

Review Article

Dynamics of Persistence and Latency of Cytomegalovirus Implicate Altered Immune Reactivity and Entry Mechanics of Virus within Host Cells

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Abstract

Paramount considerations of persistence of cytomegalovirus presence and infection within humans are central issues in the realizing of pathways of host-cell infection and of potential impact on a potentially compromised immune response. In such relative context, whole organisms are central mediated series of potential subsequent response to exposure to infecting CMV organisms. The dimensions for promoting reactivation of persistent CMV infection is a key series of mechanisms that accounts for the central importance of cytomegalovirus infection in the transplantation of both solid organs and of patients who receive hematopoietic stem cell transplants. Latency of CMV remains enigmatic in terms related to viral persistence in cells and tissues. Entry mechanisms of CMV may play an important role with regard particularly of receptor-mediated systems versus endocytotic transfer across the host cell membrane.

Introduction

Reactivation of latent cytomegalovirus, particularly in immunocompromised patients such as HIV-infected patients, is a significant mechanism of disease-related pathology in various clinical settings. Spiral ganglion neuron apoptosis is an important mechanism in cytomegalovirus-induced sensorineural hearing loss [1]. There is also evidence of such mechanism to be significant in patients undergoing organ transplantation. The myeloid stem cell and the bone marrow progenitor cells have been shown to contain latent CMV and therefore to act as potential contributors to CMV reactivation of the latent virus. Human CMV latency in the myeloid cell lineage is sustained by repressive histone modifications around the major immediate early promoter [2].

Cytomegalovirus Disease

A sharp distinction has to be drawn between CMV infection and CMV disease as biomarkers of active infection such as replicating virus in urine or body fluids, or antigenemia, may not be associated with disease to organs within the host organism.

Infections within humans are central issues in realizing pathways of CMV disease even in patients who are shown to shed virus in body fluids or who show the presence of replicating virus.

Viral Replication

Often, a given individual may show the presence of multiple different genetic variants of the CMV virus. Hence, there would arise a need for the understanding of various mechanisms that

allow replication or suppression of this virus within specific biologic and clinical contextual settings. During CMV infection, the cyclic GMP/AMP synthase senses DNA with the formation of cyclic di-nucleotide cGAMP, triggering type 1 interferon response [3]. With regard particularly to receptor-mediated systems versus the need for development of more effective antivirals there is a need to prevent replication and infection by cytomegalovirus as in post-transplant patients.

Opposing roles of protein isoforms that are encoded by the UL136 gene regulate latent and replicative viral states of infection [4]. Immunosuppression following either solid organ transplantation but particularly also in hematopoietic stem cell transplantation plays a decisive role in promoting active CMV infection, as after blood transfusion or infection transplanted by the organ transplant itself.

Immune System Evasion

The ability for CMV to evade the immune system in many subset types of human patients is a central issue that may inherently relate to the evolution of latency of the infecting non-replicating virus in different organ systems. Latent CMV infection may accelerate TCR repertoire restriction, loss of CD28, peripheral T-cell proliferation and aberrant IFN gamma responses in CMV-positive arthritis patients [5]. In such context, the cooperative effects of ongoing CMV infection with other agents that suppress or impair immune efficiency or efficacy may render available mechanisms that promote persistence of virus within various organs. CMV influences most of the immune parameters in healthy individuals, including Natural Killer cells [6].

Rare codons and their iteration along viral sequence may constitute

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major constrains that lock cytomegalovirus translation in the viral latent phase [7]. Such conditions may operate also in very low birth weight newborns born to mothers who are HIV-1 infected.

Latency

The contextual conditions of latent CMV virus and of potentiality for active viral replication play an important role in the maintenance and reactivation of latency and the entry and replication of CMV within the blood and within body fluids. Successful viral colonization depends on the virus's ability to establish and more specifically reactivate latent CMV [8]. In this regard, the presence of virus in urine has been considered particularly significant in defining the presence of CMV in newborns suffering from congenital CMV infection. Such a premise indicates the relevance of potential blood stream spread of the virus within a systemic spread series of mechanisms.

Organ Transplantation

The transfer of organ transplants from sero-positive donors to sero-negative recipients is commonly associated with sero-conversion of the recipient host and with the clinical onset of CMV infection and clinical disease in these recipients. Reactivation of immediate early gene expression and epigenetic reprogramming of the major immediate early promoter are mediated probably by activated binding of transcription factors to AP-Q and NF-kappa B [9]. It is possible to consider innate and adaptive immune systems as cooperative partners in ongoing attempts at control of CMV infection. The distributional array of various subsets of cell-mediated components of the immune response likely follow systems in enhancing also antibody-mediated systems of response in these patients.

Antigenemia

System arrays of determining antigenemia are related particularly with the presence of replicating cytomegalovirus within neutrophils found in the buffy coat of blood, and also to a lesser extent in the mononuclear cell fraction. US28, a multifunctional lytic protein, encoded by CMV is expressed during latency and may be implicated in hematopoietic progenitor cells [11].

It is therefore significant to consider the development of systemic infection by the virus in relation to primary and secondary viremic phases of the evolving infection in terms of subsequent emergence of active viral replication, persistence, and also of otherwise latency phenomena. Gene expression profiles that imply cell-autonomous intrinsic defenses may be the most effective immune control measure against latent viral reservoirs [11].

Congenital Infection

The possible complications of CMV infection in congenital cases are particularly relevant to the central nervous system and retina and may include many other organ systems as a result of the systemic spread of the virus within the fetus and newborn. The microcephaly, calcifications periventricularly, splenomegaly, hepatomegaly and also hepatitis, pneumonitis, encephalitis all would arise within

the setting conditions of systemic spread of virus after placental transfer. It is within the conditioning physiologic systems of the early pregnancy phase that clinical CMV disease will arise in the fetus affected by congenital CMV infection.

Particular relevance has to be paid to significant immunologic compromise affecting the infected individual patient once the CMV gains access to the blood stream and various organ systems. A highly diversified repertoire of immediate-early-1 protein-specific CD4 T cells targeting multiple epitopes is usually present in healthy carriers of CMV [12]. The endothelial cells are particularly susceptible to cytomegalovirus infection, and this may relate to the spread within the blood-stream. The presence of infected endothelial cells circulating within the blood has been correlated with the presence of active CMV infection and also with clinical CMV disease. Also, multiple foci of necrosis and of cell loss in such a setting would correlate with the organ dysfunctionalities found in patients suffering from systemic CMV infection.

Pathogenesis

Particularly significant, therefore, in the pathogenesis of CMV disease is related to multi-organ involvement in determining either latency or active infection and progression of the CMV infected state. Distinct sites of cellular latency could exist in the human host and multiple latent phenotypes may impact differently on the biology of the CMV *in vivo* [13]. Extracellular vesicles secreted by infected cells may play an important role in immune system evasion and disease pathogenesis.

Parameters of latency would arise in terms of substantial immune suppression as mediated particularly by cytotoxic, T-cell subsets and also by Natural Killer Cells. Latent herpes virus infections alter immune homeostasis [14]. Also significant would appear to be the responsiveness of the cytokine/chemokine systems and of the inflammatory pathways within the individual organs that are exposed to circulating cytomegalovirus.

Viral Persistence

Persistence of the CMV infection is a central issue that determines clinical and pathogenic outcome. The human CMV expresses during latency only a subset of its microRNAs, which would indicate that they play an important role in maintenance and reactivation of latency [15]. This is demonstrated by the high rate of re-activation of post-transplant infection in patients who have had their antiviral regimens stopped after a 4-6 week period of antiviral treatment; this is true both in cases treated post-transplant as a prophylactic measure or in a preemptive setting. In such cases, late-onset reactivation of the cytomegalovirus has proved a common problem in post-transplant patients, a problem that is often only partly solved by sustained and more prolonged administration of the antiviral agents after operative transplantation.

These considerations may be suggestive of the great importance of non-specific anti-viral actions of the immune system and of the cytokine/chemokine systems in suppressing CMV reactivation and replication. Direct contact with virus-infected endothelial cells

activates CD11c(+) dendritic cells with reversible suppression of CMV replication at the level of immediate early gene expression through the action of type 1 Interferon [16]. Within such context, the inflammatory response within individual organs exposed to significant viremic spread of the organisms would play a decisive role in transforming persistent viral replicative steps of infection to the onset and progression of clinical CMV disease states. Such a postulate would apply especially also to cases of congenital CMV infection whereby inflammatory responses may be ineffective biologically.

Inflammation

Inflammatory parameters of biologic efficiency and efficacy in viral clearance therefore may play a series of contrasting potential roles in either controlling CMV spread and replication, on the one hand, and also in inducing injury to exposed organs and tissues as infection becomes established within parenchymal cells. Promyelocytic leukemia nuclear bodies are recognized as nuclear protein accumulations mediated intrinsic cellular defense against viral infections via chromatin-based mechanisms, but their role in control of herpesviral latency is still controversial [17].

Viral Transcription

A series of sequential step-by-step processes of replication and production of virally-encoded proteins is demonstrated by cytomegalovirus that infects endothelial cells and parenchymal organ cell constituents, as is typically shown also by other Herpes viruses. 1,25-dihydroxyvitamin D₃ induces lytic replication marked by up regulation of CMV gene expression and production of infectious virus [18]. The species-specificity of induced CMV infection is an essential facet in the overall dynamics of potential spread of the organisms to potential hosts exposed to body fluids containing the virus. Latent infection of primary CD34(+) progenitor cells by human CMV results in increased survival in the face of pro-apoptotic signals [19]. Understanding the dynamics of such species-specificity in susceptibility to the virus is an important step in considering potential mechanisms of protection from CMV infection [20]. The evasive mechanisms deployed by cytomegalovirus with regard to the immune system is a cardinal consideration in determining the potential establishment of primary and secondary viremic phases of the infectious process. The prototypical CMV enhancer, in a restricted time-gated manner, co-opts, through DNA regulatory mimicry elements, innate-immune transcription factors that drive viral expression and replication in spite of an active pro-inflammatory antiviral series of responses [21].

Immune Response

The adaptive immune response is ineffective in preventing a persistent state of CMV infection within the organism and is significant in terms of cooperative operability of the cell-mediated immune responses. In such measure, antibody to the viral envelope glycoproteins would permit, in many instances, for the emergence of latent forms of the virus that may subsequently re-activate infection if immune suppression supervenes. In contrast

to primary lytic infection or reactivation that is associated with a regulated cascade of expression of all viral genes, latent infection involves a much more restricted viral transcription program [22]. In this regard, also, it is important to consider the increased rates of opportunistic infections by such organisms as *Pneumocystis*, *Aspergillus* and other fungi that may supervene with ongoing CMV infection in patients with AIDS or other forms of immune compromise.

Concluding Remarks

The dynamics of the whole host in infection by the cytomegalovirus relates to the overall systems of viremic and body fluid spread of the virus relative to systems of possible persistence and future reactivation of such latent virus.

Latency and persistence of infection are hence meaningful in terms of biology of immune evasion that characterize the further participation of systems of essential progression and of implied dynamic consequences of sero-conversion in particular. Within such micro-environmental milieu, the entry of CMV either via cell receptors (heparan sulfate, integrins and Platelet-Derived Growth Factor receptor) or via endocytosis may allow a permissive or non-permissive series of cellular events characterizing dynamics of active viral replication or induced latency of the virus. Paramount considerations may relate, in particular, to turnover transport mechanics from the nucleus to the cytoplasm of the infected host cells. In this regard, the derivation of the viral envelope from the nuclear membrane may prove crucial to subsequent spread within the blood stream in terms of the secondary viremic phase of CMV infection and disease.

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