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Features of the Functioning of the Third Type of Interferon - Interferon Lambda in Viral Hepatitis

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SUMMARY: In chronic viral hepatitis, there is a pronounced role of the IFN-lambda genotypes, which consists in genetic predisposition, and in achieving a stable virological response in patients with chronic viral hepatitis C against the background of treatment with drugs of genetically engineered interferon and ribavirin.
In the literature there are isolated data on the study of IFN-28B and its gene in chronic viral hepatitis B. We think that research in this area should be continued. Gene polymorphisms should be determined, which we are sure will allow predicting the probability of achieving a persistent virological response with a sensitivity of 65% and a specificity of 78%.

Key words: interferons, immunity, interferon system, antiviral protection of immunity, the third type of interferons.

Interleukin-28 (IL-28) is a cytokine that is present in two isoforms, IL-28A and IL-28B, and plays a role in immune defense against viruses, including the induction of an "antiviral state" by incorporating the Mx, 2 ', 5 proteins '-oligoadenylate synthetase, as well as ISGF3G (gene factor 3 stimulated by interferon) [2,4,5,12].
IL-28A and IL-28B belong to the type III interferon cytokine family and are very similar (in amino acid sequence) to IL-29. Their classification as interferons is due to their ability to induce an antiviral state, while their additional classification as cytokines is due to their chromosomal position, as well as the fact that they are encoded by several exons, as opposed to a single exon, like most types [6,13] . IL-28 was discovered in 2002 by Zymogenetics using a genomic screening process in which the entire human genome was scanned for putative genes. After these genes were found, a second scan was performed to look for cytokines. Both IL-28 and IL-29 have been detected in humans using this type of assay [1,4,5,9,13].
The genes for IL-28 are located next to IL-29 on human chromosome 19. Two isoforms of IL-28 (IL-28A and IL-28B) are 96% homologous. The differences in function between the two forms remain unclear. The receptor for IL-28 consists of the unique alpha chain of the IL-28 receptor that binds to the beta chain of the IL-10 receptor, prompting many to classify IL-28 as a member of the IL-10-like family [15,18].
It has also been shown that IL-28 plays a role in the adaptive immune response, as its inclusion as an immunoadjuvant during vaccination of small animals leads to increased antigen-specific release of interferon-gamma, as well as an increase in the cytotoxic potential in CD8 + T cells [4,8,15,18].

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The addition of IL-28 to vaccination results in 100% protection against lethal H1N1 influenza virus infection in a small animal model when combined with an influenza vaccine that protects only 50% of the time without IL-28 [7,8].

Studies of IL-28B in non-human primate vaccination models have confirmed small animal models resulting in an increase in interferon gamma production and cytotoxic CD8 + T cell activity in an HIV vaccine study. Scientists used this link to explain why some people infected with HSV-1 experience herpes and others do not [9].

A single nucleotide polymorphism (SNP) adjacent to the IL-28B gene predicts the response to hepatitis C treatment with interferon and ribavirin. SNP was identified in the genome-wide association study (GWAS) and is by far the best clinically relevant example of a successful GWAS hit [3,8,18].

Interferons were discovered by Isaac and Lindemann in 1957 as antiviral agents, but their subsequent study found that the functions of interferons in the cell are not limited to antiviral action: antiproliferative activity (the ability to suppress cell multiplication), which in further determined the possibility of their use to inhibit the development of malignant neoplasms, and the ability to influence the state of the immune system, that is, to act in the body as immunomodulators [12,15,19].

There are three main classes of interferons, where each class combines proteins of the same type (I, II, or III). The ratio of interferon to one type or another is determined by the type of receptor that binds them [20].

Type I interferons have one common IFN-alpha receptor (IFNAR), consisting of an alpha subunit (IFNAR1) and a short or long beta subunit (IFNAR2) (1). In mammals, this type includes the following main types of interferons: alpha, beta, omega, upsilon, kappa and tau. Type II interferons bind to the IFNGR receptor and are represented by only one species - interferon gamma. Type III interferons, lambda interferons, bind to the IFNLR1 receptor [5,7,10,14].

This review is about the type interferon. Lambda interferons were discovered in 2003. They were originally classified as interleukins and defined 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 a result of a shift in the reading frame in the lambda gene 3. Due to the structural features and the presence of its own receptor, IFN-lambda is isolated into an independent, third (III) type of interferons [2 , 5,6,17,19].

Despite the fact that 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), which leads to to a similar cell response. As a result of numerous studies, it was found that the class of lambda-interferons in the body is not "excessive" in relation to alpha-interferons, since they have different tissue specificity and different attitudes towards different types of viral infection. The main conclusion from this series of works should be considered that the unique purpose of class III interferons is to protect the skin, lungs and gastrointestinal tract from the action of viruses, mainly belonging to the rotavirus family [6,9,11,16].

The result of binding of the interferon molecule to the cellular receptor is the activation in the

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cell of the so-called "signaling pathways" - complex complexes of interrelated phosphorylation reactions involving numerous, including receptor-coupled, protein kinases. The phosphorylation cascade leads to the activation of many protein factors, in particular, the STAT transcription factors. Activated transcription factors move into the nucleus and affect the transcription of certain genes, most of them directly or indirectly associated with the process of protein synthesis. In addition to influencing genes associated with the translation process, interferons are capable of activating hundreds of other genes (known as ISGs, interferon-stimulated genes) that play a role in protecting cells from viruses. So, for example, by activating the p53 protein, which turns on the mechanism of apoptosis of an infected cell, interferons limit the spread of viral particles [8,12,17].

The second direction of action of interferons is the stimulation of cells of the immune system. In particular, interferons increase the synthesis of molecules of the major histocompatibility complex (MHC) of classes I and II and activate the immunoproteasome, which processes viral peptides. The high level of MHC class II molecules ensures the presentation of viral antigens to T-helper cells, which release cytokines that coordinate the activity of other cells of the immune system. Certain types of interferons are capable of directly stimulating cells of the immune system, such as macrophages and natural killer cells.

In humans, interferons-X are represented by a family of three genes: IL-29 (interferon-X1), IL-28A (interferon-X2), and IL-28B (interferon-X3); all of them are located on chromosome 19. Interferon-X genes have been found not only in humans [7,14], but also in other mammals, such as mice [13,16], and these genes are also present in the genomes of birds and fish [2, 4.13.17]. Unlike genes of type I interferons, which do not contain introns, interferon-X genes have an intron-exon structure; the IL-29 gene has five exons, and the IL-28A and IL-28B genes have six exons each. The search for homology did not reveal significant similarity between type I and type III cytokines, however, interferons-X have a high level of homology among themselves; the greatest homology (96% identity) is shown by IL-28A and IL-28B [7,17].

Expression of genes IL-29, IL-28A, and IL-28B in the cell is induced mainly by viruses, the genome of which is represented by single-stranded RNA [6,14,19], while induction by viruses with a different genome type is reported much less frequently; In one of the studies, it was demonstrated that the DNA of cytomegalovirus is capable of causing the production of interferon-X [8]; in another study, it was shown that viruses with ezDNA and dsRNA genomes caused the expression of type III cytokines. In addition, an interesting fact is that the expression of genes of interferons-X can be induced by type I cytokines, as well as by the interferons-X themselves, by a positive feedback mechanism [3]. The molecular events leading to the production of interferons-A by the cell are similar to the molecular mechanisms of activation of type I cytokines. It has been experimentally established that transcription factors IFR3 and NFkB, which bind to the corresponding sites in the gene promoter, are required to activate the expression of the interferon-^ 1 (IL-29) gene [3,7].

Type III interferon genes are able to be expressed in almost all cell types in vitro, while type I cytokine genes have cell-specific expression [3]. In addition, some studies demonstrate the production of interferons-A in vivo. For example, Brand et al. [7] showed the production of interferon-^ 2 in the tissues of the large intestine of mice, Mihm and colleagues [5,16] found

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a high level of interferon-A! -A2 and -A3 in humans with chronic hepatitis C.

Interferons-A exhibit their biological activities through surface receptors of the cell, which consist of two protein chains encoded by genes - IFNLR1 and IL10R2. The IFNLR1 gene is located in humans on the first chromosome and has an intron-exon structure; it has seven exons. The protein product of the IFNLR1 gene consists of an extracellular domain of 200 aa, a transmembrane domain, and a cytoplasmic portion of 223 aa [19]. It was found that mRNA of the IFNLR1 gene can undergo alternative splicing in human cells, as a result of which, in addition to the full-length protein, two other end products can be formed. The IFNLR1 gene is not expressed in all types of cells, for example, mRNA of this gene is not found in fibroblasts and endothelial cells, which is why these cells are not susceptible to type III cytokines, while IL10R2 gene expression is found almost everywhere [16,21].

The molecular mechanism of signal transduction involving the interferon-A receptor is similar to that known for type I cytokine receptors. Initially, on the surface of the cell membrane, a three-component complex is formed, consisting of two receptor chains and interferon-A itself (IFNLR1-interferon-A - IL10R2). Then this complex initiates signal transduction across the cell membrane by transforming the cytoplasmic domains of receptor molecules, which in turn are associated with tyrosine kinases Tuk2 and Jak1 [14,15,20].

It has long been known that interferons-a and -p have antiproliferative activity against various types of tumors [6,21], in particular against endocrine tumors. At present, in practice, various treatment regimens for these tumors using interferon-a are used [13]. However, these schemes, unfortunately, are often ineffective and are accompanied by various side effects. In addition, it was shown that when using interferon-a, only partial tumor reduction occurs in 15% of patients [14]. All this creates a need for the development of new treatment strategies. Representatives of the recently discovered type III interferons can play a key role in their creation and improvement. Since type I and III interferons activate similar cascade pathways in the cell [17], it can be expected that interferons-A have antitumor activities similar to interferons-a and -ß. In addition, the limited expression of the interferon-A receptor in hematopoietic cells may provide advantages for the therapeutic use of interferon-A in comparison with traditional therapy with interferon-a [7].

Following the discovery of type III interferons, work immediately began to study their antitumor properties. The first works on in vitro models showed that in most cases, interferons-A have less pronounced antiproliferative properties in comparison with interferons-a and -ß. For example, when testing IL-28A, IL-29 and interferon-ß on 12 different derivatives of brain tumors, it was shown that mainly interferon-ß has antiproliferative activity and only in one glioblastoma cell line (LN319) IL-29 was more effective. than interferon-ß. The susceptibility of cells to type III cytokines depends on the presence of the corresponding receptors on their surface. It was established by the quantitative method of polymerase chain reaction (PCR) that it is the cells of the LN319 line that have the largest number of mRNA receptors for type III cytokines (IFNLR1, IL10R2) [12, 18, 19].

In another work, Zitmann et al demonstrated that IL-28A and IL-29 are potent new agents in the treatment of neuroendocrine tumors [14]. The authors showed that the functional receptor complex of interferon-A is expressed in the BON1 neuroendocrine tumor cells, and the

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treatment of tumor cells of this line with interferons (interferon-a, IL-28A, IL-29) leads to a significant reduction in the number of cells, with IL- 29 [11.15].

The mechanisms by which interferon-a and interferon-A mediate their antitumor activity have not been completely elucidated. Apparently, these mechanisms are associated with the regulation of the cell cycle and the induction of apoptosis of tumor cells. These assumptions are partially supported by the fact that treatment of cells with interferon-a, IL-28A, and IL-29 causes the cell cycle to stop and promotes cell accumulation in the S-phase of the cycle [17]. In addition, type I interferons [10,17], as well as interferons-A, are able to activate caspases, which are involved in DNA fragmentation and ultimately induce apoptosis. Even the preliminary incubation of BON1 cells with caspase inhibitors could not completely prevent the decrease in the number of cells [7, 19].

In relation to the IFN-X genes, the first report on the presence of a genetic predisposition to spontaneous HCV clearance and the prognosis for a permanent cure was published in the journal Nature in 2009 by D.L. Thomas et al. [fourteen]. Thereafter, four independent studies established an association between SNPs in a region close to the IFN-X3 gene and the likelihood of HCV clearance. One study found a connection with the rs12979860 loci, and three others - with the rs8099917 locus [2,4,5,9]. Favorable genotypes for the major T allele (T / T genotype) [12]. Individuals with genotypes C / C rs12979860 and T / T rs8099917 differ in the high probability of recovery from HS [18]. The frequency of occurrence of the C- and T-alleles of IFN-X3 significantly differs in different ethnic groups [2,6]. In this regard, spontaneous HCV clearance occurs in 36.4% of infected Caucasians and only in 9.3% of Africans [6]. In countries inhabited by Asians (Japan, Korea, China), the frequency of occurrence of the C / C genotype rs12979860 reaches 73.0-88.5% and is largely determined by the proportion of ethnic Asians living in the territory [4.12]. In relation to T / T of the rs8099917 genotype, a stronger association with the frequency of spontaneous clearance was established for the population of residents of Japan and China (OR = 12.1), less strong - for Caucasians (OR = 1.98-5.2) [11,12, 13]. According to Y. Asahina et al. A joint analysis of the combination of both favorable genotypes rs12979860 and rs8099917 allows one to give a more accurate prognosis of the outcome of acute HCV infection than each one taken separately [12].

No relationship was found between the IFN-X3 gene polymorphism and the rate of development of liver fibrosis in patients with HS in Europe [5], but a strong association was established when examining patients of Chinese nationality and Australian residents [17]. At the same time, among CHC patients with LC, the carriage of T / T genotype rs12979860 of the IFN-X3 gene is more common, and HCC develops more often even after a successful course of AVT [17, 20].

Almost simultaneously with the establishment of genetic markers of a high probability of spontaneous clearance, studies began on the presence of a genetic predisposition to achieve a persistent virological response (SVR) in CHC patients to treatment with genetically engineered interferon and ribavirin. However, most researchers in assessing the prognosis of CHC treatment prefer two main polymorphisms: G812979860 and G88099917 [11,12].

Determination of polymorphisms 1BM- \ 3 made it possible to predict the probability of achieving SVR with a sensitivity of 65% and a specificity of 78% for SNP G812979860 [9],

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and for SNP G88099917 57% and 63%, respectively [7]. In addition, it was noted that relapses of HS in patients with C / C genotype G812979860 occur less frequently (26%) [21].

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