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Roseoloviruses and their modulation of host defenses

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Human cytomegalovirus (HCMV), the prototypical human β-herpesvirus, encodes approximately 40 known gene products that function to subvert our host defense mechanisms. From HCMV, we have learned about interferon signaling, cytokine function, chemokine signaling, natural killer (NK) cells' cytotoxicity toward tumors and virus-infected cells, antigen processing and presentation, and protective initiation of the apoptotic signaling cascade. With each successive discovery of novel host evasion mechanism encoded by the cytomegaloviruses, we illuminate what these herpesviruses have learned over the course of their 100 MYr-long evolution with their hosts. As much as we have learned from HCMV, the other members of the human β-herpesvirus family, HHV-6 and HHV-7, are closely-related and yet largely unexplored. These viruses likely have much yet to teach us.

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Introduction

To achieve optimal reproduction and spread, viruses realign host cellular processes to create a more hospitable environment. Over the course of their co-evolution, viruses have pushed their hosts to develop and fortify an arsenal of sophisticated defense mechanisms. Mammalian hosts, for example, are able to immediately sense the introduction of foreign viral products. Recognition of these viral products provokes rapid upregulation of host innate immune response genes, including soluble cytokines and chemokines, which together influence almost every other aspect of the host response to pathogens. Shortly after cytokine release and signaling, host natural killer (NK) cells are activated to recognize and destroy virus-infected cells. The adaptive immune response then ensues, usually eliminating the virus-infected cells with cytotoxic T cells and neutralizing antibodies. If all else fails, individual infected host cells are programmed to undergo selfless sacrifice – apoptosis for the greater good.

The intimate relationships that occur between hosts and viruses that establish long-lived, latent, or persistent infections have further pushed the evolution of the host defense network. Herpesviruses, for example, after primary lytic infection, remain latent or persistent within the host throughout the life of the host. In so doing, they must necessarily interact with and evade host defense mechanisms. It is therefore not surprising that herpesviruses devote as much as half of their large (~125-240 kB) genomes to counteracting host defenses.

Here, we illustrate the individual cunning of the β-herpesviruses. Human cytomegalovirus (HCMV), one of the most stealthy, successful, and well-studied human β-herpesviruses, is an example of a virus that has fought - and seems to be winning - a long evolutionary battle to live, propagate and disseminate in the face of extensive and sophisticated defense mechanisms. But HCMV is not the only β-herpesvirus that seems to be winning this battle. Human herpesviruses-6A, -6B and -7 are arguably equally as ''successful'' as HCMV. While HCMV infects 50-80% of the US population by age 40, HHV-6A, HHV-6B, and HHV-7 infect over 90% of the population before the age of 6 [1,2]. Like HCMV, HHV-6A, -6B, and -7 also remain latent or persistent throughout the life of their hosts. HCMV, HHV-6A and -6B, and HHV-7 share a core set of essential β-herpesvirus genes involved in DNA replication, packaging, and encapsidation. The other, ''non-essential'' genes in the β-herpesvirus genomes are largely devoted to escaping host defenses. Indeed, our current understanding of host defense mechanisms is derived in part from the what we have learned from HCMV, and distantly related murine CMV. Study of these viruses has shed light upon interferon signaling, cytokine function, chemokine signaling, NK cytotoxicity toward tumors and virus-infected cells, antigen processing and presentation, and protective initiation of the apoptotic signaling cascade. With each discovery of novel host evasion mechanism encoded by cytomegaloviruses, we illuminate what these herpesviruses have learned over their 100 MYr-long evolution with their hosts. As much as we have learned from HCMV, the closely-related and largely unexplored HHV-6A,

HHV-6B, and HHV-7 would seem to have much still to teach us.

The host interferon response

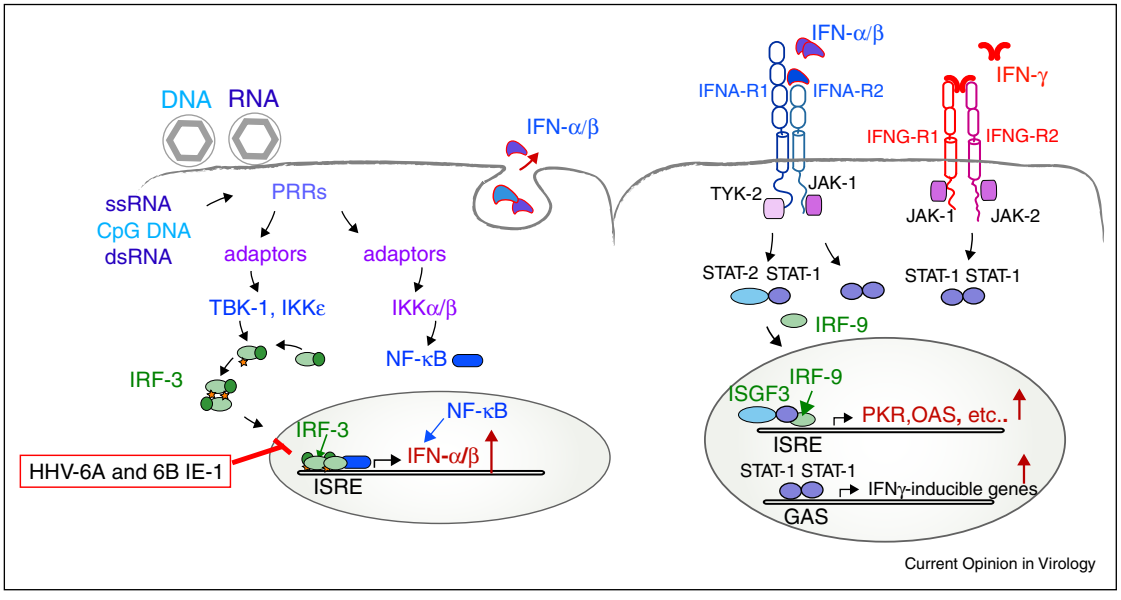
After recognition of uniquely foreign viral products such as dsRNA or cytosolic DNA by pattern recognition receptors, host signaling cascades lead to the IκB kinase- NFκB-, and IRF3/7/9-induced transcription of type I interferons (IFNα and IFNβ) (See Figure 1). Type I interferons signal through IFN receptors, JAK/STAT adaptor kinases, and ultimately use the STAT1/STAT2/IRF9 complex to induce transcription of myriad interferon-inducible genes. These interferon-responsive gene products, which include protein kinase R (PKR) and 2'-5' oligoadenylate synthase (OAS), induce an anti-viral state in the host, preventing viruses from usurping cellular protein synthesis machinery for the production of viral proteins. Type II interferon (IFN-γ), or ''immune'' interferon, is released by immune cells in response to cytokines. IFN-γ then stimulates the launch of an effective adaptive immune response, activating T and B lymphocytes.

To minimize the inhospitable environment they encounter upon entering the host cell, viruses encode multiple means of quelling the innate immune response. HCMV, for example, encodes 7 protein products that hamper the host interferon response (Table 1). HHV-6A and -6B have also been shown to impair interferon signaling: Jaworska, et al. have shown that the **HHV-6A and -6B IE-1** proteins may either prevent or disrupt the dimerization of IRF3, reducing the presence of IRF3 in the nucleus, and reducing transcription of IRF3-inducible genes downstream of IFNβ signaling [3••] (Figure 1).

Cytokine and chemokine signaling

Cellular proinflammatory cytokines IL-1β and TNFα participate in the host defense against viruses through recruitment of inflammatory cells and activate signaling cascades involved in both the innate and adaptive immune response. TNFα is secreted by activated macrophages, and binds to TNF receptors (TNFR) expressed on most tissues (for review, see [4]). TNFR signaling activates NFκB, and can induce fever, apoptosis, and inflammation, thus viruses benefit from developing means to downregulate the functions of inflammatory cytokines like TNFα and IL-1β. Lymphocyte trafficking to sites of infection depends upon the local presence of chemokines, chemoattractant cytokines which attract immune cells and play a role in the activation of their effector mechanisms.

Figure 1



The interferon response. Viral products (e.g.,single-stranded RNA, CpG DNA, or dsRNA) are sensed by pattern recognition receptors (e.g.,TLRs, RIG-I, IFI16, mda5) and a signaling cascade ensues, involving adaptor proteins, ultimately leading to interferon regulatory factor-3 (IRF-3) phosphorylation, which allows dimerization, translocation to the nucleus, and, with βcatenin and p300, binding to the interferon-stimulated response element (ISRE) to upregulate transcription of the type I interferons IFNα/β. IFNα or β is secreted and binds to IFNA-Receptors on neighboring cells, inducing another signaliing cascade mediated by JAK-1, TYK-2, and STATs. STAT-1, STAT-2, and IRF-9 comprise the interferon-stimulated gene factor-3 (ISGF3), which bind to ISRE and upregulate type I IFN-inducible genes, such as PKR and OAS. Also shown is the Type II IFN signaling pathway, induced by IFN-γ, mediated by JAK-1, -2, and STAT-1 homodimers. Type II IFN signaling results in upregulation of genes possessing an interferon-gamma activating sequence (GAS) element. HHV-6A and -6B IE-1 proteins prevent the dimerization of IRF-3, inhibiting interferon signaling.