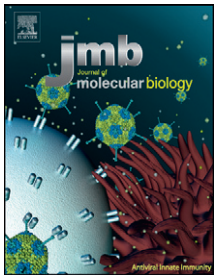

The Tiers and Dimensions of Evasion of the Type I Interferon Response by Human Cytomegalovirus

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Abstract

Human cytomegalovirus (HCMV) is a member of the β-herpesvirus family that invariably occupies hosts for life despite a consistent multi-pronged antiviral immune response that targets the infection. This persistence is enabled by the large viral genome that encodes factors conferring a wide assortment of sophisticated, often redundant phenotypes that disable or otherwise manipulate impactful immune effector processes. The type I interferon system represents a first line of host defense against infecting viruses. The physiological reactions induced by secreted interferon act to effectively block replication of a broad spectrum of virus types, including HCMV. As such, the virus must exhibit counteractive mechanisms to these responses that involve their inhibition, tolerance, or re-purposing. The goal of this review is to describe the impact of the type I interferon system on HCMV replication and to showcase the number and diversity of strategies employed by the virus that allow infection of hosts in the presence of interferon-dependent activity.

Introduction

Human cytomegalovirus (HCMV; Human Herpesvirus 5), a member of the β-herpesvirus subfamily, is an extremely widespread human pathogen. The virus contains a linear double-stranded DNA (dsDNA) genome of approximately 250 kb that encodes over 200 and perhaps as many as 751 [1] protein products and 14 microRNAs [2]. The enveloped virion contains a 105-nm icosahedral nucleocapsid surrounded by a proteinaceous tegument layer that assembles in the nucleus. The lipid bilayer contains nine virally encoded glycoproteins that are variably necessary for cellular entry. By all measures, HCMV is an evolutionarily successful pathogen with levels of seroprevalence varying between 40% and 100% in a manner that closely relates with socioeconomic conditions (reviewed in Ref. [3]). Like other herpesviruses [e.g., Varicella Zoster virus, Herpes Simplex viruses (HSV), Epstein-Barr virus], HCMV infects hosts for life and cannot be cleared by immunological processes or antiviral drugs. Thus, the virus is able to establish a latent infection involving limited viral gene expression during which no viral progeny is synthesized. However, spontaneous reactivation of productive replication can occur in response to immune abnormalities such as an immunocompromised state or pro-inflammatory signals. While latency hematopoietic myeloid tissues represent a key site of latency (and reactivation occurs from the derivative macrophages and dendritic cells), the virus is capable of replication in numerous and diverse cellular types including fibroblasts, endothelial cells, smooth muscle cells, neuronal cells, trophoblasts, epithelial cells, and hepatocytes. Importantly, cytomegaloviruses are highly species specific, and as a result, no animal model supports HCMV replication.

Acute and chronic infection with HCMV is largely asymptomatic in healthy hosts. This effect derives from millions of years of co-evolutionary fine-tuning that have molded the virus into one that employs a low virulence life cycle and thus a protracted potential transmission period. However, when hosts are immunologically underdeveloped or otherwise impaired [especially during tissue transplantation and human immunodeficiency virus (HIV)-associated immunodeficiency], the virus can cause serious disease. Congenital HCMV infection affects up to 40,000 children per year in the U.S. and is the leading infectious cause of deafness and other neurodevelopmental disorders

including microcephaly and cerebral palsy (see Ref. [4]). In immunocompromised patients, HCMV can cause severe opportunistic infections. In HIV-infected individuals, primary HCMV can lead to numerous acute conditions including hepatitis, esophagitis, gastritis, encephalitis, pneumonitis, and enterocolitis [5], a pathological diversity related to the virus' broad tissue tropism. Importantly, HCMV retinitis including retinal necrosis is especially common during HIV disease, accounting for ~85% of all such cases [6]. Immunosuppression associated with donor/recipient serostatus during solid organ and hematopoietic stem cell transplantation is similarly linked to tissue invasive HCMV diseases. HCMV is significantly correlated with diminished graft survival during solid organ transplantation [7] and artery stenosis [8]. Allogeneic hematopoietic stem cell transplantation is associated with reactivating productive infections and late-developing HCMV disease. Numerous studies tie HCMV to multiple chronic inflammatory disease states of healthy hosts including cardiovascular disease [9], cancer [10], cognitive decline [11], and functional impairment [12].

The immune response to HCMV is broad with respect to the immune cells and processes involved and continuously active for the duration of the infection. Antiviral host responses to HCMV begin quickly after virus-cell contact with pre-existing cellular factors such as nuclear domain 10-associated proteins (e.g., PML, Sp100, hDaxx, ATRX) acting to prevent initial viral gene expression (reviewed in Ref. [13]). Virus-cell contact involves interaction with a growing list of pattern recognition receptors (PRRs; discussed below) that initiate intracellular signaling and consequent expression and secretion of numerous immunologically active cytokines and chemokines [14]. Humoral responses involving production of neutralizing antibodies (predominantly targeting virion envelope glycoprotein B) invariably occur during infection, although evidence supporting their importance in control of cytomegalovirus is largely from non-HCMV animal models [15,16]. It is also widely accepted that T-cell-mediated immunity constitutes the primary mechanism by which HCMV infection is controlled (see Ref. [17]), a fact that is consistent with pathogenic manifestations described in an immunocompromised state. This control includes the activities of both CD8+ and CD4+ T-cells; remarkably, the proportion of these cells in peripheral blood directed toward HCMV-specific antigens can be up to 40% in aged hosts [18,19]. The impact of this multi-pronged attack on HCMV replication is the employment of diverse immune evasion phenotypes to counteract the antiviral effects thus ensuring persistent infection (see Ref. [20]). The large genome size of the virus has enabled it to acquire, optimize, and implement a multi-faceted, often redundant array of immune evasion strategies that target virtually all examined functions of the antiviral immune response.

Interferon and the Antiviral Response

Interferons are cytokines that are crucial for limiting viral replication at the site of infection and for coordinating adaptive responses that lead to the development of specific, long-lasting immunity. IFNs are composed of three physiologically distinct types (I, II, III). Type I IFNs include IFNβ, 13 IFNα subtypes, IFNτ, IFNκ, and IFNω that are primarily responsible for generating tissue states refractory to virus replication via paracrine induction of antiviral effector genes [IFN-stimulated genes (ISGs)]. They also coordinate functions of cellular immune constituents such as natural killer (NK) cells, dendritic cells (DC), T-cells, and B-cells and promote neutrophil survival, NK cell activation, dendritic cell maturation, T-cell proliferation, and B-cell differentiation [21–25]. Type I IFN also enhances the expression of molecules important for directing inflammatory and adaptive immunity such as major histocompatibility complex class I, CD38, interleukins (BLyS, IL-6, IL-10, and IL-15), and multiple chemokines [26–30]. As such, type I IFNs assume both direct and indirect roles in antiviral immunity.

IFNα/β activate downstream signaling pathways (discussed below) by binding to the IFNα receptor 1 and 2 complex (IFNAR1 and IFNAR2), which is ubiquitously expressed on all cell types [31]. IFNγ is the sole type II IFN, and while it is capable of upregulating directly antiviral genes, its broader function involves immune cell (NK cell, macrophage, B-cell) activation. Type III IFNs, including IFN-λ1 (IL-29), IFN-λ2 (IL-28A), and IFN-λ3 (IL-28B), activate signaling pathways that are highly similar to type I IFNs but through a distinct receptor complex (IL-28R1 or IFN-λR1 and IL-10R1) [32,33]. This review will focus largely on the directly antiviral effects of type I IFNs, their relevance for replication of HCMV, and the strategies employed by the virus to evade, withstand, or co-opt these responses.

The importance of IFNs combating cytomegalovirus and herpesviral infection is exemplified in reports of animals and humans carrying inactivating mutations in the IFN receptors or associated signaling molecules. Mice deficient in IFN responses exhibit lethal susceptibility to murine cytomegalovirus (MCMV) infection [34]. Moreover, homozygous mutations in the signaling molecule STAT1, which is an essential downstream factor in the IFNα/β- and IFNγ-signaling pathways (see below), are associated with lethal outcomes from infection with multiple herpesviruses including HSV-1 [35], HCMV [36], and Epstein-Barr virus [37]. Importantly, recombinant IFNα has also been used therapeutically to successfully control HCMV-induced retinitis during AIDS [38] and to control viremia following congenital infections [39]. These observations demonstrate the importance of properly functioning type I IFN-dependent physiological effects for controlling cytomegalovirus infection.