, most of these effector T cells die by apoptosis, whereas other enters the memory pool [13,16,19].

On the other hand, immune evasion strategies contribute to successful persistence of virus in the immunocompetent host. In the infected cell, herpesviruses use general evasion approaches, such as blocking the induction synthesis and dedicate part of their genomes to functions that modulate immune recognition. But most specific evasion strategies describe to date allow viruses to impair T cell activation by interfering with both major histocompatibility complex (MHC) class I and MHC class II antigen processing a presentation [22].

Age-dependent HCMV immunity

Congenital infection may be severe and followed by permanent sequelae CMV infection. Preconceptional immunity against HCMV provides only partial protection from intrauterine transmission of the virus and the factors that are associated with this transmission of HCMV have not been identified. Unlike adult primary HCMV infection of neonates and infants usually results in continuous or frequent shedding into urine and saliva for up to several years. The difference in duration of HCMV shedding in young children and adults is related to quantitative and qualitative differences in the T cell mediated immune response, resp. CD4+ T cell mediated immunity that in generated in an age-dependent manner [23,24].

Inflammatory mechanisms play a prominent role in the pathogenesis of many age-related diseases and possibly in the primary process of aging itself. It has become evident, that HCMV chronic infection contributes to a number of modifications that characterize immunosenescence. HCMV infection accelerates in the reduction in the naïve T cell pool, which occurs following thymic involution. However, it has been reported that elderly subject exhibit an increase in T cell specific for HCMV-derived epitopes, constituting oligoclonal T cell expansion, with phenotype of highly differentiated effector cells. HCMV-specific CD8+ T cells produce IFN-γ but no IL-4 and very little IL-12. A high type 1 combined with a low type 2 cytokine production can change the cytokine microenvironment in lymphatic tissues and trigger ubiquitous inflammatory process in elderly persons. The small number of CD8+ naïve T cells may lead to difficulties in the immunological response to neoantigens in old age [25,26,27].

HCMV infection in immunocompromised individuals

HCMV infection in immunocompromised individuals causes various clinical syndromes in different groups of patients, and the severity of infection is proportional to the degree of immunosuppression. The most severe infections develop in transplant recipients, late stage HIV-patients, and congenitally infected neonates. However, patients with T lymphocyte defects and old people are prone to reactivation and life-threatening infections. Recently, laboratory-based signs of active CMV infection have been observed in association with the onset and course of autoimmune diseases [28,29,30].

HCMV infection and primary immunodeficiencies

The primary manifestation of the immunodeficiencies is undue susceptibility to infection. It means too many, too severe, prolonged, complicated and unusual infections. HCMV infections of immunocompetent hosts are characterized by a dynamic, life-long interaction in which host immune response, particularly of T cells, restrain viral replication and prevent disease but do not eliminate the virus or preclude transmission. HCMV infection may be severe in the immunocompromised host, particularly in the face of T cell deficiency such as due to primary immunogenetic defects or acquired immunodeficiency states. HCMV is poorly adapted to survive within an immunosuppressed host, and, in this situation, there is often uncontrolled viral replication with subsequent viral reactivation [31,32,33].

Common variable immunodeficiency (CVID) is the most common primary antibody deficiency caused by a variety of inherited genetic defects. The disease in many patients is probably determined by multiple abnormalities in different cell types. Many of CVID patients have a T cell lymphopenia, which is often, associated with poor T cell proliferation to mitogens in vitro what appears to be a significant defect in cellular immunity. The same patients often show signs of persistent immunostimulation and inflammation raising the possibility that these abnormalities reflect persistent viral infection in a substantial subset of CVID patients [34].

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HCMV in immunosuppressed patients

HCMV infection is a major cause of morbidity and mortality in immunosuppressed patients, including organ and bone marrow transplant recipients, hemodialysis patients, cancer patients, patients receiving immunosuppressive drugs and HIV-infected patients [27,35]. The majority of CMV disease is caused by reactivation of a latent infection rather than by newly acquired virus. A series of mechanisms have been proposed to be responsible for CMV reactivation. These include: (a) stress, (b) inflammation, and (c) some cAMP-elevating drugs (e.g. pentoxifylline). The loss of immune control of HCMV is closely associated with an impaired function of CMV-specific CD8+ T cells. In fact, it is the reduced cytokine production rather than a lower frequency or absolute number of HCMV-specific CD4+ or CD8+ T cells that are thought to be responsible for the loss of immune control. Reduced numbers of cytokine-producing HCMV-specific CD8+ T cells were found in individuals with higher risk of HCMV reactivation [36,37,38].

AIDS patients develop cytomegalovirus disease in advanced stages of immunosuppression, at CD4 cell counts of less than 50 cells/μl when there are other defects in antigen-driven lymphocyte proliferation, natural killer activity and production of cytokines. Loss of HCMV-specific CD4+ T lymphocyte function may be key to pathogenesis of AIDS-related cytomegalovirus disease, increased HCMV-specific CD4+ lymphocytes response have been observed after initiation of highly active antiretroviral treatment (HAART). However, CD4 T cell count is only one the other factors related to HCMV virulence. In addition, the amount of circulation cytomegalovirus DNA is predictive of cytomegalovirus end-organ disease [39,40].

HCMV is a common pathogen that influences the outcome after transplantation. HCMV infection is associated with an increased predisposition to acute and chronic allograft rejection accelerates the occurrence of number of other opportunistic infection, as well as reduced overall patient and allograft survival. A consistence feature of HCMV infection in allograft recipients is the temporal sequence associated with virus replication and disease. In solid organ allograft recipient’s virus replication and clinical symptoms are commonly observed several weeks following transplantation. The seemingly prolonged interval between transplantation and expression of acute disease syndrome remains unexplained but probably HCMV must first establish a productive infection and amplify its genome copy number prior to dissemination to distant sites. CMV disease occurs only if the T cell response in compromised, so the most common predisposing factor for the occurrence of HCMV disease after transplantation is the lack of an effective HCMV-specific immunity [41,42]. Current immunosuppressive therapies used to prevent the rejection of a transplanted organ have detrimental effects upon T lymphocytes and cell-mediated immune responses, resulting in increased susceptibility to CMV infection. Moreover, the majority of donors and recipients have latent CMV infection at the time of transplantation. Infection can occur as result of reactivation of latent virus or new infection from donor tissues. That is why donor CMV positivity, especially in the absence of prior recipient infection, is the most important risk factor for post transplant infection. It is clear that pre-existing immunity modifies the course of infection [48].

In addition to the role of HCMV-specific CD4+ and CD8+ T lymphocytes, there are data to suggest that functionality of the innate immune system contributes to HCMV disease pathogenesis. It was shown, that recipients with specific polymorphism in innate immune molecules known as Toll-like receptors were more likely to develop higher levels of HCMV replication and clinical disease [46].

Although active HCMV is well-known opportunistic infection in immunocompromised patients HCMV can be reactivated in patients with sepsis and septic shock not undergoing immunosuppressive therapy. It was demonstrated that active HCMV infection develops despite functionally active HCMV-reactive Th1 cells. The hyperreactive inflammatory phase matched by increased levels of proinflammatory cytokines (e.g. TNF-α, IL-6), arachidonic acid derivates (e.g. prostaglandine and thromboxane), and chemokines, contributes to HCMV reactivation [43,44].

Importance of laboratory diagnosis of HCMV infection in immunocompromised patients

Reactivation of HCMV remains a serious problem in immunosuppressed individuals. An important proportion of immunodepressed patients are latent carriers of the virus and the lack of cellular immunity predispose these patients to an active infection in which the virus is replicating. Consequences for the immunodepressed patients are widely variable, ranging from completely asymptomatic infections to life-threatening situations. Therefore the identification of patients who are at high risk of HCMV disease is a more complex challenge for the laboratory.

Until now, serological test have been proven the most useful. The HCMV IgG results indicate past HCMV infection, while the finding of IgM may reflect a recent infection or reactivation [45,46]. Nevertheless, there is a continuous effort to develop more HCMV-specific immune-based methods, which may be of benefit in the control of HCMV disease. Because of their speed, sensitivity, and specificity, molecular diagnosis assay, resp quantitative RT-PCR testing, are increasingly used as a marker for HCMV reactivation [47]. However, the current data indicate that sometimes even active HCMV disease does not always correlate with viral load detection and a negative PCR result does not exclude HCMV end-organ disease [48].

T cells are crucial for the control of HCMV in infected individuals. Several methods are available to measure the number, diversity, differentiation and function of HCMV-specific T cells. These are predominantly flow cytometry techniques such as measurement of major histokompatibility complex class I- peptide tetramer binding, intracellular cytokine and chemokine release, cytotoxic potential and T-cell proliferation. Enzyme-linked immunosorbent assay spot (ELISPOT) can also be used to measure cytokine production at the single level [48,49].

It has been shown that cytomegalovirus IFN-γ production correlates with protection against HCMV reactivation. Several cells of the immune system synthesize and secrete IFN-γ upon stimulation, including CD4, CD8n and natural killer cells. Although the association between IFN-γ and protection against cytomegalovirus reactivation does not identify the cell type that mediates the protective effect, it characterizes the protective response as T helper cell, resp. Th type 1. Assays that detect the production of IFN-γ following stimulation with whole CMV antigens or CMV peptides have previously been used to identify the presence of HCMV-specific function/immunity and has been correlated with protection against HCMV reactivation disease in HIV-infected and transplanted individuals. One of the new, high throughput quantitative assays to detect HCMV-specific CD8+ T cell immunity is QuantiFERON®-CMV assay (Cellestis) which measures IFN-γ production in response to a range of previously defined CD8+ T cell CMV epitopes [40,50,51].
Great attention is recently been given to T regulatory cells (Treg). It has been shown that week regulatory T cell response might maintain high-generalized immune activation, potentially contributing to CD4+ decline even in the absence of clinically detectable viremia [52].

The immunological aspects of HCMV infection is very complex and displays a broad heterogeneity. Current management of HCMV reactivation and HCMV disease HCMV elicits both humoral and cellular immune responses, although the latter appear more critical for viral control. Knowledge of the characteristics of HCMV-specific CD8+ T cells as well as functional cell activity characterized by cytokine production might also be considered in diagnosis, monitoring and therapy of HCMV disease.

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