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POSSIBILITIES OF APPLYING MODERN KNOWLEDGE ABOUT THE FUNCTIONING OF THE ANTIVIRAL INTERFERON SYSTEM

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SUMMARY

Therefore, interferons are products of activated cells, lacking specificity for antigens, and serving as mediators of intercellular and intersystem interactions in the immune response, hematopoiesis and inflammation. Disorder of IFN production and reception can be the basis for the formation of many pathological processes. It is important to note that the importance of the IFN system approaches the immunity system, and even surpasses it in universality. It is this universality of IFNs, which makes them the most important factors of nonspecific resistance, that served as the basis for proposing the integral concept of "interferon status", which has the potential for application in clinical practice. The variety of the described effects of IFN indicates the broad control and regulatory functions of this system, aimed in general at preserving the body. Key words: interferons, immunity, antiviral action, interferon system, antiviral protection of immunity.

It is known that the cells of innate immunity are the first to be involved in the fight against viral infection, these are neutrophils, macrophages, natural killers (Natural killer) and dendritic cells (Dendritic ceil). With their participation, an inflammatory reaction develops, accompanied by the secretion of a number of soluble mediators, growth factors, cytokines and chemokines.[4,9,12,14] The development of innate immunity reactions is primarily associated with the recognition of the pathogen by the cells, and molecular structures that are characteristic only of microorganisms and are absent in higher organisms must be recognized.[2,5,7,14] We are talking about the so-called PAMP (pathogen-associated molecular patterns), conservative structures expressed by a wide range of infectious agents. It is not so much a special structure that is recognized as a molecular “image” of a pathogen, such as lipopolysaccharide, the main component of the cell wall of gram-negative bacteria, or double-stranded viral RNA, a typical intermediate product of viral replication.[2,5] This pathogen recognition strategy, on the one hand, helps the body prevent the escape of mutated microbes from the immune response, and on the other hand, allows a limited number of receptors to recognize a huge variety of molecular structures associated with pathogens. The group of pathogen recognition receptors (pattern recognition receptors) of the innate immune system is formed by structurally different receptors of different protein families: humoral proteins circulating in plasma, endocytosis receptors on the cell surface, and signaling receptors located both on the cell surface and in the cytoplasm.[11,16] It has been established that the cells of innate immunity have a number of signaling receptors: Toll-like receptors (TLR), mannose receptors, scavenger receptors (scavenger receptors), Fc receptors of immunoglobulins, transmembrane serpentine receptors TM7, etc.[2,3]... The most versatile is the TLR group, since it has the ability to recognize all types of pathogens: bacterial and viral PAMPs, as well as fungi, parasites, and protozoa. In addition, if the stimulation of scavenger-receptors or TM7 receptors on phagocytes leads to the activation of the phagocytosis reaction in these cells, and the process is limited by the response of one individual cell to the action of the pathogen, then TLR activation leads to the so-called alternative type of phagocyte activation, which is characterized by synthesis and secretion a wide range of cytokines, chemokines, promotes the maturation of dendritic cells and stimulates their antigen-presenting properties, which leads to the involvement of the acquired immune response cells in the process of elimination of infection.[1,5]

The profile of cytokines produced by innate immune cells directs the differentiation of naive T-helpers in four directions: towards T-helpers type 1 (Th1), T-helpers type 2 (Th2), regulatory T-cells (FOXP3) and T-helpers 17, and, thus, mediates the development of an immune response with a predominance of one type of response or another. Thus, the production of IL-12 and TNF-a by macrophages and myeloid dendritic cells is a determining factor in the development of a Th-mediated immune response that promotes the elimination of virus-infected cells by cytotoxic T-lymphocytes.[1,4] Several members of the TLR family that specialize in viral

recognition, in particular TLR3, have a unique signaling pathway leading to the induction of type I IFN. For ligand binding and signaling, TLR3 interacts with CD14 and the c-Src molecule.[1,8,9,11,13] Activation of TLR3 by the adapter protein TRIF leads to the induction of transcription of the interferon-regulatory factor IRF3, which is translocated into the nucleus and induces the expression of IFN-β.[2,4] Plasmacytoid dendritic cells play a central role in the recognition of viral infection; they are called "professional" interferon-producing cells. At the same time, it is the receptors of the TLR family that are the main receptors of viral antigens responsible for the initiation of the production of type I IFN by plasmacytoid dendritic cells.[2,4,18] Plasmacytoid dendritic cells in humans express high levels of TLR7 and TLR9, signal transmission is carried out through MyD88 and leads to the induction of IRF7, which leads to the induction of IFN-a.[2,5,7,8,11,16] Myeloid dendritic cells express mainly TLR3, TLR8 and low levels of TLR2 and TLR4, producing significant amounts of IL-12 upon activation. Receptors TLR2 and TLR4 recognize viral envelope components on the surface membrane of cells, TLR3, tLr7, TLR8 and TLR9 are expressed on the membrane of endosomes, while TLR3 recognize viral double-stranded RNA, TLR7 and TLR8 recognize single-stranded RNA of viruses, and TLR9 - unmethylated CpG DNA motifs.[9,11,12,13]

In addition to plasmacytoid dendritic cells, the so-called “non-professional” interferon-producing cells, in particular, fibroblasts, also participate in the production of type I IFN. In them, the induction of IFN synthesis is carried out in a different way, independent of the TLR, through the receptors of the recently discovered RLH family (Retinoid acid-inducible gene I (RIG-I) -like RNA helicases).[3,7] Elucidation of the RLH function and signal transduction pathways through them is one of the most urgent topics of modern immunology. RHLs are present in all cell types directly in the cytoplasm, where they detect double-stranded RNA (which is absent in an uninfected cell) or 5-triphosphate RNA, which is not typical for humans. Thus, there are 2 types of receptors for recognizing viruses responsible for the induction of type I IFN: Toll-like receptors (TLR) and RIG-I-like helicase (RLH).[8,11,12,16] The interferon system consists of cells that synthesize IFN in response to a viral infection, and cells that, in response to the action of IFN, acquire a state of resistance to viral infection.[3,6,9,13] Viruses that infect mammalian cells are IFN inducers and are sensitive to the antiviral action of IFN, although some viruses release substances that counteract IFN [3,6,7]. IFNs have autocrine and paracrine effects. IFNs exert their action through transmembrane receptors. IFN-a and -b have a common receptor consisting of two subunits, IFNAR-1 and IFNAR-2.[8,9,13,18] The action of IFN, which is to activate the transcription of genes of a number of cellular proteins, is realized through the JAK-STAT system of protein-protein interactions, named after the main actors: the signal transducer and activator of transcription (Stat) transcription factors in the inactive form in the cytoplasm, which are activated upon phosphorylation tyrosine kinases of the Janus family (JAK).[4,11,15,16,18] The signaling pathway is initiated when IFN a / b binds to receptor subunits on the cell surface. As a result of conformational changes in the intracellular domain of the receptor, kinases Jak-1 and Tyk-2 are activated, they cause phosphorylation and dimerization of Stat-1 and Stat-2 proteins, and then their subsequent translocation from IRF-9 into the nucleus.[7] A complex of these three proteins, known as IFN-stimulated gene factor 3 (ISGF-3), activates the transcription of genes induced by interferon - genes that have the enhancer element ISRE (IFN-stimulated response element) in the promoter region. Along with STAT proteins, proteins of the IRF family are the most important factors regulating the transcription of genes induced by interferon. The family of transcriptional regulators IRF (IFN-regulatory factor, IFN-regulatory factor) has 9 members, from IRF-1 to IRF-9.[14] IRF-9 was first discovered as part of the ISGF-3 trimer. IRF-1 binds directly to the ISRE enhancer. IRF-3 is constitutively expressed in most types of cells and tissues; it is activated by the interaction of the double-stranded RNA of the virus with TLR3 receptors, which leads to the induction of transcription of IFN-a and B and IFN-induced proteins. In addition to IRF-3, IRF-7 plays an important role in the regulation of IFN synthesis. In addition, information appears in the literature that upon activation of receptors to IFN, in addition to the activation of the JAK / STAT system, the so-called alternative signaling pathways are triggered, which may explain the presence of various types of biological action in IFN.[4,8,11,13]

The antiviral effect of type I IFN at the level of an individual infected cell is provided in two ways: IFNs suppress viral replication by inducing transcription of genes of a number of antiviral proteins and / or induce apoptosis of an infected cell by triggering a number of signaling pathways of apoptosis. IFN suppresses the replication of a wide range of DNA and RNA viruses both in cell culture and in vivo, inhibiting the synthesis of viral polypeptides - the first stage of the multiplication cycle of most viruses. IFN induces the synthesis of the following antiviral proteins: PKR protein kinase, 2 ', 5'-oligoadenylate synthetase (OAS) and RNase L, RNA-specific adenosine deaminase (ADAR), and proteins of the Mx family. The mechanisms of action of antiviral proteins induced by IFN are described in detail in the review by C. E. Samuel.[7] Along with the induction of the synthesis of antiviral proteins, IFN activates the apoptosis of virus-infected cells.[12] Long before the discovery of IFN, virologists faced the obscure phenomenon of viral interference (mutual suppression), and only in 1957 Isaac and Lindenman isolated a protein responsible for the interference called interferon (IFN). To date, there is no doubt that IFNs are among the most important factors of the body's resistance, taking the most direct part in various immunological reactions. Interferons are a group of biologically active proteins or glycoproteins synthesized by a cell during a protective

reaction to foreign agents (viral infection, antigenic and mitogenic effects). Currently, the concept of "interferon system" has developed, which includes IFN genes and their repressors, IFN themselves, specific cell receptors and enzyme systems that are activated by the interaction of IFN with these receptors (primarily gc-RNA-dependent 2,5, - oligoadenylate synthetase and proteine kinase).[5,17] Interferons were formed in phylogenesis at the same time when the immune system was formed, i.e. in vertebrates. However, from the very beginning they differed from the immune system, since both the object of their action - foreign nucleic acids - and the methods of their recognition and elimination do not have similarities with the recognition and elimination of foreign proteins. The immune system has specialized cells and organs, and the diversity and specificity of antibodies indicate the diversity of antigenic determinants of proteins. The interferon system has no specialized cells or organs, it exists in every cell, since every cell can be infected with a virus and must have a system for recognizing and eliminating foreign genetic information (nucleic acid). If the evolution of the immune system followed the path of increasing the diversity of antibodies and the specialization of cells of the immune system, then the evolution of the interferon system followed the path of the species specificity of recognizing "ours and others". There are close direct and feedback links between interferons of various types and other components of the immune system.[16, 18] The IFN system is disseminated in almost all cells of the body and has only relative species specificity.[3,16] This is what allows it to actively influence the entire cascade of the body's defense reactions (phagocytosis, inflammation), which makes it the most important factor in nonspecific resistance. The variety of detected and studied physiological functions of IFN undoubtedly indicates their control-regulatory role in maintaining homeostasis.[8,13,17,18] The main effects of IFN can be divided into antiviral, antimicrobial, immunomodulatory, antiproliferative, radioprotective, etc.

In humans, 3 different types of IFN are distinguished: IFN type I (a, p, u), IFN type II (y), IFN type III (A,). IFN-a, IFN-R, IFN-y are the first line of defense against viruses and act by inducing a large number of proteins.[14, 18] IFN-a, IFN-R, IFN-y interact with the common cellular receptor.[16] IFN-a is encoded by 24 different genes, IFN-R is encoded by one gene. These genes are located on chromosome 9. IFN-a is a family of 20 closely related polypeptides consisting of 166 amino acid residues, monomers. The receptor for them is the same - CD118. IFN-R also consists of 166 amino acid residues, monomer. The receptor for it is also CD118. IFN-y was discovered in 1965 by Wheelock, who reported that phytohemagglutinin can induce an interferon-like inhibitor of viruses in human leukocytes.[1,4] The gene encoding the synthesis of IFN-y is located on chromosome 12.[2] IFN-y binds to a specific cellular receptor and does not cross-react with IFN-a, IFN-R, IFN-y receptors. Genetically, there is no homology between the type I IFN genes and the IFN-y gene. The ability to secrete various types of IFN was found in immunocompetent cells, as well as in a number of connective tissue cells.[16] Thus, IFN-y producers have been identified among peripheral human monocytes.[14,17] There is a number of indirect data on the physiological secretion of a small amount of IFN-a in a healthy body. It is known that, as a rule, IFN is not found in the plasma of healthy donors, or is found in insignificant amounts (<4 IU / ml). However, this concentration may be quite sufficient for the manifestation of a biological effect. It has been established that cells of healthy individuals are not capable of producing spontaneous IFN. The secretion of IFN from producer cells is under the control of some peptide hormones, glucocorticosteroids, prostaglandins. It is interesting to note that glucocorticoids stimulate the release of IFN by lymphocytes.[5] The recently discovered type 3 interferons include IFN-A1 (IL-29), IFN-A2 (IL-28A), IFN-A3 (IL-28V). Type 3 interferons have their own receptor complex consisting of 2 chains: IL-28Ra and IL-10Rp. The mechanisms of activation of the synthesis of these interferons have not been studied enough, but it is known that the double-stranded RNA of the virus plays an important role in this process.[12, 16, 18] The functioning of the IFN system[5,9] consists of stages strictly following each other, representing a kind of chain reaction of the organism to the introduction of foreign information: induction –production –action – effects. That is, 4 main links of this chain can be distinguished: 1. Induction or "switching on" of the system leading to depression of IFN genes, transcription of their informational RNAs with their subsequent translation. When cells are stimulated with an inducer, the genes encoding IFN proteins are activated, and the translation-production of these proteins occurs. Interferon is secreted into the extracellular fluid and acts through receptors on other cells. As a result of IFN binding to receptors, the process of protein synthesis is induced, which increases the cell's resistance to a foreign agent. It is possible to transfer such proteins to neighboring cells that are not in contact with either the inducer or the interferon itself[18]; 2. Production - synthesis by cells of a-, P-, y-IFN and their secretion into the environment; 3. Action - protection of surrounding cells from foreign information by newly formed IFNs; 4. Effects - antiviral, immunomodulatory, anti-tumorigenic, radioprotective. To date, more than 100 different effects of interferons have been described.[5,10,14,17] Recently, much attention has been paid to the study of the relationship between cellular immunity and IFN. So J. Ranson and co-authors believe that IFN-y is the most important cytokine and interacts between T cells and macrophages, activates cytotoxic activity, plays a primary role in the differentiation and maturation of T cells in the thymus.[10] Interferons can affect the cells of the immune system in various ways, changing: 1) the cell surface, 2) the production and secretion of intracellular proteins, 3) the functional activity of lymphocytes, 4) stimulating or inhibiting the functions of effector cells. After the attachment of IFN to the receptors of the cell surface, the

induction of the synthesis of a number of cellular proteins or, conversely, the inhibition of their production follows. Typically, these proteins exhibit enzymatic activity. IFNs are involved in the synthesis of other cytokines, inducing and / or regulating their production. Thus, for example, it was found that IFN-y induces the synthesis of 8 peptides in resting and stimulated T cells, as well as the release of lysosomal enzymes by neutrophils, which provide the cytotoxic activity of cells. IFN-y induces the synthesis of tumor necrosis factor in macrophages.[12,13]

Large doses of all types of interferons have a suppressive effect on antibody production in the early stages of antibody genesis. This can be the result of inhibition of both T-helper cells and B-lymphocytes. IFN added in the final phase of antibody production may even increase antibody production. The degree of inhibition of antibody synthesis depends on the level of differentiation of producer cells: less differentiated cells are more sensitive to the suppressive effect of IFN.[9,12,14] Thus, IFNs are products of activated cells, lacking specificity for antigens and serving as mediators of intercellular and intersystem interactions in the immune response, hematopoiesis, and inflammation.[11] Disorder of production and reception of IFN can be the basis for the formation of many pathological processes.[13, 14] In terms of importance, the IFN system approaches the immunity system, and even surpasses it in universality. It is this universality of IFN, which makes them the most important factors of nonspecific resistance, that served as the basis for proposing the integral concept of "interferon status" (IFN-status).[17] The assessment of IFN-status is based on the definition of three main parameters: - IFN circulating in the blood, the so-called. serum IFN; - the level of production of a-IFN in response to treatment with viral inducers (interferon reaction of leukocytes); - the level of y-IFN production in response to the processing of lymphocytes by mitogens. In some cases, additional methods can be used to characterize the interferon status: production of acid-stable, acid-labile IFN, detection of NK-cell activity, detection of spontaneous IFN production; detection of enzymes induced by IFN; determination of the level of antiviral state of mononuclear cells by their ability to multiply different viruses in them and a number of others.[12] The variety of the described effects of IFN indicates the broad control and regulatory functions of this system, aimed in general at preserving the body.[5,6,15,18]

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