SIGNIFICANCE OF THE INTERFERON (IFN) IN THE THERAPY

Sabina Mahmutovic*, Edina Beslagic
Department of Microbiology, Faculty of Medicine, University of Sarajevo, Cekalusa 90, Sarajevo, Bosnia and Herzegovina

* Corresponding author

Abstract

Interferons belong to the group of the regulatory glicoproteins, of low molecular mass. They are the products of infected cell - genome, but not virus, as a consequence of the cause answer by different inductors. Human IFN are divided on the sequence of amino - acids into three groups: *Alpha, Beta and Gamma* interferons. Recently are discovered new types of IFNs: *Omega* and *Tau*, but bigger than alpha molecules. Also, has been performed the division into two types: I and II. Besides the antiviral and antiproliferative effects, they have also the effect in the treatment of malignant diseases, and act protectively against the radiation.
Key words: Interferon, IFN, Alpha, Beta, and Gamma.

Introduction

The discovery of the interferon (IFN) is closely related to the names of the investigators Issacs and Lindemann in the period of the 1957. The cells with virus infections or other ethiologic agents excrete IFN. It's product of lymphocytes (lymphokines), macrophages, fibroblasts, and other cells. They are included into physiological barrier of the mechanism of the non-specific immunity of the host. The cells could produce and excrete IFNs a few hours after sensibilization. Except viruses there are a few different intracellular micro-organisms as well as inductors: (chlamydia, brucella, ricketcia), listeria, mycoplasma, coliforms, protozoa, bacterial products (endotoxin, nucleic acids), different cells including neoplastic, and chemical compounds (synthetic double stranded RNA, tiloron, acridin stains, specific antigens for sensibilization of the lymphocytes), immune stimulators or mitogenes, double stranded polynucleotides (poly I: C, poly dA: dB), synthetic polymers (polysulphates, polyphosphates, piran), and some antibiotics (kanamycin, cyclohexamid). The basis of the IFNs activity is directed to inhibition of synthesis of the RNA (Ribonucleic acid) and DNA (Deoxyribonucleic acid) in the cells of the host. Nowadays, it's clearly known except antiviral activity (inhibition of viral replication, synthesis of proteins, and as a terminal stage excretion from the infected cells) IFN posses antiproliferative and immunoregulation effects (with enlarge activity of the macrophages, cytotoxic T lymphocytes, as well as natural killer cells - NK) too.
The United States Food and Drug Administration (FDA) for clinical use until 1986 did not approve interferon, nearly 30 years after its discovery (1,2).

Chemical and biological features of IFN

IFN belongs to the group of regulatory glicoproteins of low molecular mass from 16. 000 to 70. 000 Dalton. It has carbohydrate components except proteins, which is very important for their antigenic difference. They show the resistance related to the nuclease action, stability within the wide diameter pH from 2 to 10, and are not antigenic. From other side they show the extreme sensitivity according to the proteolitic enzymes especially trypsin. For IFN we can say that the virus is specific, which means that between the viruses that provoke formation IFN (interference virus) and virus which discover the interferon action (interfered virus) there is no antigen relation. However, according to the type of the cells in which is produced it discovers the expressive specificity ("*species specificity*") which means by the relation of the cell that selectively adsorbs and releases in itself only the homologue IFN molecules.

Division and types of IFN

Depending on the origin of IFN can be produce within human and animal organism, and in that case we speak about the endogenous or natural IFN (serum, liquor, various secrets, etc.). The exogenous IFN is the outer product of viruses or different inductors senzibilated cell in the cell culture, of human or animal origin. It is significant to emphasise also the production of the recombinant IFN which posses the minimum undesirable effects and it's significant place in the application. The second division of the IFN is according to the cell type which they produce as well as on basis on sequence of amino - acids to: Alpha (leukocytes), Beta (fibroepithelials), Gamma (immune) (3,4).
IFN α (alpha) make the greatest (more than 20 members) and mainly applicable group. They produce them by virus infected leukocytes (macrophages, B-lymphocytes, dendrite cells) and they are resistance to the low pH. They are antiviral and antiproliferative effects (induction of enzyme oligo (A) synthetaze, protein kinaze P1 and MHC (Major Histocompatibility Complex) antigens I. and II., and they belong to the cells NK activators. IFN α amplifies the cellular immune response stimulating T helper cells and increasing the diameter of T helper cells according to T suppressers.
IFN β (beta) posses only one protein molecule (I subtype) the product of fibroblast as well as the epithelial cells

resistant to the low pH. As well as α is antiviral and antiproliferative effect.
IFN γ (gamma) also has only one protein (I subtype) immune interferon the product of T lymphocytes as well as NK cells. Carbohydrate component is not necessary for biological function. Predominantly they have immunoregulation effect. It acts first of all as non-specific actor of activation (MAF) amplifies the activity NK cells and expressiveness of the molecule MHC on the target cells. Also, gamma IFN inhibits replication of viruses in the infected cells and acts synergistic with TNF α (cytotoxins) in killing the target cells. Besides the mentioned, we differ recently also IFN omega and tau which are similar to IFN only for their molecules bigger than alpha molecule. Except mentioned divisions IFNs are divided according to a type as well. IFN alpha, beta omega and tau mutually are similar according to the function and structure (consist of one molecule of amino - acids) and they belong to IFN type I (5). Contrary to this IFN gamma is built in the form of dimmer (two mutually stranded copies of protein) and make IFN type II. The basic differences type I and II are that the type I most successfully leads the cell into antiviral condition while the type II more significant influence on the immune mechanism of immune system of the host.

Biosynthesis of IFN

According up to now examinations of IFNs are the product of eukariotic cell but not virus and the information about the biosynthesis of the same is found in the nucleus DNA that is in genome of the cell of the host. Normally IFNs are not present in the cell the production to them is "inhibited" and their production is the consequence of the response to the different inductors. As an inductor of the production of IFN type I can be the interproduct of viral double stranded RNA occurred during the viral replication. It is considered that only one molecule of the viral RNA is sufficient for the induction of the production of interferon in the cell. A few hours after infection appear IFN type I while gamma IFN appear a little bit later with activation of lymphocytes T. In the cells where there are produced IFN inhibit viral replication leave the infected cell and connect with interferon receptors of the cytoplasmatic membrane of the closest cells and in it express the same effect. It is emphasised "species specificity" which means that the activity according to the definitive type of the cell. Biosynthesis of IFN begins by the synthesis of the essential enzymes: oligo (A) synthesis and protein kinaze. The activity of oligo A synthesis is expressed in the activation of endoribonucleasis who's the main task is degradation of the viral RNA while enzyme protein kinase degrades the initial factor polypeptide eIF-2, which is necessary for the synthesis of the viral protein. Nowadays is known that besides the antiviral action IFN acts antiproliferative and immunoregulatory. Antiviral and antiproliferative effect of IFNs (α And β) is confirmed on the different cells, viruses and tumors in vivo and in vitro (3,4).
Immunoregulational the effect of IFN gamma appears on macrophages, lymphocytes T and B as well as NK cells. Also, IFN inhibit the growth of same malignant cells.

Treatment

IFN is the subject of clinical examinations and all in the purpose of their application in the treatment of the various virus infection as well as different malignant diseases. It's know that the cells of some type of leukaemia osteosarcoma as well as the kidney cancer expressively sensitive to the action of IFN. Application of exogenous IFN has the significant effect in initiative phase's virus infection by the stoppage of viral replication. The use of IFN in therapeutic purposes show some an undesired effect of side phenomena in the major measure of IFN α and β. As the most significant side phenomena appeared the symptoms in the form of influence syndrome the expressive malaise, myalgia, high temperature followed by fever, inclination to bacterial infections as well as the different haematology disorders first of all thrombocytopenia and granulocytopenia. We shall mentioned some examinations and application IFN in the treatment of some diseases:

Alpha IFN
Treatment: HBV (Hepatitis B Virus), HCV (Hepatitis C Virus), papillomas, laryngeal papillomas, HIV infection, leukaemia, Kaposi sarcoma, and tumors of kidney and colon.
Investigations: chronic myeloid leukaemia, non - Hodgkin lymphoma, tumor of bladder, melanoma.
Patients with diagnosis of fulminate (progressive) form of HBV tried with application of alpha IFN.
IFN alpha is got by recombinant DNA technique on the bacteria or yeast's and acts inducing the cell enzymes, which interfere with the synthesis of virus protein. In the treatment of chronic form HBV - (HbeAg positive patients) the efficacious is the long -term application of high doses of recombinant alpha IFN (5 -10 i.m. 3x weekly s.c. during six months).
Besides the type we have also lymphoblast type which is got by the stimulation lymphoblast cell lines by virus. The younger patients, the shorter duration of the disease (before integration HBV in the cell genome of hepatocytes), the grater activity of aminotranspherases in sera, female sex, achieving HBV infection in the adult age, the lower values HBV DNA in sera - favour the factors for good response on the application of alpha IFN (6,7). IFN alpha 2b is efficient in the treatment of chronic form HBV in adolescents. Such individuals have present "surface antigen" (HbsAg) for the period of six months. All the individuals with the decompensation of the liver (encephalopathia, ascites, high values of serum bilirubin, the prolonged protrombic time) generally should not be

treated by IFN 2b. The recommended dosage for IFN alpha 2b in the treatment of the chronic form HBV is 5.000.000 units daily, whether i.v. or i.m. for the period of 16 weeks. For the time of the therapy is necessary the monitoring of patient's eventually present side phenomena reduced on minimum. There is as parental form (Roferon A, ROCHE; Intron A, Schering Plough) for i.m. or s.c. application. The half-life of the drug is from 2 to 3 hours. The most common adverse effects are the symptoms like to the flu like syndrome, gastrointestinal disturbances, and depression. By many adult with chronic HBV infection there is insufficiency of interferon but non - adequate response to IFN. Also, conjugated with polyethylene - glycol (Pegasys, Pegiliran interferon, peginterferon alpha 2b) is produced has the prolonged half - life (approximately 8 to 12h after administration) and it will be administered once per week. It is approved for the treatment of chronic hepatitis C in adults as well as in combination with oral vidarabin in patients untreated with IFN- or who have relapsed following INF α - therapy (3).
The recommended dosage for IFN alpha 2a and 2b for treatment chronic HCV is 3.000.000 units 3x weekly in i.m. or iv. injections. For IFN alphacon 1 is recommended the dosage of 9 mcg 3x weekly for the first treatment of IFN.

Beta IFN
Treatment: multiple sclerosis, neoplasm of basal cells.

Gamma IFN
Treatment: chronic granylomatosys, tumor of kidney, leischmania (5,8,9).

Conclusion

Nowadays by the application of the recombinant techniques are produced highly purified recombinant alpha IFN (recombinant alpha 2a and alpha 2b). Besides the type of the recombinant alpha IFN we have also lymphoblast type which is got by the stimulation lymphoblast cell lines by virus. It is significant to emphasise also the combined therapy of IFNs with some antiviral drugs, cytostatic or immunomodulators. So, for example in the choice of therapy of HCV the determination of genotype is also significant. For the determination therapeutic model for example the duration of combined therapy IFN and Ribavirin in genotype 1 is 48 weeks and the non - 1 genotype is 24 weeks. The treatment for the six months exclusively for therapy IFNs alpha 2a and 2b although several studies emphasise that the treatment for the period of 1 year or more also can be efficiency. The studies show that the effect of combine therapy by IFN and Ribavirin 40 - 50%; is weaker in the case of genotype 1 (30%) and better in other genotypes. FDA approves the combine therapy in June 1998. For patients with chronic form of HCV which earlier where on "single" therapy by IFN. The preliminary results with PEG interferon show the success in the treatment and to 55%. The application of IFN in the therapy in children requires the maximum caution. The pregnancy represents contraindication in the therapy with IFN. The application of IFN by itself or combined in the treatment both of viruses and malignant diseases has the final aim to achieve the maximum therapeutic efficiency in the median of survival and quality of life of such patients.

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