# HUMAN IMMUNE SYSTEM AND CHARACTERISTICS OF HERPETIC INFECTION PATHOGENESIS (REVIEW)

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In recent years the significance of knowledge of immune mechanisms of various pathological conditions is growing, since it is related to the survival peculiarities of modern human. Acute diseases are frequently protracted, the number of chronic conditions increasing. The principal tasks of human immune system study is to determine an impaired component of immunity system, make the prognosis of a chronic character of the disease, and assess the provided treatment efficiency.

Virus immunology is progressing rapidly. However, there are still many incomprehensible mechanisms of interaction between a human organism and viruses; some functions of many virus proteins enabling viruses to escape immune surveillance are understudied. Such studies will enable to comprehend significantly the pathogenesis of virus infections, and therefore develop new forms of treatment and prevention.

The review presents current views on immune response formation in herpetic infection, the interaction mechanisms of a virus and a macroorganism, the main lines of research in a clinical picture, diagnosis and management of the pathology.

**Key words:** Epshtein–Barr virus; cytomegalovirus; herpetic infections; immune response mediators.

The main immunity function is the protection against any substance foreign to the body, and maintenance of its internal uniformity, i.e. homeostasis. Ultimately, it means the preservation of biological individuality. The theory of immune response of a human body has worked a long and problematic way. The famous works of I.I. Mechnikov have been valuable up to the present since he represented a biological theory of inflammation and developed basic principles of immune system. Subsequently, the problem was further studied by such famous pathologists and internists as A.A. Bogomolets, I.V. Davydovsky, N.N. Sirotinin, A.A. Maksimov, R. Virkhov, D. Keller, J. Dausset and others. The growing social significance of the study of immune mechanisms of different pathological conditions is due to the character of human life: acute diseases frequently are protracted; the number of chronic diseases is increasing. The principal tasks in human immune system study are the identification of the disturbed component of immune system, the prognosis of infectious disease chronization, and the assessment of therapy efficiency.

***Human immune system indices.*** The impact of an agent on a human body leads to the activation of cells of macrophage-phagocytic and T-effector immune system. The cells of macrophage-phagocytic system are the basic producers of tumor necrosis factor alpha (TNF-$\alpha$), interleukins (IL) IL-1$\beta$, IL-6, called proinflammatory cytokines. The action of cytokines is mediated through specific receptors located on an outer cytoplasmic membrane of a target cell. After linking of a cytokine to a receptor, a cytokine signal is transmitted to a cell nucleus and has an effect on genetic apparatus resulting in the synthesis of new proteins and a cascade of intracellular reactions changing functional condition of a cell: proliferation, differentiation, activation or passing to programmed death (apoptosis) [1–3]. The particular characteristic of proinflammatory cytokines is an extremely wide spectrum of action including a cascade of immunopathological reactions: an impact on thermoregulatory center, activation of a lymphocytic component, increase of neutrophil activity, stimulation of fibroplastic processes, procoagulant activity stimulation,

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synthesis of acute phase proteins by hepatic cells, hematopoiesis stimulation, and the activation of macrophages [4–6]. IL-1β activates T-effector immune system and further IL-2 synthesis that stimulates blast-cell transformation processes and the differentiation of immunocompetent cells [7, 8]. One of the significant events in immune response is antigen presentation, in which antigen-presenting cells, molecules of class II histocompatibility and T-helpers take part. T-helpers are not homogeneous cell population. Differentiation of native T-cells results in the formation of two types of T-helpers — Th1 and Th2 [9–11]. The discovery of a quantitative analysis of cytokines enabled to find out T-helper heterogeneity. T-helpers have appeared to differ from each other by a set of cytokines produced: Th1-helpers produce interferon (INF-γ), TNF-β, IL-2, while Th2-helpers — IL-4, IL-5, IL-10, IL-13 [12, 13].

Currently, Th1 and Th2-helpers are generally thought to present alternative conditions of gene expression and function of CD4 T-lymphocytes. When using multiply passaged cultures with medium change, there was found maintenance stability of Th1- and Th2-helpers with a permanent set of synthesized cytokines [12, 13]. The experiments on mice proved the fact of Th1 and Th2 stability in vivo and showed the key factors determining an immunity type to be INF-γ and IL-4. So, if INF-γ gene is missing, there is immune response failure by cell type maintained by Th1, IL-4 elimination blocks Th2-depenedent humoral response [14–16]. It should be noted that the factors directing the differentiation of Th2-helpers differ from those inducing Th1. This fact seems to be absolutely reasonable, since Th2 development results in the synthesis of cytokines IL-4 and IL-10 suppressing total activity of IL-12, INF-γ, as well as leads to the synthesis of cytokines IL-1β and INF-α, which can induce the synthesis of IL-2 and INF-γ by T-cells. There is also an opposite situation, when cytokines Th1 suppress the production of cytokines typical of Th2 [15, 16].

Cytokines are characterized by pleiotropy, as well as doubling and overlapping effects, the interaction of different cytokines in cascades of an integrated regulatory network. Cascade character of cytokine action is explained by the fact that one cytokine induces the production of another (for example, IL-1β induces the production of IL-2, IL-6, IL-8, TNF-α and others) [16, 17]. Cytokine interaction is characterized by synergism (for example, TNF-α with INF-γ) or antagonism (for example, IL-4 with INF-γ). Balanced cytokine regulation is based on the balance of alternative by biological activity molecule pools, the imbalance leading to pathology [18–20].

The contact with an agent is a signal for monocytes to secrete proinflammatory cytokines IL-1β, IL-6, IL-8, IL-12, TNF-α. Autocrine stimulation of macrophages by these cytokines is accompanied by the production and secretion of other biologically active molecules: superoxide radicals, prostaglandins, leukotrienes. The targets of paracrine action of the same proinflammatory cytokines are endothelial cells of blood vessels, on which the expression of adhesive molecules is induced, by which the inflow of circulating neutrophils and monocytes in the site of infection is provided. IL-8 is an autocrine chemo-attractant for endothelial cells and can function as an angiogenic factor [19, 20].

An alternative regulatory cytokine for macrophages is a typical proinflammatory cytokine IL-10, its producers being monocytes, macrophages, Th2- and even Th1-lymphocytes. This cytokine is a physiological antagonist and inhibitor of IL-12 synthesis, suppresses the production of INF-γ and the whole Th1-response. IL-10 inhibits the production of all proinflammatory cytokines (IL-1β, IL-6, IL-8, IL-12, TNF-α) by macrophages, expression of receptors TNF-α and IL-12 on natural killers [20, 21]. In addition to IL-10, an inhibiting cytokine is transforming growth factor (TGF-β) produced by all types of leukocytes including lymphocytes and macrophages. Among TGF-β effects there have been described both proinflammatory (chemo-attractant for granulocytes, promoter of cytokine receptor expression), and anti-inflammatory (lymphocyte proliferation suppression, inhibition of proinflammatory cytokine production, inhibition of macrophage protective functions) [21]. TGF-β inhibits IL-2-dependant proliferation of thymocytes, induced IL-2 production by T-cells of cytokines, activated IL-2 cytolytic cell functions. The peculiarity of TGF-β lies in the fact that it inhibits cytokine production and the response of both alternative subpopulations — Th1 and Th2 — on cytokines. In this regard, antigen-specific T-lymphocytes producing only TGF-β have been distinguished as a special subpopulation — Th3. The most marked antagonistic relations between TGF-β, on the one hand, and IL-12 and INF-γ, on the other hand, are considered to be the cause of induction of peripheral immunological tolerance in response to antigen administration [22–24]. An inhibiting effect of TGF-β on tissue macrophages in the site of infection is mediated by limited INF-γ production. As other anti-inflammatory cytokines, TGF-β suppresses the process of excessive macrophage activation resulting in devastating consequences [23, 24].

***Immune system and herpes viruses.*** Currently, there have been discovered over 100 herpes viruses, 8 of which are human pathogenic. They are: herpes simplex virus (HSV) type 1 and type 2, varicella-zoster virus, cytomegalovirus, Epstein–Barr virus, human herpesvirus of type 6, 7 and 8. All 8 types are represented by DNA-containing viruses with common morphology, which is not differentiated by electron microscopy [24].

Pathogenesis of herpetic infection relates to clinical picture and epidemiology. Having entered the human body, herpes simplex virus persists in it for the life term from, time to time resulting in recurrences of various severity. In paravertebral ganglia herpesvirus is latent. Herpes virus is widely spread and, furthermore, is a pantropic agent affecting different tissues and causing different diseases:

skin diseases (herpes of skin, wings of nose, face, hands, buttocks, etc);

mucosal lesions (stomatitis, gingivitis, pharyngitis, etc);

ophthalmic herpes (conjunctivitis, keratitis, iridocyclitis, uveitis, etc);

herpes genitalis (inflammatory, vesicular and ulcerative diseases of genital organs, cervical canal of uterus and adnexas);

visceral diseases (pneumonia, hepatitis, esophagitis, etc);

herpetic disorders of central nervous system (meningitis, encephalitis, neuritis, encephalomeningitis, etc) [24, 25].

Herpes viruses are known to be obligate intracellular genetic parasites and reproduced in nucleus of infected cells. All non-tumor viruses cause quick degeneration and death of affected cells. Tumor viruses are characterized by long-term relations with a host cell resulting in changed biological properties of a cell, its growth potential increasing [25]. Herpes viruses are absorbed on lipoprotein receptors. The sequence of processes leading to virus formation is the following: virus protein synthesis — protein "maturation" — protein binding to a newly formed virus DNA — the formation of whole particles. Mature virions are released from a cell in a variety of ways: herpesvirus nucleocapsid is eventually "push" out of the cell nucleus first, and then — out of its cytoplasm. The outer membrane is formed due to membrane components of the nucleus and cytoplasm of a host cell. Virion replication results in the change of cell appearance. In certain parts of a cell (cytoplasm or nucleus) virus inclusions visible by a light microscope are accumulated. Cell change or the presence of inclusions in cells is of great diagnostic value [25, 26].

In the course of evolution, herpes viruses and host organism have developed different mechanisms to avoid their elimination by immune system. One of such mechanisms described in DNA-containing viruses consists in homolog encoding of a number of cytokines, chemokines and their receptors playing a key role in an immune response. The analysis of such virus cytokines and the discovery of their role in the disease pathogenesis can promote the development of new approaches to immunomodulating therapy [25, 26].

In addition to the use of cytokine homologs, other ways to evade an immune response in viruses can be realized. So, antigen variation can have a radical effect on immune reaction formation, as well as promote the appearance of new protective mechanisms. Many virus proteins block effector functions of cytokines, e.g. antivirus effect of INF or TNF-dependent apoptosis; moreover, there have been also described intracellular antagonists of signal transduction through TNF and IL-1 receptors [27]. Protein LMP1 of Epstein–Barr virus can serve as a good model of how viruses wedge in signal cascades of cytokines; this protein attracting the components of signal transduction associated with TNFR and CD40, and promoting virus replication [28].

All herpesviruses are DNA-containing, similar in morphology, nucleic acid type, reproduction type in the nuclei of infected cells, and sizes, as well as in the ability to induce latent, acute and chronic infection in human [28, 29].

Currently, a modern classification of herpesviruses is used: herpesvirus family is divided into three subfamilies — $\alpha$, $\beta$, $\gamma$.

$\alpha$-herpesviruses usually persist in central nervous system (in sensory ganglia) maintaining latent infection, which frequently develops as an intermittently aggravating disease (HSV-1, HSV-2). These herpesviruses are characterized by a short reproduction cycle with cytopathic effect in the cells if infected cultures.

$\beta$-herpesviruses are characterized by less prominent cytopathicity of cells, a long round of replication. They cause clinical and latent infection in salivary glands, kidneys and other organs, and can result in multi-system diseases in newborn children and adults in immunodeficient diseases (cytomegalovirus infection, exanthema subitum, chronic fatigue syndrome).

$\gamma$-herpesviruses are characterized by tropism to B and T-lymphocytes (but are reproduced mainly in B-cells), lymphoid cells, in which they can reproduce and persist for a long time. These viruses can cause severe, fatal lymphomas and leukaemias, Kaposi`s sarcoma, the development of which is promoted by complementary factors — exogenous, genetic and others.

The diameter of a mature herpesvirus virion is 120–200 nm. Virus has spherical shape and includes fore structural components:

1) core (a gemone is represented by virus DNA) is a linear duplex molecule with short and long components; consists of 80 genes;

2) supercapsid with an outer membrane (envelope) penetrated by glycoprotein spikes, type-specific antigens, by which certain serotypes of herpes viruses are determined;

3) inner membrane (tegumentum) is located between supercapsid and capsid;

4) capsid, formed of 162 capsomeres, 100–120 nm in diameter, is organized by cubic symmetry type, and represented by group-specific for each subfamily antigens.

In virion structure there are over 30 structural proteins (glycoproteins), seven of which (gB, gC, gD, gE, gF, gG, gX) are on the surface and induce the formation of virus neutralizing antibodies [30].

Herpes virus reproduction in sensitive cells is a complex process proceeding with the participation of virion, cellular, virus-induced and virus-modified enzymes. On virion surface there are 11 proteins, 10 of which are glycated. Glycoproteins gB, gD, gE interact with receptor molecules on the outer membrane of target cells [24]. After the fusion of a virus and a cell membrane,

tegument proteins located between the outer virus membrane and a cupsid, are released in cytoplasm. One of them (VHS) inhibits the translation of cell proteins, while another (α-TIF) enters the nucleus and initiates transcription of early (α) herpervirus genes. Capsids are transported to nuclear pores, where virus DNA (vDNA) is released from capsids, enters the nucleus and makes a ring connection [30, 31].

The mechanisms of virus evading an immune response can be divided into three groups: 1) the change of immunodominant epitopes; 2) an obstruction to cell immunity, inhibition of virus peptide presentation and inactivation of natural killers (NK-cells); 3) the inhibition of effector function realization, for example, cytokine expression, as well as apoptosis of infected cells [32, 33].

The main effector cells participating in antivirus response are NK-cells and cytotoxic T-lymphocytes, which synthesize proinflammatory mediators and directly lyse infected cells, as well as B-lymphocytes producing antibodies, which become specific for virus antigens using T-helpers. Persisting viruses have acquired some mechanisms to reduce the interaction with a host`s immune system. These mechanisms enable them to replicate and spread among healthy people [34].

Recently, humoral and cell immunity indices have been actively studied. In acute period of infectious mononucleosis the presence of Epstein–Barr virus DNA revealed by polymerase chain reaction (PCR) in blood enables to confirm the diagnosis in 100% patients, while Hoff–Bauer test is positive in 80% cases only. Capsid antibodies of class IgM to Epstein–Barr virus in an acute period of the disease and in early reconvalescence were found respectively in 85 and 90% of patients. Early antibodies of class IgG to Epstein–Barr virus in an acute period and in early reconvalescence of infectious mononucleosis were revealed respectively in 68 and 70%, and nuclear antibodies were found only in 10% of patients with acute infectious mononucleosis, while by month 12 they were found in 95–97% patients. In 1/3 of patients after infectious mononucleosis active replication of Epstein–Barr virus persisted for a long period of time (at least two years) [35].

Laboratory diagnosis of herpesvirus infections in patients with acute leukoses revealed serological and molecular markers of all herpesviruses of interest [36, 37]. Epstein–Barr virus was recorded to have reduced detection rate of markers after chemotherapy. In patients with a resistant form of acute leukosis the markers of active replication of Epstein–Barr virus were found. Detection rate of human herpesvirus 6 in blood was revealed to increase by several times, and in bone marrow — twice.

The study of the effect of asymptomatic herpesvirus infection on female reproductive system showed a reliably high detection rate of Epstein–Barr virus in endometrial cells in women with spontaneous miscarriage [38]. Hormone-dependent activation of endometritis associated with HSV, and predominance of type 1 Th in the examined patients have been revealed. Herpesvirus infection including asymptomatic has been concluded to result in infertility.

The analysis of the functional state of different organs and systems in patients with herpesvirus infections showed that infectious mononucleosis can proceed with myocarditis events [38, 39]. Malfunction of myocardial conduction was found in 1.5% patients, myocardial contractility — in 27.5%, there being made the conclusions of possible further dysfunction of automatism, conduction and electric imbalance.

The assessment of cytotoxic reactions of lymphocytes in children with infectious mononucleosis showed clinical and hematological manifestation to be accompanied by an increased content of CD4 and CD8 lymphocytes in peripheral blood against a reduced secretion of INF-γ and TNF-α, that is true for an early reconvalescence [40]. In infectious mononucleosis there activates Fas-dependent apoptosis of lymphocytes, as evidenced by an increased content of CD95 and CD95L cells in blood, it being most marked in an acute period. Dysfunction of cytotoxic T-lymphocytes in infectious mononucleosis in an acute period and in early reconvalescence is due to INF-γ and TNF-α reduction [41–43].

Epstein–Barr virus has been found to be an etiological agent of some benign and malignant tumors. Latent membrane protein of LMP1 virus (accepted as virus protein-oncogen) of different clinical and geographic origin is characterized by various types of amino acid mutations having an effect on its biological activity. Among punctuate amino acid replacements, mutations of S366T, F106Y, 185L, E328Q related to an increased transforming activity and decreased cytotoxicity of LMP1 molecules are absolutely prevail [44, 45].

The verification of HSV, cytomegalovirus DNA using PCR revealed the relation of congenital anomaly defect with intrauterine infection by these agents in 85.9% cases. Based on the presented observations, the authors suggested that intrauterine infections can result in congenital malformations [44, 45].

The study of clinical and laboratory characteristics of infectious mononucleosis in adults showed that one of specific feature of infectious mononucleosis is a liver disease, which occurs in 75% of cases and is manifested by hepatomegaly, slight bilirubinic imbalance, an increased transaminase activity (from 2 to 10 norms) persisting in the period of convalescence in 13% of patients. In 4.8% of cases the disease proceeds as acute hepatitis (jaundice), 7% of cases can be complicated by infectious toxic myocarditis and combined with reactivated cytomegalovirus infection [43, 46].

Herpetic infections have been studied as a secondary immunodeficiency forming factor in children [43, 46]. Children who had had herpetic infection in infancy were found to have decreased immune status indices and reduced level of endogenous interferons in blood. Current

herpetic infection was found to be a major factor in the formation of secondary immunodeficiency in children.

The analysis of the effect of HSV and cytomegalovirus in seminal fluid in men showed that HSV occurs more frequently in idiopathic infertility and correlates to reduced number of actively mobile sperm cells and morphologically normal forms of germ cells [47, 48].

For an objective evaluation of endogenous intoxication and immunopathological reactions in children with Epstein–Barr virus there were studied the levels of medium-weight molecules and circulating immune complexes. For the purpose of studying the intensity of immunopathological reactions there were determined titers of autoantibodies in blood serum to the tissues of heart, liver, spleen, pancreas, kidneys, intestine, thymus, lungs and brain by microtechnique in passive hemagglutination test using priority anti-organ erythrocyte diagnostica, as well as the content of immune response mediators [49, 50]. Primary infection proceeding in the form of infectious mononucleosis has been found to be accompanied by endogenous intoxication, more intense but not long-term than in the process reactivation. In under-reactivity of cell immunity and the shift of cytokine balance towards Th2-response in reactive infection there was significant increase of autosensibilization to tissues of different organs. The highest autoantibody levels were those to intestinal and hepatic tissues. It gave evidence of activation of autoimmune processes in organopathology formation in Epstein–Barr virus infection.

Complex clinical and laboratory study of the indices of cellular and humoral components of immunity in patients with demyelinising polyneuropathies (Guillain–Barre syndrome) associated with Epstein–Barr virus revealed numerous immunological changes compared to healthy subjects. The level of autoantibodies to gangliosides of cell membranes and peripheral nerves was high. There was made a conclusion of the possibility to use immunological indices (number of CD3 cells, CD3 HLA-DR cells and IgM level) for differential diagnosis of various forms of Guillain–Barre syndrome at an early stage [51–53].

A great number of researches are being devoted to the study of the prevalence of endogenous infections of a perinatal period and their clinical and neurological manifestations in children and adolescents. In children with clinical and neurological symptoms manifested by mental retardation formation, motor defects, arrested development, infantile cerebral palsy, epilepsy, cephalgic syndrome, hyperactivity, neurotic and cerebro-asthenic syndrome, HHV-6 was diagnosed in 67% cases, Epstein–Barr virus — in 36%, cytomegalovirus — in 11%, HSV type 1 and 2 — in 11% cases [52, 53].

Currently, the activity of anti-herpetic vaccines is being under study [53–56]. The advantage of combined use of vaccine — Vitaherpavac (Vitafarma, Russia) and imunomodulator — Hyaferone (Vitafarma, Russia) has been shown. A new form of administration — suppositories — was found to be able to enhance immunogenicity and protective properties of the vaccine, as well as reduce its administration and provide easy usage.

The interaction [57] of herpesvirus infections and human reproductive function is paid great attention to. The analysis of the presented findings [57] enables to conclude the following: HSV causes spermatogenesis abnormality, reduces proliferative activity of spermatogonia, increases apoptosis of germ cells. Intra-gamete localization of herpesviruses is indicated.

There being studied pathogenetic mechanisms of herpetic hepatites caused by cytomegalovirus, Epstein–Barr virus, HHV-6, described the mechanisms of antibody-dependant cytolysis of hepatocytes affected by herpesviruses, under the effect of T-suppressors and natural killers. In jaundice forms of herpetic hepatitis, DNA of viruses are revealed mainly in CD3, CD4, CD8 lymphocytes, whereas in mononucleosis — B-lymphocytes are infected [58, 59].

There being improved an early differential diagnosis of infectious mononucleosis forms associated with herpesviruses types 4 and 5 in children. Children with mixed infection (Epstein–Barr virus + cytomegalovirus) have been shown to have more marked lymphoproliferative syndrome, high fever, sore throat with purulent overlays, and positive test for heterophil antibodies [58–61].

Virus immunology is progressing rapidly. However, there are still many incomprehensible mechanisms of interaction between a human organism and viruses; some functions of many virus proteins enabling viruses to escape immune surveillance are understudied. Such studies will enable to comprehend significantly the pathogenesis of virus infections, and therefore develop new forms of treatment and prevention.

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