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Interferons during HSV-2 Infection: Immune Regulation

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Abstract:

Herpes simplex virus type 2 (HSV-2) infection is a prevalent sexually transmitted infection that disproportionately affects women worldwide. Currently, there are no vaccines or curative treatments available, leading to life-long infections. During HSV-2 infection, interferons (IFNs) play a crucial role in the body's antiviral defense. Type I IFNs (IFN-alpha and IFN-beta) and type III IFNs (IFN-lambda) are produced by host cells in response to the virus, alerting neighboring cells to its presence and inducing an antiviral state that limits viral replication and spread. Type III IFNs, produced in epithelial cells, also contribute to controlling viral replication in mucosal tissues. However, HSV-2 has evolved strategies to evade IFN-induced responses, allowing the virus to partially escape the host's immune response, establish latency, and cause recurrent infections. The delicate balance between the host's IFN response and the virus's immune evasion mechanisms determines the outcome of HSV-2 infection. Understanding the intricate interplay between HSV-2 and interferon signalling is critical for developing effective therapies and vaccines to combat this sexually transmitted infection.

Keywords: HSV-2, Interferons, Innate immunity, Immune regulation

Introduction:

Genital herpes simplex virus type 2 (HSV-2) infection is a highly prevalent sexually transmitted infection, affecting millions of individuals worldwide. African cohorts have a significant burden of HSV-2 cases, particularly impacting women. Despite its prevalence, there are currently no preventive or curative treatments available, and existing therapies only aim to suppress viral reactivation. Moreover, antiviral resistance, especially in immunocompromised individuals, poses a challenge.

Understanding the immune response required to control HSV-2 infection is crucial for developing effective therapeutic strategies. While extensive research has been conducted on various aspects of the immune response, the role of the innate immune response has recently gained significant attention. Particularly, type I interferons (IFN-a/b) have emerged as pivotal players in the early innate immune response to HSV-2.

Type I IFNs play a crucial role in limiting viral replication and containing the spread of the virus to uninfected cells by establishing an antiviral state. Notably, in vitro studies have shown that pre-treatment of certain cell lines with recombinant IFN-a/b can effectively inhibit HSV-2 replication by blocking the expression of HSV-2 immediate early genes. Furthermore, in vivo studies have revealed a correlation between resistance to HSV-2 infection and the level of IFN-a/b produced upon infection in different mouse strains.

Besides their direct antiviral effects, type I IFNs also serve as important signaling molecules to alert neighboring cells about the presence of the virus and induce an antiviral response in those cells. This ability to recruit other cellular effectors is essential for controlling viral infections.

In conclusion, the innate immune response, particularly mediated by type I IFNs, plays a pivotal role in the early defense against HSV-2 infection. Understanding these mechanisms holds great promise for developing targeted therapeutic approaches to effectively combat HSV-2 and its associated complications.

Interferon pathway during HSV-2 infection:

Type I IFNs, which include IFN-alpha and its subtypes, as well as IFN-beta, IFN-ϵ, IFN-w, and IFN-k, are essential signalling molecules during genital HSV-2 infection. They play a crucial role in promoting resistance to the infection by suppressing viral replication and enhancing antiviral immune responses. Type I IFNs initiate a signalling cascade through the interferon-alpha/beta receptor (IFNAR) and induce the transcription of interferon-stimulated genes (ISGs) to inhibit viral replication. The induction of type I IFNs is triggered by DNA sensing pattern recognition receptors (PRRs) like TLR9, IFI16, and cGAS, which activate the STING adaptor protein. Additionally, RIG-I and MDA5 recognize replication intermediate dsRNA.

During genital HSV-2 infection, IFN-a/b is primarily produced by circulating plasmacytoid dendritic cells (pDCs) upon recognition by TLR9. Recurrent HSV-2 patients with genital lesions show pDC infiltration, indicating a role for type I IFNs in controlling HSV-2 reactivation. Classical CD8a DCs are also a significant source of IFN production, independent of TLR9 signalling.

Type II IFNs, represented by IFN-g, are primarily produced by NK cells and T cells during genital HSV-2 infection, stimulated by type I IFN-mediated IL-18 signalling. IFN-g signalling occurs through the IFN-g receptor present on the majority of immune cells. IFN-g plays a critical role in mediating protection against genital HSV-2 infection. Dysregulated IFN-g production, associated with genetic variations in the STAT4 gene, has been linked to recurrent genital herpes in humans. IFN-g is necessary for HSV-2 clearance during both primary and secondary challenges.

Type III IFNs, including IFN-l1, 2, 3, and 4 in humans, also play a crucial role in antiviral responses to HSV-2 infection. DCs and pDCs are the primary producers of type III IFNs in response to TLR7 ligands and HSV-2 infection. The type III IFN receptor is not expressed on the surfaces of immune cells, leading to less inflammatory responses. Type III IFNs may possess direct immunoregulatory functions.

Susceptibility to HSV-2 infection can be influenced by hormone-mediated alterations in IFN responses. For instance, estradiol treatment in women increases the capacity to produce type I IFN by pDCs after just one month of treatment. On the other hand, depot medroxyprogesterone acetate (DMPA) treatment impairs TLR9 ligand-mediated IFN-a production in human pDCs by inhibiting IRF7 nuclear accumulation following CpG stimulation.

Interferons regulating innate immunity during HSV-2 infection:

Innate immunity plays a critical role in initial viral infection and replication; however, their dysregulation can also be the cause of severe inflammation and tissue damage. In this section, we will explore the innate immune responses regulated by IFNs toward HSV-2 infection. Type I IFN signalling during HSV-2 infection critically regulates both the induction and control of NK cell-mediated type II IFN signalling.

Monocytes/Macrophages:

During HSV-2 infection, the accumulation of monocytes is crucial to control viral infection and stimulate antiviral immunity in the vaginal mucosa. Monocytes and macrophages increase the expression of Fas and FasL during infection. Type I IFN signalling can regulate the protective effects of monocytes/macrophages during HSV-2 infection. Although type I IFN has been shown to induce FasL expression in murine immune cells during influenza infection, its role in regulating Fas/FasL pathways during genital HSV-2 infection is not fully defined. However, it is believed that type I IFN may contribute to monocyte-mediated inflammation and the induction and recruitment of adaptive immune responses. Type I IFN has been shown to promote inflammatory monocyte (IM) recruitment during murine HSV-1 and HSV-2 infections, promoting survival and antiviral responses. In addition, type I IFN signalling during HSV-2 infection is associated with Fas/FasL-induced inflammation, which contributes to the clearance of infection. In addition, type II IFNs produced by NK cells and T cells also play a role in promoting macrophage responses during HSV-2 infection. IFN-g signalling stimulates nitric oxide production by macrophages, and mouse macrophages infected with HSV-2 show increased nitric oxide release upon IFN-g stimulation. IFN-g, a Th1-

promoting cytokine, supports macrophage M1 polarization, proinflammatory cytokine production, and increased MHC class II expression, facilitating effective adaptive immune responses in a murine model of HSV-2 infection. In conclusion, both type I and type II IFN facilitate the recruitment and activation of antiviral functions of inflammatory monocytes (IM) and macrophages during HSV-2 infection.

Neutrophils:

Neutrophils can play a protective role in HSV-2 infection by limiting early viral replication. However, dysregulated neutrophil responses can lead to damaging inflammatory outcomes and increased disease severity during viral infection. Induction of IL-36g has been shown to increase sensitivity to IFN-a/b during HSV-2 infection in mice through increased IFNAR expression on keratinocytes, likely contributing to the protective function of IL-36. Additionally, IFN-l has been demonstrated to suppress neutrophil-mediated damage in the intestinal mucosa of mice. Dysregulated and prolonged type I IFN signalling was recently described to promote epithelial damage in response to mouse HSV infection by neutrophils.

NK Cells:

Natural Killer (NK) and NKT cells are critically required for innate protection against HSV-2 infections. Individuals with severe NK cell deficiencies have been associated with recurrent HSV infections. In mouse models, NK cell-deficient mice are highly susceptible to HSV-2 infection, with higher viral load and mortality. NK cell recruitment is facilitated by chemokines CXCL9 and CXCL10, and the absence of the CCR5 receptor leads to increased susceptibility to intravaginal HSV-2 infection in mice. Type I IFN production during infection is essential for the activation of NK cells. Type I IFNs are critical mediators of indirect NK cell activation and IFN-g production during mouse HSV-2 infection. IFN-g production during mouse HSV-2 infection is significant in providing antiviral defense.

The Role of IFNs in HSV-2 Vaccine Development:

Mouse models of HSV-2 vaccination have shown promising results with potent memory T cells and neutralizing antibody responses that confer protection against subsequent HSV-2 challenges. However, these preclinical findings have not translated into effective vaccines for humans during clinical trials. Several candidate vaccines have exhibited poor efficacy in clinical trials, with varying induction of neutralizing antibody or cellular responses. Unfortunately, most clinical studies in humans focus primarily on neutralizing antibody titers and provide a limited examination of CD4+ T cell specificity or IFN-g production.

While type I IFNs may not be required for vaccine-induced memory responses in mice, HSV-2's evasion of type I IFN signalling in humans, as demonstrated by a lack of type I IFN in human lesion biopsies compared to mice, could diminish the efficacy of vaccine-induced memory responses. Multiple clinical trial failures despite successful pre-clinical models highlight the differences between human and animal models in developing protective adaptive immunity to genital HSV-2 infection. Additionally, vaccination studies in mice often overlook the role of type I IFN in terms of the longevity of established protective immunity, as secondary challenges are administered within a month post-vaccination.

The role of type III IFNs should also be considered carefully in future vaccine development. Using IFN-l3 as an adjuvant in a mouse vaccination model has shown enhanced humoral and cellular immune responses, resulting in improved vaccine efficacy. Therefore, the lack of type I, II, and III IFN induction by HSV-2 vaccination in humans may hinder the development of protective adaptive immunity and should be a critical consideration in future vaccine design.

Conclusion:

The development of effective preventative and prophylactic treatments for sexually transmitted HSV-2 has been challenging due to the difficulty in inducing a strong, protective immune response in the genital mucosa. they also play a crucial role in the development of local protective innate and adaptive immune responses to viral infection. Type I and II IFN signalling, directly and indirectly, regulate the development of immune memory and adaptive responses to viral infection through the induction of innate immunity. Additionally, type III IFNs are vital in controlling viral replication and likely have unexplored functions in regulating innate immune responses in the genital mucosa.

Impairment of type I IFN signalling during genital herpes infection can lead to a decline in type II IFN responses, which are essential for the development of adaptive immunity and HSV-2 clearance. As previously mentioned, recurrent HSV-2-infected individuals often exhibit dysregulated responses to IFN-g, which hinders their ability to combat the virus effectively.

For future treatments or vaccines, it will be crucial to restore responsiveness to IFN-g signalling and elicit potent CD4+ T cell-derived IFN-g production. IFN-g plays a multifaceted role in immune regulation and antiviral immunity, making it a critical component for combating HSV-2 infection effectively.

In summary, understanding the complex role of IFNs in regulating innate and adaptive immune responses in the genital mucosa is essential for developing novel and effective treatments or vaccines against HSV-2. Restoring and enhancing IFN-g responsiveness could be a promising avenue for improving the immune response and ultimately controlling and preventing HSV-2 infection.

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