# CHANGES IN THE IMMUNE STATUS OF INDIVIDUALS INFECTED WITH HSV VIRUS

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**Abstract**

The problem of opportunistic infections becomes an actual problem in modern times. This is related to a number of factors, including the increase of chronic diseases treated with immunodepressants, which weaken the immune system. Opportunistic infections are caused by various microorganisms, including bacteria, fungi, parasites, and viruses. These microorganisms, which often cause asymptomatic infections in healthy individuals, can cause infections that pose a threat to life in the presence of weakened immune systems.

This article examines the role of cytokines, chemokines, macrophages, T and B cells produced by immune cells during HSV infection, which is one of the opportunistic infections.

**Keywords:** HSV 1 and 2, cytokines, chemokines, keratinocytes, macrophages, NK cells, T and B lymphocytes.

## Introduction

Opportunistic infections are increasingly becoming an important topical problem, which leads to a steady increase in the number of HIV-infected individuals and the emergence of new methods in the treatment of oncopathologies. However, many people are asymptomatic carriers of opportunistic infections. Clinical polymorphism and lack of specific symptoms of opportunistic infections make diagnosis and treatment a serious multidisciplinary problem.

For the manifestation of opportunistic infections, infection with pathogenic microorganisms - viruses, bacteria, fungi and protozoa - is a must. Up to 20 typical agents of opportunistic infections are known, and this list is constantly growing in modern infectious diseases. Herpeviruses are one of these infections.

Herpes viruses are large double-stranded DNA viruses. Human herpesviruses HSV-1 and HSV-2 (HSV) are major human pathogens in the simplex virus family. Both viruses infect people of all ages, with HSV-1 being more common than HSV-2 [1]. the seroprevalence of the latter tends to increase with age in various populations [2]. In the most extreme cases, HSVs can cause fatal systemic infections or encephalitis, problems commonly associated with immunocompromised patients [1]. Therefore, it is important to provide antiviral intervention for those infected with this virus. Eight types of herpes virus affect people.

In older age groups, viral factors together with host immune responses determine virulence and invasiveness. After initial infection, the virus establishes a chronic infection in the host and remains dormant until reactivation [2].

Herpes simplex viruses types 1 and 2 (HSV1 and 2) are members of the Alphaherpesvirinae family and are known for their broad tissue tropism and ability to establish and maintain latency in sensitive ganglia [3, 4, 5]. HSV1 and 2 usually enter the deeper layers of the epidermis of the oropharyngeal and genital mucosa to spread primary infection. From these sites of infection, HSV spreads to the axons of sensory neurons in the epidermis and then travels to the trigeminal/dorsal root ganglia, where it escapes immune eradication and establishes a chronic infection. After HSV1 and 2 relapse, it usually causes self-limiting lesions, mainly in the mouth, face and eyes (HSV1) or genital area (HSV1 and 2), or asymptomatic infection. Infrequent complications include encephalitis, blindness, susceptibility to HIV, and fatal outcome in severe cases in neonates and immunosuppressed individuals. HSV1 and 2 (as of 2016) are highly prevalent in the human population [6]. Transmission of HSV1 and 2 to others occurs through contact with an asymptomatic active person through saliva or genital secretions.

HSV1 and 2 often reactivate asymptomatically with occasional noticeable lesions in both the oral and genital areas. It is constantly reactivated by the immune system to ensure that reactivation cycles are limited.

Several types of immune cells and their products function to contain and clear HSV infections, such as keratinocytes that produce chemokines that attract T cells to the site of infection [7] and keratinocytes that infiltrate interferon-γ (IFN-γ)-secreting CD4 T cells [8] secrete effector CD8 T cells that clear infected lesions by direct killing of HSV-infected cells or by IFN-γ control [9]. These immune responses are initiated by epidermal type 2 conventional dendritic cells (Epi-cDC2s) of Langerhans cells (LC) in the epidermis [10]. LCs undergo apoptosis and migrate to the dermis, where viral transfer of HSV antigen to uninfected dendritic cells (DC) in the dermis occurs [11] . All these processes require the secretion and action of cytokines and chemokines. Cytokines and chemokines are major soluble modulators of immune cells and are initially secreted by resident epidermal and dermal cells—LC, DC, macrophages, and keratinocytes—and then infiltrate immune cells. Some of these communications can be hijacked and modulated by HSV to allow the virus to persist and prevent antiviral immune responses, discussed below. However, unlike other Herpesviruses, HSV has not been shown to produce any functional cytokine and chemokine homologues [12].

Cytokines are important modulators and communicators between immune cells and non-immune cells. Cytokines are best known for regulating local and systemic inflammation, but they can also be involved in the processes of cell migration and cell proliferation. Both pro- and anti-inflammatory cytokines play an important role in host defense against disease by participating in the regulation of inflammation. Cytokines and cytokine receptors can be divided into several groups depending on their biological activity and molecular structure. Cytokines include interleukins (denoted by "IL"); interferons (IFN: eg IFN-α, β and γ), tumor necrosis factors (TNF: TNF-α and lymphotoxin), growth stimulating factors (including granulocyte macrophage-colony stimulating factor (GM-CSF)) and chemokines [13]. These groups consist of structurally related but not always functionally similar cytokines.

Chemokines regulate cell migration in the immune system and are a component of the immune response. Chemokines are secreted into the extracellular space by all major immune cells and either remain as soluble proteins or bind to extracellular matrix components to form a hemotactic gradient to attract other cells [14]. Chemokines can be classified as either inflammatory or homeostatic in nature.

Primary HSV lesions are an understudied source because they are rarely acquired. Although HSV stimulation cannot be detected in primary herpetic lesion biopsies in animal or cell culture models, it can provide important information about the immune response in human tissue. The role of cytokines and chemokines in human primary lesions has not yet been investigated. Cytokines and chemokines present in recurrent lesions were investigated. Human recurrent lesion studies showed that IL-1α, IL-1β, IL-6, IL-10, IL-12, CCL4, CCL3, and CCL5 were detected on day 1 from onset. [7].

**Keratinocytes**

Although not usually considered immune cells, keratinocytes can detect pathogens, including HSV, through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). Keratinocytes are the first cells infected with HSV, which is initially detected by TLR2 binding of viral glycoproteins. Induction of TLR2 signaling results in the production of pro-inflammatory cytokines such as TNF, IL-1, IL-6, and antiviral cytokines, including type I interferons. These cytokines can act on surrounding keratinocytes and immune cells to reduce viral spread. IFN-α/β induces an antiviral state in surrounding keratinocytes and increases MHC-I production in HSV-infected keratinocytes, allowing them to be more easily targeted and eliminated by CD8 T cells. IFN-α/β also induces apoptosis. However, HSV inhibits apoptosis and counteracts this effect in most cell types. IL-1 is produced by keratinocytes, but its release is inhibited by HSV infection. IL-1β, a proinflammatory cytokine, is active in its cleaved form, but HSV suppresses this activation. IL-1α is biologically active in its pro form, with its release further promoting inflammation and neutrophil infiltration. Another indirect effect of TLR2 stimulation is the enhancement of tight junctions between keratinocytes to reduce viral spread through the intercellular interstices. Keratinocytes secrete low levels of the complement factors, C3a and C5a, and TNF increases this expression, resulting in chemokine secretion that attracts innate immune cells [15].

In general, the response of keratinocytes to HSV is complex and important in early infection. They produce many cytokines in interaction with HSV. Cytokine production increased along with the production of chemokines released after interaction with other resident and infiltrating immune cells. Cross-signaling between them is important for optimizing early host defense and HSV control.

**Dendritic cells**

DCs are an important part of the immune response to HSV due to their ability to mediate between the innate and adaptive immune systems. Their main role is patrolling for pathogens, presenting antigens to T cells in the lymph nodes after infection is detected.

LCs are among the first immune cells to encounter HSV, and thus they are vital in the formation of an immune response to HSV [16]. Thus, LCs become infected with HSV and migrate to the dermis and fuse with dermal DCs, which then present HSV antigens to T cells [17, 18]. Cytokines and chemokines are hypothesized to be involved in this process, but little is known about the chemokines and cytokines that may be involved. HSV-infected human monocyte-derived DCs (MDDCs) have been shown to produce TNF, CXCL10, and IL-8, which may be important in the clustering of LCs and DCs.

In addition to releasing their own chemokines and cytokines, DCs stimulate T cells to release cytokines and chemokines. A study in the vaginal tract of HSV2-infected mice showed that inflammatory monocyte-derived DCs were required to induce Th1 CD4 T cells to secrete IFN-γ. This process was based on Type I IFN

signaling and CCR2-mediated migration of inflammatory monocytes to the vaginal tract. Another study showed that vaginal submucosal CD11c + DCs were important in stimulating CD4 T cells to release IFN-γ when mice were infected with HSV2 [19]. Thus, regardless of the origin and type of DC, they are crucial for the stimulation of an effective antiviral T cell response.

**Macrophages**

Macrophages are particularly important for the formation of an immune response against HSV, contributing to the reduction of viral load in mouse models. Resident macrophages are present in the skin, but their role in human HSV infection is poorly understood. During infection, the primary function of macrophages is phagocytosis of cellular debris and secretion of cytokines, including TNF, IFN-α, IL-6, and IL-12 [20]. IFN-α and -γ activate macrophages and modulate their cytokine production. Recent studies in mouse eyes indicate that the primary role of macrophages during HSV infection is to serve to process HSV antigens and present them to T cells [21].

**Natural killer cells**

NK cells help clear HSV by two main mechanisms; Infected cells that down-regulate MHC-I expression are cytotoxic to CD56 dim CD16+ subsets and release IFN-γ from the CD56 subset. As discussed above, this IFN-γ is a key antiviral effector, upregulating MHC-I and -II expression in infected keratinocytes, activating macrophages and DCs, and stimulating B cells. NK cells and γδ T cells are considered to be the main producers of IFN-γ prior to activation. IFN-γ induction in NK cells is also induced by IL-12 secretion involving activated myeloid cells and precedes the attenuation of the immune response by regulatory T cells. The relative importance of iNKT cells in HSV infection is still poorly understood, although their role has been demonstrated in mouse models [22]. Therefore, the relative roles of NK and iNKT cells in HSV infection should be investigated, in part, in human ex vivo model systems.

**T cells**

CD4 and CD8 T cells are a key part of the adaptive immune response to HSV. CD4 T cells are an effector cell involved in the immune response to recurrent human HSV infection 12–48 h after infection and are activated 4 days after the onset of primary lesions in humans [23]. CD4 T cells help DCs to activate CD8 T cells, which produce IFN-γ, which modulates the immune response and limits HSV replication and spread, and helps clear HSV by activating B cells. IFN-γ production by CD4 T cells is critical and is produced by Th1 CD4 T cells [24]. Chemokines such as CCL5 attract CD4 T cells to sites of infection, where cytokines such as IL-12 produced by DCs initiate the differentiation of CD4 T cells toward the Th1 subtype, producing IL-2 and IFN-γ.

**B cells**

In human vaccine studies, systemic anti-HSV antibody has been implicated in protection against genital herpes, while the role of systemic antibody diffusion in murine eye infection cornea has also been shown. The role of local infiltrating B cells in HSV infection and other sexually transmitted viruses has been less studied than other infiltrating adaptive immune cells. Antibody-secreting cells and detectable and increased levels of neutralizing anti-HSV antibodies are present in lesional biopsies and are clustered with CD4 T cells showing cross-talk. In addition to the antibody response, B cells have been observed to secrete IFN-γ, IL-4, IL-6, and several other cytokines [25, 26]. However, the role of these cytokines by activated B cells in lesions in the context of HSV infection would be negligible compared to other immune cells in existing lesions [8].

Thus, cytokines and chemokines are integral to the immune response to HSV because they control the function and effector functions of many immune cells. However, these responses have been neglected in vaccine and drug design in the past. Vaccines that specifically use cytokines and chemokines to stimulate the cells needed for a robust response to HSV are currently being developed. It is important to unravel the key immune cell interactions required for optimal protection against HSV infection and therefore to guide the development of vaccines and immunotherapies.

The aim of this study is to review and collect published data on the role of cytokines, chemokines, macrophages, T and B cells produced by immune cells in response to HSV infection in the immune response to HSV. changes have been noticed. Thus, the following changes are found in a group of patients infected with HSV-2 infection.

As a person ages, the immunity of cells decreases, which increases the risk of contracting herpes zoster (HZ). Although oxidative stress plays a crucial role in the development of HZ, serum biomarkers of antioxidant activity of the disease are scarce. The aim of this study is to investigate the blood levels of key antioxidants in HZ patients. To the best of our knowledge, this is the first study on this issue in the literature. Serum levels of antioxidants, including uric acid (UA), total bilirubin (TBI), albumin (ALB), vitamin D levels, and inflammatory markers such as homocysteine (Hcy) and C-reactive protein (CRP) in 53 age- and sex-matched HZ and analyzed retrospectively with healthy controls (HC). The relationships between these markers and the clinical severity of postherpetic neuralgia (PHN) and HZ were also evaluated.$p < 0.001$), no statistical differences were found in vitamin D levels between the groups. Hcy and CRP levels were significantly increased in HZ patients compared to HCs. Significant differences in serum levels of UA, Hcy, CRP and vitamin D were observed in the PHN group versus the non-PHN group ( p ). < 0.001). The presence of inflammatory markers was found to be positively associated with disease activity. Furthermore, these biomarkers were statistically significantly increased in severe clinical type compared to mild or moderate clinical types of HZ. These results suggest that uncontrolled varicella-zoster virus reactivation, acute nerve injury, and PHN may be associated with low antioxidant levels. These biomarkers may be a protective factor for HZ, but more research is needed to elucidate the underlying mechanism [27].

Thus, indicators such as T and B cells, cytokines, chemokines, macrophages, keratinocytes, monocytes, etc., which occur during herpes infection from opportunistic infections, were investigated. In addition, the treatment and prevention of these infections, as well as the development of vaccine strategies, were investigated. research is needed.

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