

INTERFERON- γ AND ITS INDUCTORS. A REVIEW

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ABSTRACT. Interferons (IFN) are regarded to the class of cytokines and are the family of proteins, which possess antiviral, immunomodulating and antiproliferative activity. It permits to refer them as polyfunctional bioregulators of wide spectre of action. Of many years experience of IFN preparations use in clinical practice permitted to determine its effectiveness for prophylaxis and treating of viral, bacterial and some of oncological diseases. At the same time there is the other alternative way of obtaining all positive IFN effects in organism and deprivation of peculiar to IFN preparations. The idea of such approach brings to action the own interferon-productive organism system: while using interferon inductors. At present this method has got the name "endogenic interferogenesis". The possibility of use of such method has become obvious after IFN synthesis discovery practically by all organism cells.

It is necessary to mention the fact that owing to crossing of IFN gene activation ways as well as a number of cytokines, the IFN inductors also induct tumor necrosis factor synthesis and interleukins, which play an important role in organism immunoreactiveness regulation.

Purposeful skring among the wide spectrum of high and low molecular combination of natural origin as well as synthetically one having revealed some preparation with high chemical-theurapeutical index, permitted to consider them as possible for use in medical practice.

Thus, the broad studying of potential interferon inductors with the purpose of their instillation of the most perspective in medical practice is the actual trend of modern virology and immunology.

KEY WORDS. interferon, cytokines, lectins, low-molecular substances.

Interferons are the family of secretory glycoproteins, possessed antiviral, antimicrobial, immunomodulating and antiproliferative activity (SPIVAK et al., 2002). Interferons (IFN) are divided into 2 main types: the first (IFN-1) includes IFN- α , IFN- β , IFN- ω , IFN- τ have been characterized only recently. It was determined that they are 45-55% homologous to IFN- α/β and possess the same antiviral activity. The second IFN type is presented by IFN- γ that is formed by stimulation of different antigens and mitogenes of T- lymphocytes (MOORE, 1996).

In most properties IFN- α/β resembles IFN of the type 1, but its immunomodulating properties are more expressed. At present it is known natural interferons of the first generation - their producers are animals cells. Recombinant interferons (of the second generation) are products of genetic modified microorganisms (TAYLOR et al., 1984).

Natural interferons are more physiological than preparations of recombinant interferons, however difficulties of their obtaining and purification make them very expensive (DUMANSKIJ et al., 1993).

Interferon preparations of the type I are mainly used in medical practice and IFN- α/β have complicated, long-termed clinical trials. Use of IFN preparations of the type I in medicine for treating and prophylaxis of many infection diseases and pathological processes has showed their high effectiveness. At the same time in veterinary medicine these preparations are used insufficiently. It is connected with conservatism of veterinarians as well as with deficiency in high effective species-specific cheap interferon preparations (GRUZDEV, 1989).

As a result of it were elaborated effective, profitably economic means of obtaining of α/β and γ -interferons for treating and prophylaxis of pigs and calves diseases (ZOTZENKO et al., 2001).

Besides it were obtained interferons of birds, dogs, rabbits, minks and sheep. For increasing effectiveness of domestical animal interferon preparations it were worked out original pioneers biotechnologies. The essence of them was the use of immunocytes suspension from healthy animals lymphoid system, experimental selection of inductor schemes and interferon co-inductor, synthesis and ready preparations obtaining. In spite of it is necessary to mark that some cytokines of tumor necrosis I phase immune answer fact are kept in physiological quantities and interleukin 1, defensives that make interferon preparations more physiological and natural (SPIVAK, 1999).

While studying of biological properties of α/β - preparations obtained (splenoferon, animaferon, virecses) and γ - (boviferon, suiferon, sediferon, transferon) interferons of pigs and cattle it was determined that antiviral activity of α/β -interferon was more than in γ -interferon. However immunomodulating properties of the latter 2-3 times exceed the same of γ -interferon. It was shown on phagocytes, NK-cells and populations T- and B-lymphocytes (SPIVAK et al., 2002, TIMOSHOK et SPIVAK, 1999). Taking into account immunomodulating properties of α/β and γ -interferons on experimental bacterial infections (*E. coli*, *Staph. aureus*, *Klebsiella pneumonia*, *Salmonella typhy*, *S. typhimurium*, *Pseudomonas. aeruginosa*,

Coronaviruses, Calves parainfluenza, etc.) it were worked out optimal schemes and interferon preparations of dose introducing (SPIVAK, 1999).

It was also elaborated schemes of interferon use with vaccines for prophylaxis of pigs and calves infection diseases. After carrying out of control tests interferon preparations have been widely used in veterinary medicine practice. While using of interferon for prophylaxis of bacterial and viral diarrhea new-born pigs and calves it was used 3 times introducing of 1000 IU preparation with intervals of 48 hours (animals preservation from 82,2 till 92,9%) (LAZAREV et al., 1989, KISHKO et al., 1990, ZOTZENKO et al., 2001). It was shown high effectiveness of pigs and cows α/β -interferon preparations under viral enterocolitis in pigs and parainfluenza-3 virus in calves that was introduced by the same scheme as in γ -interferon. (ZOTZENKO, 1989). At present it is obtained and has its clinical tests a new preparation - transferon. Biotechnological basis of its obtaining are connected with use of elements of vaccines prophylaxis and obtaining technology of γ -interferon. Preliminary tests of this preparation show that it is more effective than α/β and γ -interferon according to its characteristics. Thus obtaining of high effective interferon preparations in original technology and its high treating prophylaxis action opens perspectives for its wide use in veterinary medicine practice (SPIVAK et al., 1989, KISHKO et al., 1992, KISHKO, 1998).

At the same time there is the other alternative way of obtaining all positive IFN effects in organism and deprivation of peculiar to IFN preparations. The idea of such approach brings to action the own interferon-productive organism system: while using Interferon inducers. At present this method has got the name "**endogenic interferogenesis**". The possibility of use of such method has become obvious after IFN synthesis discovery practically by all organism cells (ERSHOV, 1996).

It is necessary to mention the fact that owing to crossing of IFN genes activation ways as well as a number of cytokines, the IFN inducers also induct tumor necrosis factor synthesis and interleukins which play an important role in organism immunoreactiveness regulation (ERSHOV, 1996).

Purposeful skring among the wide spectrum of high and low molecular combination of natural origin as well as synthetical one (natural and synthetical RNA two chains, polycations, lectines, polysaccharides, fluorenon, acridanones, phenilmidazothyasoles, gosy poles analogues and others) having revealed some preparation with high chemical-theurapeutical index, permitted to consider them as possible for use in medical practice. The following preparations have been worked out on their base: "Amiksin", (fluorenon class), "Tsikloferon" (akridanons class), "Poludan" and "Poliguatsil", "Kagotsel", "Ragosin", "Savrats" (SPIVAK, 1999, TIMOSHOK, 2002, SPIVAK, 2003).

The T-cell mitogens – lectins from pulse plants fall to the inducers stimulating the synthesis of IFN- γ , as well as lectins with microbial origin (PODGORSKIJ et al., 1992, TIMOSHOK et al., 2004), bacterial lipopolysaccharides, oxidants, anti-lymphocyte serums, specific antigens in crops with sensibilized lymphocytes, and alloantigens, participating in the process of antigen identification (ERSHOV, 1996).

The lectins are a large group of substances capable to combine with polymeric glycoproteids of plant and animal origins. Greater part of them could interact with the membrane proteins containing hydrophilic hydrocarbon groups. Another group of lectins is combined with different cells through hydrocarbons of their cell membrane (PODGORSKIJ et al., 1992).

Widely known are two mitogens on the basis of plant lectin-phytohemagglutinine (PHA) and concanavalin A (ConA). Phytohemagglutinine interacts with oligozaharides (specific to N-acetylgalactosamine), and the concanavalin is combined with sugars containing terminal D-mannose and D-glucose. These lectins interact with all cells of the peripheral blood of human, but most efficiently with the T-lymphocytes. PHA and ConA-preparations in a wide range of concentration (5-20 mg/ml) stimulate the induction of IFN- γ in mixed crops of lymphocytes with high titers – 1600 IU/ml and higher ones (ITO et al., 1984).

Great attention attracts the non-mitogenic lectins of plant origin, namely agglutinin of germinated wheat. It connects sialic acids, non-uramine acid with fetuin, as well as with oligozaharides. The inducers of IFN- γ of plant origin lectins (nutrition pulse crops) are considered to be quite perspective. In the last several years “Sigma” Corporation (USA) has produced inducers of interferon- γ on the basis of plant lectins double in number and now it includes 257 names. The high price of this preparation makes the researchers look for new highly efficient inducers of IFN- γ . The aloe extract that in mixed crops of lymphocytes produces interferon- γ with activity to 1600 UI in concentration of the preparation 1:2500 – 1:5000 could also fall to the plant lectins (VINTUHOV, 1993).

The bacterial lectins have not less γ -interferonogenic activity. Thus the bacteria from *Bacillus* species induce interferon in T-lymphocytes from healthy donors in optimal concentration of 40mg/ml protein. The induced interferon is of type II. The level of γ -interfenogenicity of bacterial lectins is similar to that of the lectins of plant origin. The researches of Spivak and all. (2000) showed the high concentration of interferon activity of *Bacillus subtilis*, *Bacillus mesentericus* and *Bacillus polymyxa* [SPIVAK et al., 2000].

The most perspective in this respect is the sialic specific lectin of *B. subtilis* 668/MB and intercell lectin *B. subtilis* 316 G (KOVALENKO, 2002).

It is well-known that also other products with microbic origin – glycopolymers, bacterial toxins and lipopolysaccharides (LPS) have a significant interferon activity. Active inducers are the staphylococcus enterotoxines A and B (CEA and CEB). It must be outlined that in the sensibilized cells the synthesis of IFN- γ flows quicker at stimulation with antigen than at stimulation with mitogen. Thus, for example at interferon induction with mitogens, the secretion of IFN comes after 48-72 hours, while at induction with antigen (CEA or CEB) the secretion is made two hours after the contact with antigen with the specific target (VACHROMEVA et BOBKOVA, 1983, DUMANSKIJ et al., 1993).

This phenomenon is related with the formation of natural barrier that hinders the development of infectious process in organism. At the same time, however, the substances with microbial origin together with mitogens plant lectins are extremely

dangerous for the organism and that is why the technology for industrial generation of IFN- γ with their help must include further purification of the final product (KISHKO, 1998).

From the synthetic low-molecular compounds in medical and veterinary-medical practice the derivatives of phenylimidazole – levamisole and kamisole are widely used. These substances have good interferon-inducing effect, and they have immune-modulating activity as well. Their protective effect in case of parasitic and bacterial infections is connected with these properties (KISHKO et al., 1987, BRATUS, 1991, DEMIDOV et POTYOMKINA, 1989, P ONOMAR, 1995).

It is known that the kamisole is very efficient in cases of salmonella and staphylococcus infections (BRATUS, 1991, ZOTZENKO et al., 2001). The mechanism of this effect is connected with the restoration of functional activity of macrophages and NK-cells, which is suppressed in case of staphylococci and salmonella persistence in organism. It has been founded out that injecting levimasole or kamisole two times causes activation of peritoneal and splenic macrophages, as well as of NK-cells in white mice, experimentally infected with *Staphylococcus aureus* or *Salmonella typhimurium* (BRATUS, 1991). The derivatives of phenylimidazole are successfully applied against diarrhea in calves, coccidiosis and Gumboro's disease in chickens, theileriosis in calves, etc (KASSISH, 1986, PONOMAR, 1995, KISHKO et al., 1990).

These substances have also adjuvant action as in case of combined application with viral and bacterial vaccines the titer of antibodies increases ten times (KISHKO et al, 1987).

The inductors of IFN- α/β of type I (ridostine, polyguacil) have similar adjuvant action. (SELIVANOV et al., 1987, GRUZDEV, 1989). On the grounds of these facts Kishko concludes that the combined application of IFN- γ together with vaccines increases the efficiency of immunoprophylaxis (KISHKO et al., 1992, SPIVAK et al., 1989).

From the above stated we could make a conclusion that the use of interferon preparations, as well as their inducers in medical and veterinary-medical practice is a perspective trend in the fight and prophylaxis against infectious and parasitic diseases (CUMMINGS et al., 1993, M , 1998).

The speed of researches made in this field allows us to expect that more efficient and powerful specific preparations of such kind would be obtained soon.

There are a number of various substances possessing the inductive activity for interferon-g. However, neither of them is an universal inductor. For therapeutical use, the inductors of interferon can be applied simultaneously with the interferon- γ preparations (endogenic interference).

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