Journal of Clinical and Experimental Transplantation

Mini Review Open Access

Organ Transplantation Consequences of Immuno Regulation of Human Herpesviruses

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Abstract

Human herpesviruses, such as cytomegalovirus, Epstein-Barr virus, HHV6, HHV7, and HHV8, herpes simplex virus (HSV)-1 and HSV-2, and varicella zoster virus (VZV), have formed intricate connections with the human immune system. This is characterized by the interaction between viral immune evasion mechanisms that encourage the onset of a chronic infection that lasts a lifetime and the induction of a broad moral and cellular immune response that prevents viral disease. In order to develop immunological strategies to prevent and control herpesvirus-associated diseases and understand why immunological dysfunction in transplant patients can lead to disease, as well as the immune parameters that control herpesvirus infection, it has been critical to comprehend the strategies the viruses use to evade immune recognition.

Keywords: Antiviral immunity; Cell-mediated immunity; Cellular immunity; Cellular immunology; Immunotherapy, Cytomegalovirus

Introduction

The ability of human herpesviruses to establish a lifelong latent infection in the host is one of a kind. This means that the virus can persist within specific host cells and avoid immune recognition by limiting viral gene expression. The productive phase of infection is activated in some clinical settings, leading to the lysis of the infected cell and the release of the virus's offspring. Because these viruses co-evolved with the human host, they developed a multifaceted antiviral immune response. This response is driven by the complex array of strategies these viruses use to persist in the face of these obstacles. Both innate and adaptive immunity, as well as humoral and cell-mediated immune responses, play a crucial role in controlling both primary and latent infection, according to human and murine models of herpesvirus infection. Before the establishment of an adaptive response, natural killer (NK) cells and other in-nate mediators play a crucial role in controlling infection. These mediators control and destroy virally infected cells while CD4+ and CD8+ T cells control and limit viral spread. Despite this, immune control is not enough to stop latency from developing [1,2].

During primary and persistent infections, the human immune system is generally successful at controlling infection and minimizing symptoms; However, herpesviruses are the cause of a number of diseases, including primary infection-related conditions and malignancies triggered by some herpesviruses' oncogenic properties. Due to an impaired adaptive immune system, immunocompromised individuals, such as transplant patients on immunosuppressive medication and HIV-infected individuals, are more likely to experience these clinical issues. The possibility that herpesviruses play a role in rejection of organ transplants is of particular significance. In fact, cytomegalovirus (CMV) can cause cytopathic effects in capillary endothelial cells and glomerular and tubular epithelial cells during a renal transplant. In addition, CMV infection can cause an increase in MHC class I expression on the engrafted tissue, which can trigger acute rejection by activating cytotoxic T cells and simultaneously stimulating alloantigens. It is now well known that people with immunosuppression frequently develop severe clinical complications caused by the herpesvirus in people with T cell immunity, highlighting the significance of cell-mediated immunity in controlling herpes infections after the latency period has passed [3,4].

In this review, we summarize our knowledge of global regulation of human herpesviruses, its potential implications for human transplantation, and how this knowledge can be used to develop novel immunotherapeutic tools for transplant patients' treatment of herpesvirus-associated diseases.

Method

In the early stages of herpesvirus infection control, innate immunity is very important. The early production of inflammatory cytokines and chemokines, which both promote the induction of an adaptive immune response and provide antiviral effects (see box 1 for mediators of innate immunity), is traditionally thought to be the hallmark of innate inflammation. Signaling via pattern recognition receptors, which include the family of Toll-like receptors (TLRs), is crucial for triggering innate inflammation. Through the recognition of viral or bacterial determinants by these receptors, extracellular and intracellular pathogens are initially perceived as dangerous, triggering an inflammatory response cascade. The release of inflammatory cytokines and chemokines, such as the type 1 interferons (IFN-a/b), interleukin 12 (IL-12), and tumor necrosis factor (TNF), coordinates these signals [5,6].

These proinflammatory molecules directly kill the virus or cells that are infected with the virus, recruit additional inflammation-producing cells into the environment, and activate antigen-presenting cells to trigger adaptive immunity. A number of TLRs, including TLR2, which recognizes virion components like surface glycoproteins, TLR3, which recognizes dsRNA, and TLR9, which recognizes genomic DNA, have been shown to be involved in signaling in both animal and human

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Received: 02-Jan-2023, Manuscript No: jcet-23-86005; **Editor assigned:** 05-Jan-2023, PreQC No: jcet-23-86005 (PQ); **Reviewed:** 19-Jan-2023, QC No: jcet-23-86005; **Revised:** 23-Jan-2023, Manuscript No: jcet-23-86005 (R); **Published:** 30-Jan-2023, DOI: 10.4172/2475-7640.1000156

Citation: Ulrich G (2023) Organ Transplantation Consequences of Immuno Regulation of Human Herpesviruses. J Clin Exp Transplant 8: 156.

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herpesvirus models [7,8].

Result

Following primary infection, the antigen-specific memory compartment is made up of antigen-specific CD4+ and CD8+ ab T cells, antigen-specific memory B cells, and plasma cells, and these populations are maintained at a higher frequency with increased functionality or antigenic specificity to control repeated exposure to the same antigenic stimuli, according to the traditional paradigm of immunological memory (Figure 1). Even though this paradigm still holds true, little attention has traditionally been paid to the effects that viral infection has on cellular mediators of innate immunity, such as NK cells, CD4+ T cells, and other populations of invariant T cells like NKT cells. Several studies have demonstrated that innate immune cells, such as NK cells, are highly resistant to immunosuppression after transplantation and may play a significant role in regulating viral replication. Additionally, recent research has demonstrated that CMV, a viral infection, is responsible for the imprinting of a "memory signature" on both NK cells and CD4+ T cells.

In response to ligands expressed on the surface of target cells, NK cells express a complex array of stimulatory and inhibitory receptors that either promote or suppress NK cell activation (13). Studies in humans demonstrated that CMV infection promoted the expansion of NKG2C+ NK cells, following initial observations from a mouse model of murine CMV (MCMV) that MCMV promoted the expansion of NK cells expressing the Ly49H receptor, which can recognize the MCMV m157 protein (14). By recognizing HLA E molecules, NKG2C functions as an activating NK receptor.

Individuals who were only positive for HSV or Epstein-Barr virus (EBV) did not show these findings. Interestingly, these NK cells and CMV-specific effector memory CD8+ T cells, which are distinguished by the expression of CD57, have recently been shown to share some phenotypic similarities. In response to NKG2C stimulation, the NKG2C+ NK cells can degranulate and exhibit a decrease in the expression of the inhibitory receptors KIR3DL1 and NKG2A. The NK cell population's ability to control infection and viral reactivation may be enhanced by these observations, which demonstrate how CMV infection leaves a permanent mark. Using the MCMV model, researchers observed that memory phenotype NK cells were more resistant to MCMV challenge, supporting this improved capacity to control infection.

Discussion

More than 40% of the repertoire of T cells in the peripheral blood of some elderly people is comprised of T cells that are specifically for CMV-encoded antigens, making up the majority of the T cell memory compartment in the peripheral blood of CMV-seropositive healthy donors. T cell responses in healthy human donors and MCMV models have been characterized, and it has been demonstrated that CMV-specific T cell immunity increases over time. In spite of the fact that memory expansion of White blood cells explicit for other herpesviruses may happen, the high recurrence of CMV-explicit CD8+ White blood cells and less significantly CMV-explicit CD4+ White blood cells is exceptional and isn't clear in benefactors asymptomatically tainted with other herpesviruses. This dramatic CMV-associated memory inflation is thought to be driven by constant viral reactivation from latently infected monocytes and other nonhematopoietic viral reservoirs. CMV-specific T cells exhibit a highly differentiated phenotype, which is consistent with the high frequency of CMV-specific T cells in CMV-positive individuals' peripheral blood. Within the CMV-specific T cell population, cells with the classic phenotypic and functional characteristics of effector memory cells predominate.

Costimulatory molecules CD27 and CD28 are no longer expressed, and the IL-7 receptor CD127 is no longer expressed, making these cells less able to respond to IL-7-driven homeostatic proliferation. In addition, CMV-specific T cell populations have high levels of the senescence-associated marker CD57 (35–37), and although they continue to proliferate in response to antigen, for optimal expansion, either CD4+ T cell support or cytokines are required (38). However, CMV-specific T cells in healthy individuals do not exhibit other characteristics of chronically activated T cells, such as the high levels of expression of inhibitory markers, despite phenotypic similarities with effector T cells found in other chronic viral infections.

The association of immuno compromism with the uncontrollable proliferation of EBV-transformed B cells suggests that T cells recognizing latently infected cells are the essential mediators in controlling EBV-associated disease, despite the fact that a breakdown in immunosurveillance by T cells specific for lytic cycle antigens is likely the cause of disease in immunocompromised individuals. Expression of the EBV nuclear antigens (EBNA) as well as the latent membrane proteins (LMP) 1 and 2 is linked to EBV latency.

Conclusion

A comprehensive description of the immunodominance hierarchy of the EBV latent associated antigens has been obtained through extensive analysis. In the majority of healthy individuals, immunodominant T cell responses are directed directly toward EBNA. These highly immunogenic antigens can be effectively recognized by specific T cells in EBV-transformed lymphoblast cell lines. In contrast, in EBV-transformed lymphoblastoid cell lines, subdominant T cell responses are produced against EBNA1, LMP1, and LMP2, which are essential for establishing and maintaining latency but are less effectively recognized. T cell immunity to lytic cycle antigens likely plays a significant role in controlling primary infection, although the role of T cells specific for lytic cycle antigens in controlling EBV-associated malignancies in immunocompromised settings is less clear. Immunodominant T cell responses are elicited by the IE lytic cycle proteins BZLF1 and BRLF1, while less dominant responses can also be observed against a wide variety of other antigens, such as the early antigens BMLF1 and BMRF1, as well as surface glycoproteins, such as gp350. Immunity to the other human gammaherpesvirus, HHV8, which is also linked to cancer in immunocompromised individuals, appears to be dependent on the induction of responses to both lytic and latent cycle antigens, although this is less well understood.

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