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Review

Modulation of the innate immune response by human cytomegalovirus

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ABSTRACT

The interplay between human cytomegalovirus (HCMV) and the innate immune response is a critical process that has attracted the attention of many research groups. The emerging scenario is that the immune response of an HCMV-infected host is mediated by a plethora of viral DNA sensors acting as pattern recognition receptors (PRRs), which are capable of inhibiting indirectly viral infection through the activation of two distinct downstream signaling cascades. The first one triggers the production of cytokines, chemokines and interferons (IFNs), while the second one leads to inflammasome complex formation, which in turn promotes the maturation and secretion of pro-inflammatory cytokines such as interleukin-1β (IL-1β). An additional first line of defense against HCMV is represented by a multiplicity of constitutively expressed restriction factors that inhibit viral replication by directly interfering with the activity of essential viral/cellular genes. Here, we take a closer look at some of the most representative intrinsic restriction factors involved in HCMV infection (e.g. IFI16, ND10 complex, viperin and APOBEC3) and review our current understanding of the mechanisms that HCMV has evolved to counteract both IFN and inflammasome responses.

1. Introduction

The human cytomegalovirus (HCMV) is a β-herpesvirus with the largest genome of all known human viruses (~235,000 bp) able to cause lifelong infections in humans. In the developed world, 40–60% of individuals are infected by time they reach adulthood, with seroprevalence approaching 100% in some populations (Cannon et al., 2010; Griffiths et al., 2015).

Although initial HCMV infection is often asymptomatic in healthy individuals, it can cause severe and sometimes fatal disease in immunocompromised individuals and neonates (Britt, 2017). In this regard, HCMV is one of the most common cause of birth defects resulting from an infectious agent, with 20% of congenitally infected infants exhibiting permanent neurological sequelae, including blindness, deafness and/or mental disability (Rawlinson et al., 2017). HCMV can also cause severe diseases in organ transplant recipients and AIDS patients after either primary infection or reactivation of latent infection (Navarro, 2016). To make things worse, immunosuppressed individuals are at potential risk of HCMV primary infection or re-infection and, eventually, reactivation of their endogenous latent virus.

Even though a vaccine is not yet available, HCMV can be treated with several inhibitors of viral replication. Five compounds are currently licensed to treat established HCMV infections: ganciclovir (GCV), its oral prodrug valganciclovir (VGCV), foscarnet (FOS), cidofovir (CDV) and fomivirsen (Ahmed, 2011). However, despite encouraging clinical outcomes, their use has been hampered by major associated adverse effects. One of these is represented by haematopoietic toxicity, which, along with long-term toxicity, low potency and poor bioavailability, limits the therapeutic efficacy of antiviral therapies in neonates and precludes their use in pregnant women (James and Kimberlin, 2016; Rawlinson et al., 2017). Another important issue concerning HCMV-related diseases management is the emergence of antiviral-resistant HCMV strains, especially in severely immunocompromised patients (Komatsu et al., 2014). Moreover, while these drugs are effective against the lytic replication cycle of HCMV, they do not affect the latent virus (Poole and Sinclair, 2015; Wills et al., 2015).

Throughout evolution, HCMV has acquired a number of different strategies to modulate and evade the human immune response, thereby achieving high infection efficiency and widespread dissemination in the host body (Christensen and Paludan, 2017; Noriega et al., 2012). Nevertheless, the human immune system is still capable of building a robust immune response against HCMV infection. This is clearly supported by the observation that all primary infections in immunocompetent hosts are virtually asymptomatic, whereas HCMV disease occurs mostly in individuals with an immature or compromised immune system. (Luecke and Paludan, 2015).

In this review, we will discuss the interplay between HCMV and the innate immune response together with the multiple strategies devised by HCMV to escape from immune surveillance. We will also highlight the different DNA sensing mechanisms and the viral restriction factors

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(RFs) involved in keeping this virus in check. Finally, we will focus on two of the main players of innate immunity, the interferon (IFN) and inflammasome systems.

2. Sensing HCMV by the host DNA sensors

Infection of host cells by HCMV triggers rapid intracellular innate immune responses largely initiated by pattern recognition receptors (PRRs), germline-encoded molecules able to detect evolutionarily conserved pathogen-associated molecular patterns (PAMPs) (Brubaker et al., 2015). During HCMV infection, viral DNA is detected by a myriad of PRRs that promote the activation of antiviral responses to protect the host cells. Infected cells detect the presence of HCMV very early, and by 4–8 hour post-infection they start producing pro-inflammatory cytokines, such as type I IFN (IFN-I) and activating RFs to antagonize viral replication (Luecke and Paludan, 2015; Orzalli and Knipe, 2014).

PRRs can be divided into two main groups depending on their subcellular localization. The first one consists of PRRs located on the plasma and endosomal membranes able to recognize extracellular PAMPs. These include Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) (Dambuza and Brown, 2015; Takeuchi and Akira, 2010; West et al., 2012). These membrane-bound PRRs are largely expressed by antigen presenting cells, such as macrophages and dendritic cells. The second group includes intracellular PRRs found in the cytoplasm or nuclei of mammalian cells. These include NOD-like receptors (NLRs) (Kim et al., 2016), retinoic acid-inducible gene-I (RIG-I), I-like receptors (RLRs) (Loo and Gale, 2011), cyclic GMP/AMP synthase (cGAS) (Chen et al., 2016), AIM2-like receptors (ALRs) (Dell'Oste et al., 2015; Huang et al., 2017a), and Z-DNA-binding protein 1 (ZBP1), also known as DNA-dependent activator of IFN-regulatory factors (DAI) (DeFilippis et al., 2010).

In the following sections, we will review the main PRRs involved in HCMV DNA sensing activity (Fig. 1).

2.1. TLR

The first evidence of a role played by TLR signaling during the innate immune response triggered by HCMV was obtained while studying TLR2. In the "classic" TLR2 pathway, PAMP binding to the receptor induces the enrollment of the adaptor protein MyD88 and interleukin (IL)-1 receptor-associated kinases (IRAK-4 and -1) via death domain interactions. The following phosphorylation and ubiquitination cascades switch on the NF-κB and MAP kinase (MAPK) pathways that in turn trigger the transcription of numerous pro-inflammatory cytokines such as IL-6, tumor necrosis factor (TNF)-α and IFN-β (Oliveira-Nascimento et al., 2012). In particular, TLR2 was shown to recognize HCMV gB and gH on the plasma membrane, resulting in the activation of the NF-κB pathway in a MyD88-dependent manner, followed by the production of inflammatory cytokines, such as IL-6, IL-8, IL-12 and IFN-β (Barbalat et al., 2009; Boehme et al., 2006; Compton et al., 2003; Juckem et al., 2008). Consistent with these results, impaired TLR2 function is often correlated with clinical cases of HCMV. Specifically, liver transplant recipients carrying an inactivating point mutation in the Toll-IL-1 receptor (TIR) domain of TLR2 show a higher HCMV load, indicating that TLR2 recognition is critical in controlling HCMV infection (Kijpittayarit et al., 2007). Recently, HCMV miR-UL112-3p (HCMV-encoded miRNA) has been associated with efficient down-regulation of endogenous TLR2 during infection and significant inhibition of its downstream signaling cascade (Landais et al., 2015).

In addition to TLR2, endosomal TLR3 and TLR9 are also involved in HCMV DNA detection. In this regard, a recent study has shown that HCMV infection upregulates TLR2, TLR3 and TLR9 in monocytes in the presence of the human scavenger receptor A type 1 (SR-A1) (Yew et al., 2010). TLR2, Lyn kinase and the p35 subunit of IL-12 were all upregulated within 10 minutes of HCMV infection in THP-1 monocytes. Interestingly, inhibition of Lyn kinase, which is correlated with SR-A1, causes the inhibition of TLR9 signaling and moves the response to both a primarily TLR3 driven IFN-β response and a non-canonical TLR3 driven NF-κB response. Additionally, CpG-B-mediated stimulation of TLR9 can enhance HCMV infection in fibroblasts through an unknown mechanism, indicating that TLR9 signaling plays an important role during viral replication (Iversen et al., 2009). Finally, a particular polymorphism (T-1237C) altering the TLR9 promoter activity (Novak et al., 2007) has been shown to correlate with symptomatic HCMV infection in stem cell transplants (Carvalho et al., 2009).

Altogether, these results highlight the involvement of multiple TLR-associated pathways in the recognition of and response to HCMV.

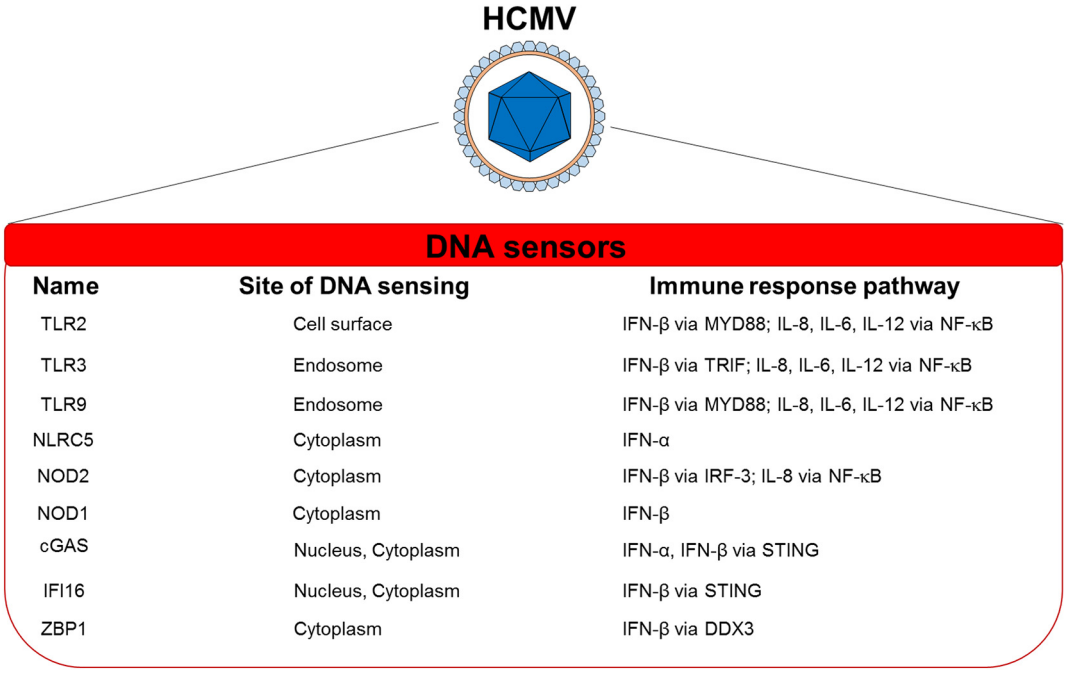

Fig. 1. Proposed HCMV DNA sensors.