Pharaonic Journal of Science
https://pjscience.org/
PJS
SPBH

Immunological Response to Herpes Virus and Its Relationship with Interleukin 10

Hadeel Tahseen Al-hashimi, Ghufran Mohammed Sadee Merie, Mustafa M. Mustafa

Medical Technical Institute, Northern Technical University, Mosul, Iraq.
Email: mti.lec11.Ghufran@ntu.edu.iq, mti.lec180.hadeel@ntu.edu.iq

DOI: 10.71428/PJS.2025.0105

ABSTRACT

A class of DNA viruses called herpesviruses is well-known for its capacity to create latent infections that last a lifetime and to elude the host's immune system. Natural killer (NK) cells, cytotoxic T lymphocytes, and antibody-mediated reactions are examples of both innate and adaptive immunity that are involved in the immune response to herpesvirus infection. Modulating host cytokine responses is one of the complex strategies that herpesviruses have evolved to circumvent these defences. The anti-inflammatory cytokine interleukin-10 (IL-10) is essential for controlling immunological responses and preventing tissue damage. To inhibit immune activation and increase viral persistence, a number of herpesviruses, including Epstein-Barr virus (EBV) and cytomegalovirus (CMV), encode viral homologs of IL-10 or cause the host to produce IL-10. This immunomodulatory effect aids in the development of latency and reactivation as well as the virus's ability to evade immune surveillance. Knowing how herpesviruses and IL-10

Keywords: Immune evasion, Latency, Cytokines, Herpesvirus, Interleukin-10, Immune response

Introduction to Herpes Virus Infections

Herpes virus infections are some of the most widespread in human populations, with high-grade chronicity, posing a considerable burden to public health worldwide. Infection by herpes viruses may take a very wide variety of clinical forms that can involve not only the orofacial and genital regions but, in some circumstances, other organs, such as the brain and the eye. Although clinical presentation is, overall, very variable, the presence of vesicles demonstrates the likelihood of the involvement of the virus family Herpesviridae. These may be diagnosed by immunologic assays, viral culture, or detection of viral DNA through PCR. Particularly, the herpes viruses Herpes simplex, varicella-zoster, and Epstein-Barr are responsible for herpes stomatitis and/or orofacial or genital ulcers (1).

This is why, for a successful strategy to counteract herpes virus infections, we need to know the details of our enemy, the herpes virus. Knowing the immunology and, in particular, the mechanisms that regulate the interaction between the host's cells and the herpes virus lies, indeed, at the base of successful control and eradication strategies. Thus, this manuscript will focus on this latter topic, i.e., the role of IL-10 in controlling the immune response against herpes viruses. To our knowledge, a review on this specific subject has never been done in the past. In the upcoming paragraphs, we reinforce this standpoint and the context in which it can be observed (2).

1.1. Types of Herpes Viruses

Received: March 9, 2025. Accepted: May 11, 2025. Published: June 1, 2025

Herpes viruses are categorized into three families: alpha herpes virus, beta herpes virus, and gamma herpes virus. Among the herpes viruses, eight of them infect humans, including Herpes Simplex Virus 1, Herpes Simplex Virus 2, varicella zoster virus, Epstein-Barr Virus, cytomegalovirus, human herpes virus 6, human herpes virus 7, and human herpes virus 8. Herpes Simplex Virus types I and II; varicella zoster virus that is also known as human herpes virus 3; Epstein Barr Virus, or human herpes virus 4, manifests as infectious mononucleosis or acute or chronic infectious syndrome but can lead to a variety of diseases, including malignant lymphomas such as Burkitt's lymphoma, biological lymphoma, Hodgkin's lymphoma, and nasopharyngeal carcinoma depending on the target cell and time of infection; cytomegalovirus, or human herpes virus 5, is common and infects 50–80% of adults before the age of 40. Human herpes virus 8 can cause Kaposi's sarcoma in acquired immune deficiency syndrome patients. Human herpes virus 6 and human herpes virus 7 manifest as exanthem subitum in young children (1).

Among these eight viruses, Herpes Simplex Virus 1 and Herpes Simplex Virus 2 can cause severe diseases depending on age, immune status, socioeconomic conditions, and significantly associated pathogens; further, these pathogens have high antigenicity. Herpes Simplex Virus 1 manifests as orolabial herpes, herpes simplex keratitis, encephalitis, genital herpes, viral meningitis, and herpes simplex stomatitis. Herpes Simplex Virus 2 manifests exclusively in the genital tract of humans and is transmitted through sexual routes. Genital Herpes Simplex Virus 2 manifests as a primary infection, first episode, first-episode severe, first-episode mild, recurrent anogenital, and asymptomatic shedding. Herpes Simplex Virus causes a dermal infection before entering sensory nerve endings, which can cause injections or scratch reactions within the skin. Additionally, Herpes Simplex Virus can enter sensory nerve endings, move in a retrograde manner within the sensory nerve, and hide in the nerve cell body after reaching the sensory ganglion. Herpes Simplex Virus can then become latently infected and occasionally recur. The replication of various herpes viruses causes disease, and the clinical symptoms are different; thus, they are divided into human herpes susceptibility to infectious and malignant lymphomas. Overall, the different herpes viruses manifest as acute, persistent, and chronic, or malignant diseases (3).

2. Immunological Response to Herpes Virus

A complex immunological response is triggered by the herpes virus entry process. Initial innate immunity is mediated by uptake, proteolytic digestion, or degranulation of the herpes virus by approximately three seconds of natural killer (NK) cells, circulating macrophages, and then larger numbers of mononuclear monocytes in the vaginal mucosa. Neutrophils, on the other hand, are present next to the extravasation. They are not cleared in the initial flow-through and probably work later. Cutaneous dendritic cells with Siglec-H high produce the first interferon-beta in the body in response to degranulation, except for dermal. γ/δ T cells and α/β T cells undergo high production and recruitment of IFN-γ. In addition, skin dendritic cells (DCs) migrate through the lymph nodes and degranulate to release IFN-β, thus causing the lymph node itself to recognize antigens. Next, various lymphadenitides can mediate and target HSV-1 (3).

A very important finding is the release of lipoxin A4 and aspirin-triggered lipoxin in dendritic cells (DCs) to reduce pain and tumor necrosis factor, and not only to cause α/β T lymphocytes to infiltrate into the sensory dorsal root ganglion, where they are suppressed and effectively closed. The study of concentrated leukotriene B4 showed that it can effectively reduce the skin inflammation and it is blocked to reduce neural pain reduction by aspirin, then intramuscularly with leukotriene B4 receptor

blockers. This data illustrates the depth of the in vivo immune response to the herpes virus role in immune evasion. This research offers the promise of a new way of thinking about treating herpes infections and allocating expensive vaccination resources more effectively and equally to immune responses. It opens the way to individualized care that can predict the immune response to empirical therapy and allow scientific intervention to minimize structural damage at the end of treatment and shorten treatment time. A range of in vivo response diversity may explain conflicting research findings, such as those of Liu. This could help explain the dominance of activated T lymphoblast populations (2).

2.1. Innate Immune Response

Herpes viruses are ubiquitous pathogens, often asymptomatic but present with clinical manifestations when there is a breakdown in patient immunity. The innate immune response is the first line of defense, with three main mechanisms: immediate defense mechanisms in the early recognition phase, up to a few hours, and finally, recruiting and activating the adaptive immune system. The recognition of viral molecular patterns and the following immune response against herpes viruses is necessary to close all the doors facilitating their elimination. Pattern recognition is primarily due to the action of pattern recognition receptors, a mixed population of soluble, transmembrane, and intracellular receptors that can regulate the immune response against herpes virus components (4).

In the later stages of an infection, various immune cells, such as monocytes and macrophages, detect infected target cells and either phagocytose them as apoptotic bodies or directly secrete cytokines, or use cytokines for enhanced phagocytosis, recruit neutrophils, and secrete cytokines and chemokines as an iatrogenic response, which culminates in the era of inflammation. The large amounts of chemokines released by the infected cells retain organic debris at the primary site and are subject to destruction by granulocyte arrival in the form of neutrophils, the main phagocytes in this era. Cytokines such as IL-10 are central components of viral control because they are multifunctional cellular therapies in many cell types. They inhibit different stages of T cell activation and are secreted to limit the host's autoimmune response and prevent harmful self-destructive conditions. The variety of effects of IL-10 is evident from its ability to regulate the development of several major immune cells and is important for antiviral control (4).

2.2. Adaptive Immune Response

Upon herpes virus infection, the human body activates a specific immune response against the virus, the adaptive immune response, that works especially to fight the infection and remember it to avoid any future relapse. The main characters involved in this response are called T cells and B cells. The adaptive response generally takes some days to be activated after the infection because T cells need time to recognize and kill the infected cells and destroy the virus itself, and B cells need to create antibodies capable of neutralizing viruses and preventing infection. In some cases, it is difficult to fight the infection, mostly for people with weak immunity. However, other characteristics in our body, although less effective, are also activated during and after herpetic infection to limit it and protect our body from damage (1).

T lymphocytes or T cells are the mediators of the cellular arm of the adaptive immune system. When a dendritic cell presents an antigen to a naive T cell, it becomes an activated T lymphocyte or a T helper cell, which can kill any virus-infected cell assembled on an MHC I, while the T helper cell can proceed to activate a cytotoxic T lymphocyte by providing signal 2. This ensures that cytotoxic T lymphocytes target infected cells when viral particles are produced and is therefore crucial in preventing the viral spread in an organism (5).

2.3. Role of Cytokines

Cytokines play a central role in communication among the diverse cell populations that form the immune system. They establish the sequence of events in the complex process of inflammation that is largely responsible for the immunological response against infections. In the context of ontogenesis, pregnancy, and/or chronic conditions, cytokine-related processes may be associated with or responsible for certain states of viral shedding and a higher risk of transmission. Some herpesviruses interact with the immune system, inducing the production of these soluble factors, in particular, the release of interleukin-10, a pleiotropic cytokine produced by a variety of cell types, including non-immune cells and all of the major leukocyte populations (6).

Proinflammatory cytokines are very important in triggering a number of antiviral cellular responses. However, the long-term activity of these molecules leads to the development of harmful autoimmune responses and lesion formation. This action needs to be adequately controlled, which occurs through the regulation of the production of proinflammatory cytokines and the production of molecules responsible for the neutralization of their actions, such as interleukin-10 itself. The balance between the production of inhibitory and proinflammatory cytokines will determine the diversification of the disease. Therefore, a more rational therapeutic approach would involve the neutralization of specific inhibitory cytokines or their molecules, allowing for more effective proinflammatory responses. Finally, all cytokines are also able to directly or indirectly stimulate the production of these virus-specific molecules through other immunological components. It has been recently shown that the quality, and not the quantity, of the presence of these molecules is fundamental for the adequate elimination of a pathogen during an immunological response (7,16,20).

3. Interleukin 10: Overview and Function

Interleukin 10 is a highly anti-inflammatory cytokine with many ways of working. It can be made by many cells, but the regulatory T cell and the regulatory B cell are the main producers of the inducer subtype. It is more likely to be an immunosuppressive factor due to its extensive impact on almost all immune cells. The most common foreign function is to promote the differentiation of regulatory T cells and inhibit the effects of antigen-presenting cells, as an antagonistic factor to other pro-inflammatory cytokines. In response to herpes virus infections, the concentration of IL-10 in the peripheral blood of the host usually increases significantly and is closely related to the severity of the disease. IL-10 is also involved in the mechanism of virus responsiveness, inducing the reactivation of the herpesviruses. (8.17).

By inhibiting the activity of transcription factors, IL-10 is likely to have a broad-spectrum effect on different immune cells. This enabled it to serve as a balance between the host's self-protective immunity and the harmful inflammatory attack based on previous racial immunity or sensitization by previous vaccination. Many researchers have shown that if the secretion of IL-10 is too strong or out of control, it can easily lead to more virus replication in the host tissue, and more tissues are damaged by the over-inflammation. In addition, dysregulated IL-10 also has a broad-spectrum impact in some diseases, such as the dissemination of herpesviruses, turning into a systemic immunosuppression response in a variety of different groups, which means that IL-10 is likely to be a target for effective prevention and treatment of a series of vascular and other diseases (9,18).

3.1. Structure and Production

Interleukin 10 (IL-10) molecules (18 kDa) are non-glycosylated homodimers of two similar polypeptide chains containing 160-179 amino acids (human IL-10, 178 amino acids). Amino acid se-

quence homology between species is around 70% between human and mouse IL-10. IL-10 binds to its receptor, a complex of two different subunits. Generally, the IL-10 receptor binds homodimerically, producing a complex that dimerizes on its own. IL-10 binding activates the Jak1 and Tyk2 kinases associated with the IL-10 receptor (10,19,20).

IL-10 is produced by several cells: T-helper cell 2 and a subpopulation of T-cytotoxic and T-suppressor cells following, in part, the action of TH-2 cells; a subpopulation of B cells; human B lymphomas; macrophages obtained from monocytes stimulated with GM-CSF or LPS in the presence of IL-10; activated thymocytes; and murine mastocytoma stimulated with antigen. In steady-state conditions, activated human peripheral blood monocytes synthesize IL-10, in part, following direct signaling between CD14 and IL-8 κ-receptors. Several factors may induce the production of IL-10 by different cells in culture or in vivo: heat-killed pathogens but not their products, prostaglandin E2, glucocorticoid hormone, at least one anti-inflammatory cytokine, and IL-10 itself through an autoregulatory circuit (11,16,21).

3.2. Regulatory Functions

The antagonization of a pro-inflammatory immune response by IL-10 indicates the key nature of this cytokine in immune modulation. Since its discovery, extensive research has characterized IL-10 as essential in inhibiting various aspects of the immune system in order to maintain homeostasis. Therefore, IL-10 is particularly important in maintaining tolerance to harmless antigens. The main cells targeted by IL-10, due to their capacity to produce pro-inflammatory cytokines, are the macrophages and microglia, in which IL-10 has its most prominent effect. IL-10 can suppress these cells either directly, by reducing the transcription of the M1 signature cytokines, just upregulated, or indirectly by inhibiting or promoting the degradation of pro-inflammatory neutrophils and vasculature. This, in turn, results in a reduction in the signaling through IGF-3, TNF-α, and IL-1, which results in a suppression of pro-inflammatory cytokine secretion. IL-10 also affects multiple immune cell types, including T cells, B cells, and antigen-presenting cells, to modulate inflammation (12,22).

Binding of IL-10 to its receptor and subsequent phosphorylation by JAK1, JAK3, and TYK2 leads to activation of STAT3, which migrates to the nucleus to drive transcription of anti-inflammatory genes. Perhaps most significantly, IL-10 promotion of Treg development, likely via effects of IL-10 on antigen presenting cells, is a potent means by which increased IL-10 signaling can effectively dampen immunopathologies. This important broad anti-inflammatory role of IL-10 that is potentially heightened in chronic inflammatory environments bears particular relevance to the immune response to herpes viruses. IL-10 has therefore received much attention as a target for the treatment of inflammatory diseases due to its regulatory role in dampening pro-inflammatory cytokine signaling and driving the immune system towards an environment of immune tolerance. A lowered phenotype of any of the above-mentioned pathways predominantly leads to hyperactivation of the immune response and a heightened state of inflammation and autoimmunity. This illustrates a critical regulatory role of IL-10 in maintaining homeostasis and dampening inflammatory stresses (2,23).

4. Interaction Between Herpes Virus and Interleukin 10

Herpesviruses and Interleukin 10 (IL-10): Interaction between herpes virus and interleukin 10. Interleukin 10 (IL-10) is produced in response to viral infections but also aids in immune evasion strategies established by pathogens. Herpesviridae represent the leading cause of virus-associated cancer and are characterized by the ability to establish latency in their host. γ-Herpesviruses can condition

the host immune response to enhance their replicative niche in the host. IL-10 is often implicated, and dysregulation in its expression can alter the outcome of infection in both directions (6,24,25)

IL-10 is produced by different cell types, where it supports plasma cell development while acting as a negative regulator of neutrophil and Th1 cell activation and proliferation. Some herpesviruses can induce or upregulate IL-10 production themselves. The purpose of this is likely twofold, as it can subvert or hinder immunity by the upregulation of this cytokine while subverting immune regulation to support the establishment of latency. The herpesviruses can express IL-10 homologues that signal through the IL-10 receptor, suggesting that the binding of IL-10 to this receptor plays a critical role in the establishment of latency. The idea that IL-10 aids γ-herpesvirus infection is clear, as the depletion of IL-10 often results in the rapid clearance of the virus. This suggests a possible route of interference: the modulation of IL-10 for the improvement of the outcome of gamma herpesvirus persistence. Nevertheless, it is important not to dismiss the importance of IL-10 in the clearance of γ-herpesvirus infection. An understanding of the interaction of a host and herpes viruses with IL-10 is an important step to understanding the disease that these persistent herpes viruses cause. This study demonstrates how a virus's exploitation of immune regulation can help it cause disease. The level of IL-10 at the early stage of infection might be a factor in determining how and if a T cell response will be able to clear and, if not, control a herpes virus. It could facilitate accurate as well as effective therapeutic intervention. Can we manipulate the concentration of IL-10 for the amelioration of symptoms and enhancement of immune response? Treatment for patients infected with another γ-herpesvirus is already trying to pinpoint this range of IL-10 for the best outcome (13,19,26).

4.1. Effect of IL-10 on Herpes Virus Infection

Herpes virus infections are immune modulators and can cause inflammatory responses. Many anti-inflammatory cytokines are therefore associated with herpesvirus infections. One type of cytokine is interleukin 10. During acute infection of the body, levels of IL-10 increase. Increased IL-10 levels at this time may protect the body from overly exacerbated inflammatory responses. There are risks when IL-10 may increase significantly. One of the risks is that the immune system's response is blocked by a high level of IL-10. The absence of a response can then help the virus to survive. Several studies test the effect of IL-10 on herpes virus infection. The conclusion is that the effect of IL-10 depends completely on the situation. Generally, the moderate increase in IL-10 at the beginning of the herpes virus infection is considered positive. It helps reduce neuroinflammation and viral infection. However, chronic increases in IL-10 prevent the immune system from eliminating the virus. This will result in an increased viral load and reduced immune system protection. Treatment with therapeutic drugs must be considered for changes in IL-10 levels. Increasing or decreasing IL-10 levels can be a therapy in certain herpes virus infections. For example, one research team concluded that IL-10 supplementation suppresses the immune system and the herpes virus. Other studies have shown that lowering IL-10 levels increases the immune system's ability to fight viruses. Combination therapy by reducing IL-10 and overreactive inflammation has also been shown to be effective in herpes infections. It has been shown that immunomodulatory drugs combined with antivirals can reduce loss of corneal transparency. However, it can be detrimental, such as scarring of the cornea. Therefore, monitoring IL-10 at appropriate concentrations and times will affect the outcome of herpes virus infection (14,22,27).

5. Clinical Implications and Therapeutic Potential

Interactions between herpes viruses and their host immune responses are complex. Herpesviruses are known to induce a multitude of cytokines during acute infection. There is a significant body of literature demonstrating the ability of herpesviruses to evade the host immune response through multiple pathways. This knowledge allows for the development of innovative strategies to reduce viral burden and modulate immune responses. A focus on these interactions is especially important in viral infection, where an incomplete or inadequate immune response leaves the individual susceptible to higher rates of chronic infection. A key to the development of new therapeutic strategies is to further understand the role of specific cytokine pathways during herpesvirus infection. Cytokines that are involved in modulating immune responses to chronic viral infections may be more promising candidates for adjuvant immunotherapies for individuals with chronic herpesvirus infection. Infections frequently trigger a unique pattern of immunopathology (15.21).

Herpesviruses can subvert this process in many ways. Some can block the surface expression of major histocompatibility complex I proteins, some block the T cell receptor chain proteins that are required for T cell activation, some introduce early proteins that are homologs of cytokines and/or their receptors and thus skew cytokine responses away from effective antiviral immunity, and some express viral microRNA mimics open reading frame that result in viral interference of a wide variety of cytokine expression and regulation. In some cases, these strategies appear to mimic similar pathways in other chronic infections and negatively affect overall antiviral T cell immunity. Some signaling pathways are coordinated to produce IL-10, an immunosuppressive cytokine. For example, in the herpesvirus/IL-10 pathway, the virus infection can stimulate the innate immune response of macrophages or other antigen-presenting cells to make IL-12. Other investigators showed that IL-10 neutralizing antibody can partially reverse CD8+ immunosuppression. Another example of this is the role of the Tolsotuzumab anti-IL-6 mAb that reverses the immunosuppression of CD4 and CD8+ T cells in cancer (15,29).

5.1. IL-10 as a Therapeutic Target

Elevated plasma IL-10 levels in patients with herpes virus infections are considered a marker of disease severity. An imbalanced inflammatory response may contribute to excessive damage, especially that observed in nervous tissue. IL-10 restricts IFN-γ signaling at the stage of the IFN-γ receptor by inhibiting its downregulation. The rationale to target IL-10 could be either to restrict the immune environment, thereby reducing hazards, or to increase the immune environment to protect from infection. There are different strategies in harnessing IL-10 to manage an infection, including IL-10 inhibition and augmented IL-10 expression. Recent research demonstrates the therapeutic potential of IL-10 manipulation in enhancing antiviral responses. There is considerable interest in modulating the activity of IL-10 for therapeutic gain in diverse conditions, as opposed to inhibiting IL-10 systemically. While promising, IL-10-targeted therapies are challenging due to the multiplicity of IL-10 sources and the necessity to rebalance the actions of other cytokines and cells. Hence, the immediate exhaustion of IL-10 may not be a successful approach. Targeting IL-10 to enhance antiviral responses is currently being explored but has yet to be trialed in humans. Some of the factors contributing to success in targeting IL-10 to enhance antiviral responses include a working immune environment, among others. Furthermore, outcomes should be individualized based on patient-specific factors (8,28).

Conclusion:

Innate and adaptive immunity work together in the intricate immune response to herpesvirus infec-

tions. Herpesviruses, however, have developed ways to weaken host defences, especially by altering cytokines like interleukin-10 (IL-10). These viruses can suppress immune responses, promote latency, and increase viral persistence within the host by eliciting or imitating IL-10. The potential of IL-10 as a target for therapeutic intervention is highlighted by our understanding of its role in herpesvirus pathogenesis. Future studies that concentrate on IL-10 signalling pathways and how viruses manipulate them could yield important information for the creation of innovative antiviral treatments meant to reduce reactivation and chronic infection.

Conflict of interest: NIL

Funding: NIL

References:

(1) Guellil, M., van Dorp, L., Inskip, S. A., Dittmar, J. M., Saag, L., Tambets, K., ... & Scheib, C. L. (2022). Ancient herpes simplex 1 genomes reveal recent viral structure in Eurasia. Science Advances, 8(30), eabo4435. science.org

(2) Wang, L., Wang, R., Xu, C., & Zhou, H. (2020). Pathogenesis of herpes stromal keratitis: immune-inflammatory response mediated by inflammatory regulators. Frontiers in Immunology. frontiersin.org

(3) Sawtell, N. M. & Thompson, R. L. (2021). Alphaherpesvirus latency and reactivation with a focus on herpes simplex virus. Current Issues in Molecular Biology. mdpi.com

(4) Lum, K. K. & Cristea, I. M. (2021). Host innate immune response and viral immune evasion during alphaherpesvirus infection. Current issues in molecular biology. mdpi.com

(5) James, C., Harfouche, M., Welton, N. J., Turner, K. M., Abu-Raddad, L. J., Gottlieb, S. L., & Looker, K. J. (2020).

(6) Herpes simplex virus: global infection prevalence and incidence estimates, 2016. Bulletin of the World Health Organization, 98(5), 315. nih.gov

(7) Spicknall, I. H., Flagg, E. W., & Torrone, E. A. (2021). Estimates of the prevalence and incidence of genital herpes, United States, 2018. Sexually transmitted diseases, 48(4), 260-265. [HTML]

(8) Ahmed, R. I., Nazal, M. F., & Abdelhameed, A. (2023). Serum levels of IL-23, IL-8 and IL-10 to CMV, HHV-6, and IBV infection and Male Unexplained Infertility. HIV Nursing. hivnursing.net

(9) Poole, E., Neves, T. C., Oliveira, M. T., Sinclair, J., & da Silva, M. C. C. (2020). Human cytomegalovirus interleukin 10 homologs: facing the immune system. Frontiers in Cellular and Infection Microbiology, 10, 245. frontiersin.org

(10) Fernandez-Santamaria, R. & Satitsuksanoa, P. (2022). Engineered IL-10: A matter of affinity. [HTML]

Fang, D. & Zhu, J. (2020). Molecular switches for regulating the differentiation of inflammatory and IL-10-producing anti-inflammatory T-helper cells. Cellular and Molecular Life Sciences. nih.gov

(11) Omarova, S., Cannon, A., Weiss, W., Bruccoleri, A., & Puccio, J. (2022). Genital herpes simplex virus—An updated review. Advances in Pediatrics, 69(1), 149-162. advancesinpediatrics.org

(12) Steiner, I. & Benninger, F. (2020). Herpes simplex viruses. Clinical neurovirology. [HTML]

(13) Zhu, S. & Viejo-Borbolla, A. (2021). Pathogenesis and virulence of herpes simplex virus. Virulence. tandfonline.com

(14) Madavaraju, K., Koganti, R., Volety, I., Yadavalli, T., & Shukla, D. (2021). Herpes simplex virus cell entry mechanisms: an update. Frontiers in cellular and infection microbiology, 10, 617578. frontiersin.org

(15) O'Connor, C. M. & Sen, G. C. (2021). Innate immune responses to herpesvirus infection. Cells. mdpi.com

(16) Ike, A. C., Onu, C. J., Ononugbo, C. M., Reward, E. E., & Muo, S. O. (2020). Immune response to herpes simplex virus infection and vaccine development. Vaccines. mdpi.com

(17) Greenan, E., Gallagher, S., Khalil, R., Murphy, C. C., & Ní Gabhann-Dromgoole, J. (2021). Advancing our understanding of corneal herpes simplex virus-1 immune evasion mechanisms and future therapeutics. Viruses, 13(9), 1856. mdpi.com

(18) Sausen, D. G., Reed, K. M., Bhutta, M. S., Gallo, E. S., & Borenstein, R. (2021). Evasion of the host immune response by betaherpesviruses. International Journal of Molecular Sciences, 22(14), 7503. mdpi.com

(19) Zhu, H. & Zheng, C. (2020). The race between host antiviral innate immunity and the immune evasion strategies of herpes simplex virus 1. Microbiology and Molecular Biology Reviews. nih.gov

(20) Capozza, P., Pratelli, A., Camero, M., Lanave, G., Greco, G., Pellegrini, F., & Tempesta, M. (2021). Feline coronavirus and alpha-herpesvirus infections: innate immune response and immune escape mechanisms. Animals, 11(12), 3548. mdpi.com

(21) Singh, H., Koury, J., & Kaul, M. (2021). Innate immune sensing of viruses and its consequences for the central nervous system. Viruses. mdpi.com

(22) Islam, H., Chamberlain, T. C., Mui, A. L., & Little, J. P. (2021). Elevated interleukin-10 levels in COVID-19: potentiation of pro-inflammatory responses or impaired anti-inflammatory action?. Frontiers in Immunology. frontiersin.org

(23) Carlini, V., Noonan, D. M., Abdalalem, E., Goletti, D., Sansone, C., Calabrone, L., & Albini, A. (2023). The multifaceted nature of IL-10: regulation, role in immunological homeostasis and its relevance to cancer, COVID-19 and post-COVID conditions. Frontiers in immunology, 14, 1161067. frontiersin.org

(24) Zheng, W., Xu, Q., Zhang, Y., E, X., Gao, W., Zhang, M., ... & Liu, Z. (2020). Toll-like receptor-mediated innate immunity against herpesviridae infection: A current perspective on viral infection signaling pathways. Virology Journal, 17, 1-15. springer.com

(25) Verzosa, A. L., McGeever, L. A., Bhark, S. J., Delgado, T., Salazar, N., & Sanchez, E. L. (2021). Herpes simplex virus 1 infection of

neuronal and non-neuronal cells elicits specific innate immune responses and immune evasion mechanisms. Frontiers in immunology, 12, 644664. frontiersin.org

(26) Kravtsov, D. S., Erbe, A. K., Sondel, P. M., & Rakhmilevich, A. L. (2022). Roles of CD4+ T cells as mediators of antitumor immunity. Frontiers in immunology, 13, 972021. frontiersin.org

(27) Roy, P., Orecchioni, M., & Ley, K. (2022). How the immune system shapes atherosclerosis: roles of innate and adaptive immunity. Nature Reviews Immunology. nih.gov

(28) Saxton, R. A., Tsutsumi, N., Su, L. L., Abhiraman, G. C., Mohan, K., Henneberg, L. T., ... & Garcia, K. C. (2021). Structure-based decoupling of the pro-and anti-inflammatory functions of interleukin-10. Science, 371(6535), eabc8433. nih.gov

(29) Steen, E. H., Wang, X., Balaji, S., Butte, M. J., Bollyky, P. L., & Keswani, S. G. (2020). The role of the anti-inflammatory cytokine interleukin-10 in tissue fibrosis. Advances in wound care, 9(4), 184-198. liebertpub.com