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VIRUSES AND THE IMMUNE SYSTEM
VIRUSI I IMUNI SISTEM

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Abstract

Recognition of the importance of the role of viruses in disorders of immune homeostasis has altered some of the previously held standpoints in immunology and virology. Newly discovered viruses present a specific problem. Disorders of immune homeostasis caused by viruses can develop due to: the mechanism of complete or abortive viral replication in lymphocytes and macrophages; the activity of soluble cytokine factors; the effects on antigen-presenting cells, as well as on cells involved in the process of phagocytosis; and due to excessive stimulation of the suppressor function of T-lymphocytes. Viruses sometimes affect the immune system by multiple mechanisms.

Key words
Disorders of immune homeostasis, new viruses.

Ključne reči
Poremećaji imunološke homeostaze, novi virusi.

Recognition of the importance of the role of viruses in disorders of immune homeostasis has altered some of the previously held standpoints in immunology and virology. [1,2,3].

Facing the diverse and interwoven mechanisms of the host's immune defense (connected, regulated and stimulated by immunocytokines - soluble substances whose role is so significant they can lead to essential changes in the flow and outcome of immune reactions, especially in cooperation with additional co-stimulating factors, presence or absence of adhesive co-stimulating molecules, etc.), viruses as obligate intracellular parasites avoid immune response by the following mechanisms:

1. By their own ability to change and thus "deceive" the host's immune system (a feature possessed, first and foremost, by viruses with segmented genome – particularly HIV and influenza virus).

2. By incorporating viral genome into the cellular genome and establishing a proviral status with disrupted reproduction inside the cell, i.e. by inducing virus latency which, at least temporarily, protects the virus against the immune system.

3. By producing defective virus particles (during longer reproduction of viruses in the cell), which compete with mature (replicable) virus particles for host cells and necessary cellular enzymes, leading to decrease in the number of mature (replicable) virions, and hence reducing their stimulation of the immune system. Thus, the virus is not completely defeated, and it changes into the persistent form of infection.

4. By inducing the production of a cytokine profile during the immune reaction (particularly during T-B cooperation – the obligatory reaction to most thymus-dependent antigens), so that the secreted cytokines, instead of contributing to the efficient immune response, cause a failure of host's defense reaction [3].

This phenomenon has recently been described in the first phase of HIV infection, during which there are still enough CD4 "helper" lymphocytes, and the virus in them is still in the form of a proviral DNA (i.e. not yet replicated). Interestingly, a similar phenomenon has been observed in the new coronavirus causing SARS, although there are no similarities between these two viruses. While HIV has a segmented genome (therefore very changeable), the new SARS coronavirus is not variable. It belongs to viruses that cause mild respiratory infections (in the upper parts of the respiratory tract), and mild gastrointestinal infections in humans and animals. Human and animal coronaviruses cannot be recombined with each other, as in the case with human and animal (or bird) influenza A virus, when a new subtype of influenza A virus can develop. Since the human population is not immune to this new virus subtype, influenza pandemics can occur. Although the new SARS coronavirus has none of the potentially fatal virus characteristics, it has caused severe clinical picture in affected patients, as well as a

great number of deaths. Namely, after the initial disease with mild respiratory and digestive symptoms, temporary remission occurs followed by an unfavorable turn of the immune reaction caused by the virus (similar to the initial phase of HIV). It is the secretion of TH2 profile cytokines with subsequent severe interstitial pneumonias followed by respiratory insufficiency, acute distress syndrome and death. This turn of events in the third phase of SARS results from a completely inadequate immune response to the viral infection due to the induced secretion of TH2 profile cytokines by CD4 T lymphocytes (helpers) in the so called T-B cooperation. TH2 group of cytokines includes, among others, interleukins [3,4,5 and 10]. Their activity directs the immune reaction toward the humoral response (the most suitable response to a viral infection is cellular - destruction of the virus infected cells by CD8 T lymphocytes). Even the induced humoral response is not adequate.

Interleukin 4 causes the production of IgE class antibodies (and partially IgG4 subclass as well) by the plasma cells; interleukin 5 induces eosinophil infiltration, whereas interleukin 10 suppresses the production of TH1 profile cytokines, i.e. interleukins 2, 3 and gamma interferon, whose secretion in the immune response would be adequate. In other words, interleukin 2 is the main autocrine and paracrine factor of the specific clonal proliferation of T lymphocytes. This means that it increases the number of CD4 and CD8 antigen-specific lymphocytes, as well as the cytotoxic effect of CD8 T lymphocytes on the virus infected cells, with a simultaneous induction of B lymphocyte proliferation and stimulation of Lo lymphocytes in their antiviral action (done by gamma interferon as well). In addition, gamma interferon activates the antigen-presenting cells, enhancing all their functions in the process of phagocytosis, processing and presentation of antigens. It also increases the number of class I and II HLA molecules on the cell surface, where both endogenous antigens (on HLA I molecules) and exogenous antigens (on HLA II molecules) are presented to the immune system. In addition to that, TH1 group of cytokines induces the production of IgG subclass of antibodies which bind the complement (with IgM antibodies, which also activate the complement in the classical complement pathway). Thus TH1 profile cytokines help accelerate antigen presentation and adequate virus elimination, stimulating both cellular and humoral defense mechanisms. Unlike these cytokines, TH2 group cytokines make this reaction inadequate, despite the absence of real deficiency of the host's immune response.

IgE class antibodies do not bind directly to the antigen (there is no virus neutralization), nor activate the complement (there is no lysis, opsonification or phagocytosis, i.e. elimination of the causes of these processes). Due to the suppressing effect of interleukin 10, there is no stimulation of the specific clonal proliferation of T lymphocytes, cytotoxic activity of CD8 lymphocytes and Lo lymphocytes, and no activation of antigen presenting cells in all their functions. The number of class I HLA molecules does not increase on the surface of the virus infected cells (where the virus antigens should be presented to the immune system). Therefore, the secreted TH2 profile cytokines induce a completely inadequate and inefficient immune reaction, although the host organism is not immunodeficient, and has all the necessary effector mechanisms of the immune system. Interestingly, the TH2 profile cytokine induction is the only similarity between HIV and the new SARS coronavirus, besides the fatal outcome of both viral infections [8,9,10,11,12]. This immune reaction seems to also occur in cases of severe pneumonia caused by the new influenza virus A (H1N1).

A virus-induced disorder of immune homoeostasis, which is usually temporary, may occur due to the complete or abortive replication of certain viruses in lymphocytes and macrophages (antigen presenting cells). It can also be caused by the action of viruses or soluble factors secreted by them onto the cells involved in the process of phagocytosis, or by inhibiting the activity of HLA complex genes responsible for the synthesis of class I molecules and/or class I and II molecules on the cell surface [3,4,5]. This is another reason, besides the damage to ciliary respiratory epithelium caused by the viral infection, why secondary bacterial infections frequently occur after a viral disease [5,6,7].

Morbillivirus was the first one suspected to cause disturbance of immune homeostasis. This virus replicates in CD4 lymphocytes, CD8 lymphocytes, NK cells and B-lymphocytes. Because of this, lymphocytes have a decreased response to antigens and mitogens, the activity of NK cells is reduced, as well as the inhibition of leukocyte migration. Morbillivirus induces changes in the membrane and damages the receptors on these cells. Hence the activity of CD4 lymphocytes as central regulatory cells is inhibited, and so is the phase of induction, proliferation and differentiation of CD8, B and NK lymphocytes into effector cells of the immune system. Apart from the inhibition of lymphocyte activity, there is also a decrease in production of interleukin-2. According to other authors, this inhibition of lymphocyte activity can be a consequence of increased suppressive activity of CD8 lymphocytes. Immunosuppression caused by morbillivirus occurs in the acute phase of the disease and it is temporary [2,3].

Influenza virus causes epidemic disease frequently followed by secondary bacterial infections. This virus replicates rapidly in the upper respiratory tract. Soon the lymphocyte reaction to antigens decreases. Early lymphocytopenia is a consequence of lymphocyte migration into the respiratory tract. The CD4+/CD8+ index changes, but the NK cell activity (antibody-dependent cytotoxicity) is not damaged [2,3,14].

Epstein-Barr virus infects human B-lymphocytes, with evident viral antigen expression on the membrane of the infected lymphocytes. Transformed T-lymphocytes are atypical lymphocytes and virocytes. Polyclonal activation and proliferation of lymphocytes causes synthesis and secretion of various antibodies. The CD4+/CD8+ index is reduced. This all results in a decrease in immune response of lymphocytes to antigen, increased sensitivity of the host to infective agents, and increase of the suppressive activity of CD8 lymphocytes [1,2,3,15].

Cytomegalovirus infects T-lymphocytes and monocytes. Lymphocytes therefore have a decreased response to antigens. NK-cell activity is unchanged. The suppressive activity of CD8 cells is increased. The CD4+/CD8+ index is decreased and a temporary immunosuppression occurs [1,2,15].

Herpes simplex virus replicates in T-lymphocytes only if they are activated by an antigen or mitogen. Activity of the genes of the major histocompatibility complex responsible for synthesis of class I and II antigens is decreased. Cytokine and especially interleukin-2 production is reduced, as well as the synthesis and secretion of antibodies to various antigens. It is considered that this virus stimulates the suppressive activity of CD8+ lymphocytes [1,2,3,15].

HIV infects CD4+ lymphocytes decreasing their number and the CD4+/CD8+ index. The activity of the remaining CD4+ lymphocytes is decreased, as well as the effector activity of CD8+ cytotoxic lymphocytes (due to decreased secretion of cytokines by the T-helper cells), NK cells, B-lymphocytes and monocytes. CD4+ lymphocytes present an increased number of receptors for interleukin-2. Lymphocytic proliferation occurs as well [1,3,4,13].

Rubella virus decreases functional activity of B-lymphocytes which are infected. Functional activity of lymphocytes is also decreased by hepatitis A virus infection. Rhinovirus and enterovirus cause a decrease in total number of T-lymphocytes, but not B-lymphocytes, which correlates with the severity of the clinical picture. Number of CD4+ lymphocytes is decreased, whereas the number of CD8+ lymphocytes is unchanged [1,2,3,14].

Apart from immune disorders caused by viral infections of lymphocytes and monocytes, virus proteins may affect the immune reactivity of the organism as well.

Adenovirus E29 protein reduces the activity of cytotoxic T-lymphocytes. Other adenovirus proteins are being studied as well. Some of them may have a similar effect (inhibition of major histocompatibility complex genes, which are responsible for synthesis of class I molecules) [1,2,3,14].

Some retroviruses (established on feline leukemia virus) contain protein E15 with immunosuppressive effects (the number of lymphocytes in the paracortex of lymph nodes is decreased, interleukin-2 production is decreased, as well as the sensitivity to the effects of this cytokine). Some other retrovirus proteins bind and inactivate interleukin-2, but without damaging receptors for this interleukin. IL-2 neutralizes this effect [1,3,4].

Certain virus-induced tumors produce proteins (similar to E15 protein) which cause immunosuppression. This contributes to survival of tumor cells [2,3].

H and F proteins of parainfluenza virus, as well as some proteins of adenovirus and G protein of the vesicular stomatitis virus inhibit interleukin production [1].

All these mechanisms cause a lasting immunosuppression. Immunosuppression exists in the acute and convalescent phase of infection, and in some viruses persists even longer [1,2].

During viral infections immune disorders may develop due to viral infection of phagocytes. Phagocytes are responsible for digestion of microorganisms. They present antigens to the immune system cells and produce immunoregulatory substances and co-stimulatory signals. Macrophages, depending on the age and genetic constellation (existence or lack of receptors and presence of more or less strong enzymes in them) can exhibit different levels of susceptibility to viral infections. Viruses infect phagocytes by cytolytic or slow infection depending on whether they replicate completely or abortively. If the virus manages to avoid the effects of macrophage enzymes and replicates within them, macrophage migration contributes to virus dissemination [1,3].

Many viruses can damage phagocytic functions. Influenza virus and herpes simplex virus inhibit the chemotaxis of phagocytes. Furthermore, influenza virus, parainfluenza virus and cytomegalovirus inhibit the contact necessary for phagocytosis. Influenza virus and parainfluenza virus inhibit the process of phagocytosis itself and the digestion inside a phagocytic cell. Even if the phagocytosis occurs, there is a longer survival of phagocytized particles. Inhibition of the accessory function of macrophages is caused by influenza virus, parainfluenza virus, poliovirus, cytomegalovirus, LCM virus. A certain number of viruses can inhibit the production of various interleukins [1,2,13].

Some viruses inside phagocytes inhibit the major histocompatibility complex gene expression responsible for synthesis of class I and class II molecules, while others use class II molecules as receptors. Thus the number of phagocytes that can successfully present antigen to immunocompetent cells of the immune system is decreased. As the process of presenting antigens to lymphocytes is inhibited, lymphocyte response to various infecting agents is reduced [3].

Cytomegalovirus and LCM virus inhibit synthesis and secretion of interleukin 1 [1,2,3].

During viral infections, a disorder of monocyte function may occur (influenza virus) as well as in the function of polymorphonuclear leukocytes (morbillivirus inhibits chemotaxis, phagocytosis and digestion of polymorphonuclear leukocytes, whereas influenza virus inhibits only phagocytosis and digestion) [1,2,3].

Lymphocytopenia may occur during the acute phase of viral infections. It is caused by lymphocyte redistribution under the influence of viruses [2].

Disorders in activation, proliferation and differentiation of lymphocytes into effector cells can also be caused by viruses. Epstein-Barr virus, which infects precursors of B-lymphocytes, prevents their differentiation into plasma cells [1,2,13].

Constant follow-up and adequate explanation of changes during viral infections which cause disorders of immune homeostasis is necessary in work with patients with viral diseases.

Viral infections in humans are often associated with autoimmune diseases, and various viruses can cause autoimmune diseases in different ways: by polyclonal activation of lymphocytes (also a property of bacteria), by cell destruction (cytopathogenic effect of viruses) and release of intracellular structures into the extracellular space, alterations in identification (due to viral antigens in the cell membrane, which causes a reaction against own antigen components), antigenic mimicry, ectopic induction of HLA antigens through interferon. Viruses can act directly by causing infections, whose consequences may be functional damage of certain subpopulations of regulatory cells. As mentioned above, an infection may cause change in local tissue (with possible release of own sequestrated antigens), polyclonal lymphocyte activation, increased cytokine secretion, engagement of antigen presenting cells with effective co-stimulatory signals [3].

The most important possible cause of autoimmune disease is Epstein-Barr virus, especially due to its property to affect cells of the immune system. This virus acts as a polyclonal activator of B-lymphocytes, and stimulates secretion of immunoglobulins. It also induces the creation of rheumatoid factor. Sera of patients with rheumatoid arthritis contain antibodies which recognize viral antigens. They are present in the extract of B-lymphoblastoid cell line infected with Epstein-Barr virus [1,2,3].

T-lymphocytes of these individuals have a decreased ability to suppress the transformation of B-lymphocytes induced by Epstein-Barr virus [1,2].

Many other viruses (paramyxoviruses, hepatitis viruses, cytomegalovirus, coxsackievirus, retroviruses...) may cause temporary production of autoantibodies during natural infections, whereas some of them also cause immune changes (as in autoimmune diseases). Namely, during these infections, vasculitis and glomerulonephritis are caused primarily by immune complexes [3].

Although sera of patients with systemic lupus contain high titers of antibodies to various viruses (for example antibodies to morbillivirus), these findings are considered to be a consequence of hypergammaglobulinemia in these patients.

Some studies have tried to connect parvoviruses with the appearance of rheumatoid arthritis, but the arguments for such conclusion were insufficient. The same applies to Epstein-Barr virus.

In sera of patients with systemic lupus, an increased level of interferon was recorded (interferon alpha, which differs from the normal interferon alpha because it is sensitive to acid reaction and is inactivated at pH 2). Interferon is produced by leukocytes reacting to viral, but also to nonviral agents and other stimuli. However, the significance of the interferon finding in patients with systemic lupus erythematosus has not been determined. Correlation of this finding with symptoms and prognosis of autoimmune disease have not been established either [3].

Investigations performed in mice with lupus syndrome have revealed that viruses can induce immunopathologic lesions, but that they are not the primary cause of the disease.

A mice model with systemic lupus was used to describe that the lymphocytic choriomeningitis virus, polyomavirus and some retroviruses increase the titer of antinuclear antibodies in infected animals. Other autoantibodies were also increased, and an increase of immune complexes was observed as well (thus worsening the autoimmune disease) [3].

Other infectious agents and the inflammatory process in general also affect autoimmune diseases. However, effects of viruses have been the most studied, considering that viruses are polyclonal activators of B-lymphocytes, and that some of them have tropism for certain subpopulations of lymphocytes. Apart from that, they have a cytolytic ability and probably can associate with autoantigens, changing them and making them foreign to the immune system of the organism [3].

After infections in general, including viral ones which were extensive and long-lasting and followed by secretion of inflammatory cytokines, local phagocytes activated by cytokines as co-stimulating factors can start presenting to the immune system their own intracellular immunogens from the cellular detritus, which had been sequestrated (hidden from the immune system) until then, so that the tolerance towards them did not develop during the intrauterine growth in the thymus (by the negative selection process), as it is the case with other own antigens (to which the immune system does not react under normal conditions postnatally). Therefore, an autoimmune reaction can start in the organism after extensive viral infections. Likewise, accumulation of immune complexes (virus – specific antibodies) may cause a disease of immune complexes, often resulting in a damage greater than the one caused by the viral infection itself (hepatitis B virus) [1,2,3,5].

Many viruses (Epstein-Barr virus – known as a polyclonal activator of lymphocytes, parvoviruses, polyomaviruses, LCM virus, as well as paramyxoviruses, hepatitis viruses, cytomegalovirus, coxsackieviruses, retroviruses, etc) may cause transitory production of autoantibodies during a natural infection. Some of them cause immunopathological changes (as in autoimmune diseases). Namely, vasculitis and glomerulonephritis during these viral infections are caused primarily by immune complexes [3,5,6,7].

Viruses also frequently use intracellular mechanisms in order to avoid the attacks of the immune system and disable its defensive role. They inhibit transportation of virus peptides with the help of their proteins using the TAP molecules. The consequence of that is a low number of class I HLA molecules presented on the cell surface. Furthermore, they can retain class I HLA molecules in the endoplasmic reticulum, thereby preventing the expression of viral antigens. They can also cause breakdown of class I HLA molecules.

The research work on class I HLA molecules and TAP1 and TAP2 molecules, which take part in this transportation, is therefore very important in order to recognize all mechanisms and processes involved in the development of these molecules during their transportation to the cell membrane and presentation on the cell surface, hoping to make a contribution to better treatment of viral infections in the future [3,16].

Constant follow-up and adequate explanations of changes during viral infections which cause disorders of immune homeostasis are necessary in work with patients with viral diseases.

Apstrakt

Saznanje o značajnoj ulozi virusa u poremećaju imunološke homeostaze, izmenilo je neke ranije stavove u imunologiji i virusologiji. Poseban problem predstavljaju novootkriveni virusi. Poremeæaj imunološke homeostaze pod dejstvom virusa može nastati: mehanizmom kompletne ili abortivne replikacije virusa u limfocitima i makrofazima, delovanjem solubilnih faktora citokina, dejstvom na ćelije koje prezentuju antigen, na ćelije koje su uključene u proces fagocitoze, prekomernom stimulacijom supresorske funkcije T-limfocita. Ponekad virusi deluju na imunološki sistem sa više mehanizama.

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