About interferons

INTERFERONS (IFN) is a common name that currently combines a number of proteins with similar structural and functional properties, which in the vast majority of cases are actively produced by the body cells when they are infected with a virus. These proteins are the most important components of the body's innate non-specific defense against infections and tumor transformations. Interferons were discovered by Isaacs and Lindemann in 1957 as antiviral agents, however, during their subsequent investigation it was detected that the functions of interferons in the cell are not limited to antiviral action: the properties common to this vast group of proteins also include antiproliferative activity (the ability to suppress cell reproduction), which later determines the possibility to inhibit the development of malignant neoplasms, and the ability to influence the state of the immune system, i.e., to perform the role of immunomodulators in the body.

The diversity of Interferons

There are three main classes of interferons, where each class combines proteins of the same type (I, II, or III). Interferon belongs to a particular type according to the type of receptor that binds it.

Type I interferons have one common IFN-alpha receptor (IFNAR), consisting of an alpha subunit (IFNAR1) and a short or a long beta subunit (IFNAR2) (1). In mammals, this type includes the following main types of interferons: alpha, beta, omega, ypsilon, kappa, and tau.

Type II interferons bind to the IFNGR receptor and are represented by only one species – interferon gamma.

Type III interferons are interferons lambda that is bound to the IFNLR1 receptor.

Interferon alpha

Interferon alpha is produced by various types of cells, but the white blood cells, in which its synthesis is sharply activated in response to a viral infection of the body, are its main source in the body (1). In this regard, it is usually called "leukocyte" interferon. It is encoded in mammals by a whole family of genes, forming the corresponding family of "products" (IFN-alpha subtypes): for example, in humans there are about 20 of them, in cats – 14, in dogs – 8, etc. (2). Representatives of the family are very similar in structure (the percentage of sequence homology is 96-99%).

Interferon alpha complex with interferon alpha receptor (PDB 3SE4) (Fig. 1*)

Interferon alpha is the most widely used drug of the interferon nature in medicine and veterinary medicine today. It is used for all possible indications: as immunomodulator, as antiviral, and as antitumor agent. Natural and recombinant IFN-alpha is an active component of a huge number of drugs produced in Russia and abroad. Today, interferon alpha is used in treatment of hepatitis B and C, encephalitis and meningoencephalitis, conjunctivitis, keratoconjunctivitis, cytomegalovirus and herpesvirus infections, chlamydiosis, toxoplasmosis, various oncological diseases (acute lymphoblastic leukemia, hair cell leukemia, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, chronic myeloid leukemia, multiple myeloma, thrombocytosis, renal cell carcinoma, ovarian cancer, superficial bladder cancer, malignant melanoma, basal cell carcinoma of the skin), flu, ARVI, and others.

The main vector of action and target is antiviral activity and activation of natural killers.

Interferon tau

Interferon tau was first discovered in 1982 in sheep, later in cows, and also in some birds. Interferon tau is encoded in animals by several genes and is represented in the body by a whole group of corresponding protein products, which is also typical for two other variants of type I IFN, namely interferons alpha and omega.

Interferon tau (PDB 1B5L) (Fig.2*)

Interferon beta

The synthesis of interferon beta is carried out by many types of cells: fibroblasts, epithelial and endothelial cells, lymphoid cells and astrocytes are able to produce this form of IFN; however, the most active producers of interferon beta are fibroblasts. Therefore it is often called "fibroblast" interferon. Functional interferon beta in all mammalian species, including humans, is encoded by only one gene, and like interferon gamma, it is a strictly species-specific protein. Interferon beta, like all other types of interferons, can be used in viral infections, but it is preferably used in treatment of multiple sclerosis (MS) and a number of chronic diseases of the nervous system, where it currently demonstrates the best results (in comparison with other forms).

Crystal structure of interferon beta (PDB 1AU1) (Fig. 3*)

The most famous MS drugs based on interferon beta-1 are Rebif (Serono Farma Int, Italy), Avonex (Biogen, Netherlands); Genfaxon (Tutor, Argentina). However, at present, the last clinical trials in the United States are being conducted on a drug (oral) for the treatment of MS based on interferon tau. Its essential feature is better stability and it practically does not cause side effects typical for interferons (4).

The main type of biological action is antiviral activity.

Interferon beta – interferon receptor complex IFNAR1 (PDB 3WCY) (Fig. 4*)

Interferon omega

Interferon omega (most often a family of closely related proteins encoded by several genes) has many common features with interferon alpha: white blood cells as the main producers; a high level of homology of amino acid sequences; interaction with the same receptor (type I); a similar spectrum of action and the level of antiviral activity. Human interferon omega was discovered in 1985 by three different groups of researchers independently from each other (5, 6, 7). Due to its above mentioned structural and functional similarity to interferon alpha, the first group of authors initially proposed to consider it as a subclass of IFN-alpha (alpha subtype II). However, later, significant differences were identified between these forms; the main difference includes the different mechanism of interaction with the receptor (binding to different parts of it), which leads to the launch of different signals; and, most importantly, there are the differences in the antigenic nature, as a result of which antibodies to interferon alpha do not block the activity of interferon omega.

Recombinant human IFN-omega has been proposed and successfully used in treatment of many human diseases: various viral infections, in particular AIDS, herpesvirus infections, atypical pneumonia, hepatitis B and C, as well as various forms of cancer. It should be particularly noted that the use of IFN-omega in conditions of ineffective treatment with IFN-alpha is successful,

especially when the patient has initial or acquired resistance to the drug as a result of long-term previous treatment with alpha-form. By "triggering" other signals different from interferon alpha, IFN-omega is functional where the action of the alpha form is inhibited.

Interferon gamma

Interferon gamma occupies a special position in the interferon family not only because it has its own receptor on the cell surface, but also due to a set of functional features that bring it closer to some interleukins. Although interferon gamma was discovered for its ability to cause an antiviral effect, it was later found that, like others, it is a pleiotropic lymphokine with multiple effects, mainly on the growth and differentiation of different cell types associated with natural immunity: interferon gamma induces differentiation of myeloid cells, as a result of which they acquire the functional properties of more mature monocytes; it stimulates the expression of antigens of the main histocompatibility complex (MHC) class II and MHC class I, and is a powerful activator of macrophages that destroy antigenic molecules and forms that have entered the cell. Possessing all three functions typical for interferons, this type of interferon implements them mainly through the immune mechanism. Hence its household name is "immune interferon".

Crystal structure of interferon gamma (PDB 1HIG) (Fig. 5*)

Endogenous interferon gamma producing cells are T-helpers (CD4), immunological memory cells (CD45PA), T-killer cells (CD8), NK cells (CD16, CD56), dendritic cells (CD23, CD35), and B-lymphocytes (CD22, CD23), which synthesize certain levels of it even in the absence of viral infection. Both in humans and in all animals, interferon gamma is encoded by a single gene and is a protein characterized by high species specificity. Interferon gamma is widely used in treatment of infectious, oncological, autoimmune and allergic diseases. Among the most well-known drugs containing it as an active principle are the drugs with recombinant IFN-gamma 1b Immukin (Boehringer, Germany) and Actimmune (InterMune Pharm., USA), as well as the Russian Ingaron (Pharmaklon,Russia).

Their main function is to activate macrophages, enhance the Th1-type T-helper response, and induce the expression of antigens of type II main histocompatibility complex on the antigen-presenting cells. In addition, interferon gamma exhibits antiviral and antiproliferative (antitumor) activity.

Interferon gamma complex with its own receptor. (PDB 1FG9) (Fig. 6*)

Interferons lambda

Interferons lambda were discovered in 2003. They were originally classified as interleukins and identified as IL-29 (now IFN-lambda1), IL-28A (now IFN-lambda2), and IL-28B (now IFN-lambda3). Later, a fourth form, IFN lambda4, was discovered, which is expressed in small amounts and is determined as the result of a shift in the reading frame in the lambda 3 gene. Due to the structure features and the presence of its own receptor, IFN-lambda is separated into an independent, third (III) type of interferons.

Although interferons alpha and interferons lambda bind to different receptors, they trigger the same cascade of JAK-STAT phosphorylation reactions and ultimately modulate the activity of

the same group of interferon-stimulated genes (ISGs), resulting in a similar cell response. As a result of numerous studies, it was found that the class of interferons lambda in the body is not "excessive" in relation to interferons alpha, since they have different tissue specificity and different attitude to different types of viral infection. The main conclusion from this series of studies should be considered as follows: the unique purpose of class III interferons is to protect the skin, lungs and gastrointestinal tract from the action of viruses, mainly belonging to rotaviruses family.

Mechanism of action

The result of binding the interferon molecule to the cell receptor consists in activating of the so called "signaling pathways" in the cell which include complex interrelated phosphorylation reactions involving numerous protein kinases, including those associated with receptors. The phosphorylation cascade leads to the activation of many protein factors, in particular, STAT transcription factors. Activated transcription factors move to the nucleus and affect the transcription of certain genes, most of them directly or indirectly related to the process of protein synthesis.

In addition to affecting the genes associated with translation, interferons can activate hundreds of other genes (known as interferon-stimulated genes, ISGs) that play a role in protecting cells from viruses. For example, by activating p53 protein, which activates the apoptosis mechanism of an infected cell, interferons limit the spread of viral particles.

The second direction of interferons action consists in stimulation of the immune system cells. In particular, interferons increase the synthesis of molecules of classes I and II main histocompatibility complex (MHC) and activate the immunoproteasome, which processes viral peptides. A high level of class II MHC molecules provides presentation of viral antigens to T-helpers, which secrete cytokines that coordinate the activity of other cells of the immune system. Some types of interferons can also directly stimulate immune system cells, such as macrophages and natural killer cells.

It is obvious that the simultaneous use of multiple cellular (biochemical, molecular-biological, and immune) mechanisms by interferons for the implementation of their functions provides an extremely high efficacy of these agents in implementing any of the three main functions.

At the same time, including a large number of multidirectional biochemical reactions under the influence of interferons increases the possibility of unpredictable and not always favorable effects (side effects) for the body. Indeed, according to the practical use of various interferon preparations, the side effects are often observed during the course of treatment from the central nervous and cardiovascular systems, gastrointestinal tract, hematopoietic organs and sensory organs. In particular, ischemic retinopathy, nerve paralysis, and significant visual impairment may develop in the sensory organs. Skin side effects include urticaria, itching, burning, dryness, furunculosis, as well as various skin rashes.

There were cases of neurological and psychopathological disorders, including interferon-induced depression. It is believed that in most cases side effects occur during the parenteral use, but their development is possible when using suppositories, ointments and other pharmaceutical forms, especially in the case of long-term treatment. According to the above specified, it can be concluded that when using interferon-based drugs for treatment of humans and animals, special attention should be paid to a thorough study of their effective concentrations, multiplicity and dosage forms.

Literature

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