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Viral manipulation of the host immune response

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Abstract

Viruses are obligate intracellular parasites that require a host for essential machinery to replicate and ultimately be transmitted to new susceptible hosts. At the same time, the immune system has evolved to protect the human body from invasion by viruses and other pathogens. To counter this, viruses have developed an arsenal of strategies to not only avoid immune detection but to actively manipulate host immune responses to create an environment more favorable for infection. Here, we describe recent advances uncovering novel mechanisms by which viruses skew host immune responses through modulation of cytokine and chemokine signaling networks, interference with antigen presentation and T cell responses, and preventing antibody production.

Introduction

A successful host immune response to virus infection requires the host to both contain the spread and eventually eliminate the virus. Innate defenses, such as interferons and other inflammatory cytokines, phagocytic cells like macrophages and dendritic cells (DC), and natural killer (NK) cells, play a role in the initial response to viral infection (Figure 1a). Activation of the adaptive immune response is critical for resolution of infection, with a T helper (Th) 1 CD4 T cell response driving the coordinated effort of CD8 T cells to recognize and kill infected, virus-producing host cells and B cells to produce antibody to neutralize and eradicate free virus. Avoiding immune clearance is a major factor in successful virus infection. While some viruses employ evasion strategies such as establishing latency or

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inducing syncytia formation to escape immune detection, other viruses take a more aggressive approach, actively distorting the immune response to make resolution of infection more difficult (Figure 1b).

Inflammatory Cytokines

Cytokines play a crucial role in intercellular communications, enabling the immune system to orchestrate responses to a wide variety of pathogens. Interleukin-10 (IL-10) is one of the most pivotal cytokines manipulated by viruses [1]. IL-10 suppresses inflammatory cytokines, impairs DC maturation, and inhibits effector T cell responses due to down-regulation of major histocompatibility complex (MHC) and co-stimulatory molecules on antigen presenting cells (Figure 2) [2]. Many viruses stimulate host cellular IL-10 production, including human immunodeficiency virus (HIV), hepatitis C virus, and hepatitis B virus, while other viruses, particularly herpesviruses and poxviruses, encode their own viral orthologs of IL-10 (i.e. vIL-10) [3,4]. Induction of host IL-10 is critical for supporting virus persistence during lymphocytic choriomeningitis virus (LCMV) infection in mice, and blocking IL-10 signaling facilitates virus clearance [5]. In rhesus macaques, reduced DC trafficking to draining lymph nodes, decreased CD4 T cell activation, and diminished antibody responses occur in animals infected with Rhesus cytomegalovirus (RhCMV) compared to a vIL-10 (vIL-10) deletion mutant [6], showing that vIL-10 has wide-ranging effects on both innate and adaptive immune responses during the course of infection. Immunizing macaques with a non-functional vIL-10 protein reduces virus replication at the site of inoculation, decreases shedding in urine and saliva, and stimulates production of neutralizing antibodies [7], suggesting that vIL-10 has potential as a therapeutic target.

For human CMV (HCMV), the role of vIL-10 may be more complex, with at least two [8] and as many as five [9] alternatively spliced variants of the vIL-10 transcript. The two main protein isoforms are known as cmvIL-10, produced during lytic infection, and latency associated cmvIL-10 (LAcmvIL-10), produced during both lytic and latent infection [8,10]. The full-length cmvIL-10 protein has been well-characterized to bind to the host cell IL-10R complex and induce immunosuppressive effects [3,11,12], whereas the truncated LAcmvIL-10 protein exhibits a more limited range of functions [10,13,14]. A mutant HCMV lacking vIL-10 was recently observed to be less efficient at establishing latent infection than the wild-type [15]. In addition, LAcmvIL-10 suppressed the cellular miRNA hsa-miR-92a leading to increased expression of both host IL-10 and MCP-1/CCL8 [15], mediating immune suppression that facilitates maintenance of latent HCMV infection. Understanding viral manipulation of the IL-10 pathway and downstream consequences may provide critical clues to requirements for viral persistence.

Other Inflammatory Mediators: Chemokine Signaling

While IL-10 is a highly conserved target, nearly every aspect of the chemokine system has been exploited by viral pathogens [16–19]. Manipulation of chemokine signaling networks can aid in virus dissemination, modulate host cell trafficking to inhibit immune clearance, or alter intracellular signaling to promote a favorable environment for virus replication (Figure 3). Chemokines direct the movement of leukocytes by binding to specific chemokine

receptors. CXCR4 and CCR5 were identified early on as critical co-factors for HIV entry into host cells [20,21], but signaling from these receptors is inhibited by the Kaposi's sarcoma-associated herpesvirus (KSHV)-encoded chemokine vMIP-II [22]. vMIP-II is a broad spectrum antagonist that hinders NK cell migration by blocking CCR5 and CX3CR1/fractalkine receptor signaling [23]. The ability of vMIP-II to antagonize both receptors permits exquisite control of the host immune response, as naïve NK cells express high levels of CX3CR1 [24], while mature NK cells down-regulate it concurrent with up-regulation of CCR5 [25]. Thus, KSHV is able to effectively block the migration and anti-viral activity of NK cells at two different stages through the actions of a single viral chemokine. The crystal structure of vMIP-II bound to CXCR4 has provided critical insights into the binding of the viral chemokine and several known CXCR4 inhibitors [26]. Understanding the structural basis for binding of the KSHV chemokine to CXCR4 could ultimately facilitate the development of effective viral entry blockers for HIV.

Besides KSHV, many viruses encode proteins with homology to chemokines and chemokine receptors [19,27]. The G protein of respiratory syncytial virus (RSV) contains a CX3C motif that mediates binding to cells expressing CX3CR1, reducing inflammatory cytokines and resulting in impaired innate and adaptive immune responses [28]. HCMV US28 has 38% sequence identity to human CX3CR1, binds CX3CL1/fractalkine and several other host chemokines [29], and exhibits both ligand-induced and ligand-independent constitutive signaling activity. Because CX3CL1 is tethered to the surface of endothelial cells by a long mucin-like stalk, binding of US28 to this chemokine may facilitate dissemination of virus-infected cells to distant host tissues. The crystal structure of US28 bound to CX3CL1 identified the molecular basis for constitutive signaling activity [30]. The key lies in the orientation of the DRY box residues [31], resulting in stabilization of the active state. HCMV US27 and KSHV ORF74 have similar modifications which likely convey constitutive signaling and enhanced pathogenesis [32,33]. Epstein-Barr virus (EBV) BILF1 not only interacts with host chemokine receptors to impair signaling [34] but also affects MHC expression [35], as discussed below.

CD4 T Cell Response

The adaptive immune system plays a critical role in the clearance of many virus infections. Viruses have evolved mechanisms to evade pathogen recognition by averting host innate cell responses that in turn also prevents optimal activation of the adaptive immune response. However, some viruses have developed mechanisms to specifically target and inhibit the adaptive immune response. CD4 T cell production of antiviral Th1 cytokines such as IFN- γ and TNF- α is critical for host defense. However, viruses have found ways to alter the CD4 T cell response by skewing the CD4 T cell response away from the Th1 phenotype. RSV has been found to influence the polarization of CD4 T cells into different phenotypes [36,37]. Both Th2 [38] and Th17 [39,40] cells contribute to RSV pathogenesis. However, the mechanism by which RSV alters the differentiation of the CD4 T cells remains unclear. The RSV fusion (F) protein has been implicated in mediating Th2 skewing in a strain dependent manner in vivo [37]. More recently, the RSV non-structural proteins NS1 and NS2 were found to play a role in altering CD4 T cell polarization [41,42]. NS1 inhibits MHC expression resulting in reduced CD4 T cell polarization [41]. NS1 also inhibits the

proliferation of Th17 cells while promoting activation of Th2 cells [42]. This data indicates that F and NS1 may play important roles in determining the CD4 T cell response that is induced following RSV infection and thus controlling the disease course.

In addition to altering the CD4 T cell response to prevent acute viral clearance, viruses may induce regulatory CD4 T cell (Treg) responses to maintain viral persistence. Recently, HCMV was found to induce IL-10 and TGF- β production by CD4 T cells specific to the latently expressed peptides but not in response to lytic derived peptides [43]. CD4 T cells specific for the latent proteins UL138 and LUNA isolated from healthy HCMV-infected donors express the Treg markers CD25 and FoxP3 while CD4 T cells specific for the lytic protein gB do not [43]. Previous studies with EBV have also reported the induction of a suppressive CD4 T cell response targeting latent genes [44,45]. It is unclear how these viruses induce a suppressive CD4 T cell response specifically targeting latent antigens while lytic antigens induce a conventional Th1 response. It is possible that the immunosuppressive environment created by expression of latent genes [13,15,46,47] promotes the activation of regulatory CD4 T cells. However, it is clear that viruses have developed effective mechanisms to alter the CD4 T cell response in order to prevent pathogen clearance.

CD8 T Cell Response

The CD8 T cell response plays a critical role in mediating viral control and clearance following an infection. However, like CD4 T cells, viral proteins can inhibit CD8 T cell activation and killing. Viruses have devised many tools to prevent MHC class I expression on infected cells to prevent CD8-T-cell mediated cytotoxicity. HCMV expresses a family of US2-11 evasion proteins that are expressed both early and late after infection to prevent MHC class I expression on the surface of infected cells [48]. Expression of these proteins prevents peptide transport [49], retains MHC class I molecules in the ER [49], and targets MHC class I molecules for degradation [50]. A recent publication noted that of the US2-11 family, specific expression of the HCMV proteins gpUS2 and gpUS11 were both required to reduce MHC class I expression on infected cells and inhibition of CD8 T-cell-mediated killing of virally infected cells [51]. However, not all MHC haplotypes are equally inhibited by these viral evasion proteins [52]. A recent paper identified human leukocyte antigen (HLA)-C restricted epitopes for CD8 T cells that are protective against viral infection [52]. This prevents HCMV from fully hiding from the CD8 T cell response. EBV is also able to down modulate MHC class I expression. Recent work has demonstrated that the viral G protein-coupled receptor BILF1 is able to inhibit expression of multiple HLA molecules [35]. BILF1 was found to bind to a specific amino acid sequence shared by both HLA-A and B but not HLA-C molecules on the MHC class I heavy chain targeting the protein complex for lysosomal degradation [35]. This mechanism may also be shared by the HCMV US2-11 proteins and could explain why HLA-C molecules are able to induce CD8 T cell responses. Virus-mediated alterations in MHC class I expression is a key mechanism for viral evasion of the CD8 T cell response.

B Cell Response

Antibody production by B cells helps to clear persistent viral infections and prevent reinfection. Viruses have developed many mechanisms to prevent effective B-cell-mediated viral clearance such as hiding within B cells, inhibiting B cell maturation, and altering B cell survival [53]. Recent studies have shown that influenza virus directly infects antigen-specific B cells in the lung resulting in the death of the infected cell and a reduced antibody response [54]. However, influenza virus infected individuals are still able to induce a neutralizing antibody response that prevents reinfection by the same strain. In contrast, the antibody response induced by RSV infection appears insufficient to prevent re-infection, particularly of the upper respiratory tract. A recent study tracking RSV infection in healthy adults noted a lack of RSV-specific IgA memory B cells [55]. The presence of nasal IgA did protect against viral replication in nasal passages in individuals that had a preexisting IgA titer while IgG did not [55]. However, very few of the individuals tested expressed RSV-specific IgA prior to challenge potentially due to the brief existence of the RSV-specific IgA memory B cells in response to RSV infection [55]. While it is unclear how RSV prevents an effective antibody response, the lack of antibodies is advantageous to the virus by allowing reinfection of individuals by closely related strains. Thus, preventing the development of a neutralizing antibody response can be beneficial for viral propagation.

Conclusions

Despite recent advances in our understanding of the various strategies utilized by viruses to evade and redirect host immune responses, there are still many gaps to be filled. Targeting of virus-encoded genes that mimic the actions of host cytokines and chemokines may represent an attractive anti-viral target. However, a deeper understanding of these complex virus-host interactions is necessary to enable us to develop safe, effective vaccines and immunotherapies.

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Highlights

- IL-10 signaling is a common target for altering a variety of immune responses.
- High resolution structures reveal how chemokine binding can alter cell signaling and migration.
- Impairing antigen presentation and T cell differentiation reduce antiviral effector activity.
- Blocking production of neutralizing antibodies is beneficial for preventing immune clearance.
- Viruses have ways to manipulate many immune responses to favor virus replication and persistence.

Figure 1. Elements of the anti-viral immune response and viral skewing of those responses

A) Virus infection of an epithelial cell leads to production of interferons, which recruit macrophages, dendritic cells, and natural killer cells to the site. Dendritic cells engulf dead cells and process viral antigen for presentation to CD4 T cells. A Th1 response with activation of CD8 T cells is most effective for elimination of virus-infected cells. Antibody production is also important for neutralizing extracellular virus, promoting phagocytosis, and blocking viremic spread to other tissues. Ribbon arrows represent anti-viral immune functions. B) Many aspects of the immune response are hindered by viruses, including production of IL-10 to reduce inflammatory cytokines and impair Th1 CD4 T cell activation. Viruses also prevent NK cell activation and migration, shift the balance away from Th1 responses toward Th2 CD4 T cells and Tregs, interfere with CD8 T cell killing, and inhibit antibody production. Thick arrows represent skewing of host immune responses, as described in the text.

Figure 2. Role of IL-10 signaling during virus infection

Many viruses stimulate production of host IL-10 upon infection to inhibit anti-viral inflammatory responses (HBV, HCV, LCMV), while other viruses encode their own ortholog of IL-10 to suppress anti-viral responses (HCMV, RhCMV, EBV, poxvirus Orf). The effects of IL-10 on monocytes and dendritic cells impact downstream immune activation by blocking inflammatory cytokines and down-regulating MHC and co-stimulatory molecules. Both IL-10 and vIL-10 form dimers that bind to the cellular IL-10R complex. LAcmvIL-10 is shown in brackets with a wedge missing because it is a truncated protein with a limited range of functions and it is unclear whether this protein forms dimers or interacts with IL-10R.

Figure 3. Modulation of chemokine signaling networks by viruses

An infected cell is shown expressing a chemokine receptor and various ways that chemokine signaling can be skewed are indicated. 1) Some viruses encode chemokines or induce production of host chemokines to attract susceptible cells as new targets for infection to aid in virus dissemination (RSV, HCMV). 2) Other viruses encode chemokine receptors that are expressed on infected cells, facilitating migration of infected cells to other sites in the host, to aid in the spread of virus (HCMV). 3) Viral chemokines and/or receptors may alter the activity of host chemokine receptors, preventing immune activation or migration (KSHV, HCMV, EBV). 4) Viral chemokine receptors may function as chemokine “sponges”, sequestering inflammatory chemokines and preventing recruitment of immune cells (HCMV). Host chemokine receptors may also be internalized, preventing the infected cell from being able to respond to chemokine signals.