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Congenital and Acquired Interferonopathies: Differentiated Approaches to Interferon Therapy

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Abstract

This chapter reviews various interferon (IFN) system disturbances—interferonopathies. The authors describe clinical specifics of type I interferonopathy associated with overexpression of IFN α —which is a rare Mendelian genetic disease. Certain autoimmune diseases (systemic lupus erythematosus (SLE), vasculitis, immune dysregulation syndrome, etc.) are also characterized by overproduction of IFN α . Furthermore the most common interferonopathies are described—deficiencies of IFN, congenital or acquired IFN α /IFN β and IFN γ deficiencies in children and adults. Deficiency of IFN α /IFN β associated with severe recurrent viral infections and deficiency of IFN γ cause mycobacterial infection. Interferon-corrective therapy methods are described. The target therapy of type I interferonopathies (biologics) binds IFN α and normalizes the high level of IFN α . From the other side, patients with congenital IFN α deficiencies are needed in replacement IFN therapy. In case of acquired IFN α deficiency, the differentiated interferon-corrective therapy is performed. In both replacement and interferon-corrective therapies, recombinant human IFN α 2b in complex with antioxidants (Viferon[®]) can be used, because their application is safe and has good clinical efficiency and no side effects.

Keywords: interferonopathies, interferon deficiency, interferon overexpression, IFN-corrective therapy

1. Introduction

Type I interferonopathies are congenital genetic disorder of the interferon (IFN) system, characterized by certain clinical symptoms resulting from the overproduction of IFN α [1–3]. In our opinion, the term interferonopathy means a general pathology of the interferon system, congenital or acquired, which includes the following types of disorders of the IFN system: *deficiency*; *paralysis* of the IFN system; inadequate response on viruses, bacteria, and mutated tumor cells; and *overproduction* of type I IFN. Interferons are the cornerstone of immune defense against viral infections and are also involved in the regulation of immune responses. Currently there are isolated type I, II, and III interferons in accordance with their

ability to interact with the three types of receptors. Type I interferons include IFN α /IFN β ; type II interferons, IFN γ ; and type III interferons, interferon-like cytokines (IL-29, IL-28A, IL-28B) [4].

2. Molecular mechanisms of the induction of type I interferon synthesis

The main role of type I interferons is to control viral infection. The synthesis and secretion of type I IFN is activated when our immune cells come in contact with viruses. Type I IFN is synthesized by epithelial cells, many cells of the immune system, including plasmacytoid dendritic cells (pDC) that recognize foreign or auto nucleic acids. Although both epithelial and pDC synthesize type I IFN simultaneously in different tissues, pDC-derived type I IFN actually exerts various immune responses through its cognate receptors on target cells. This results in modulation of diverse processes such as antigen presentation and activation of adaptive immunological process involving B and T cells [5]. For the synthesis of interferons in the body, cell activation is necessary. Toll-like receptors (TLRs); RIG-like receptors (RLRs), RIG-I; melanoma differentiation-associated protein 5 (MDA5); and cyclic GMP-AMP synthase (cGAS) participate in the recognition of foreign and host nucleic acid sites [6]. The main inducers of the synthesis of type I interferons are double-stranded and single-stranded RNA of viruses, as well as bacterial DNA [7]. RIG-like receptors recognize both single- and double-stranded viral RNAs, whereas cGAS (cyclic GMP-AMP synthase), in contrast, recognizes double-stranded DNA and RNA: DNA duplexes are formed during the replication of retroviruses and catalyze the synthesis of cGMP-AMP, which is the main agonist of the adapter protein—STING. After binding RNA, RIG-I and MDA5 bind the mitochondrial antiviral-signaling (MAVS) adapter protein. Both STING and MAVS stimulate downstream signaling cascades that include multiple kinases and finally lead to phosphorylation of IRF3 and induction of interferon synthesis [8]. Then type I IFN binds to the corresponding IFNAR

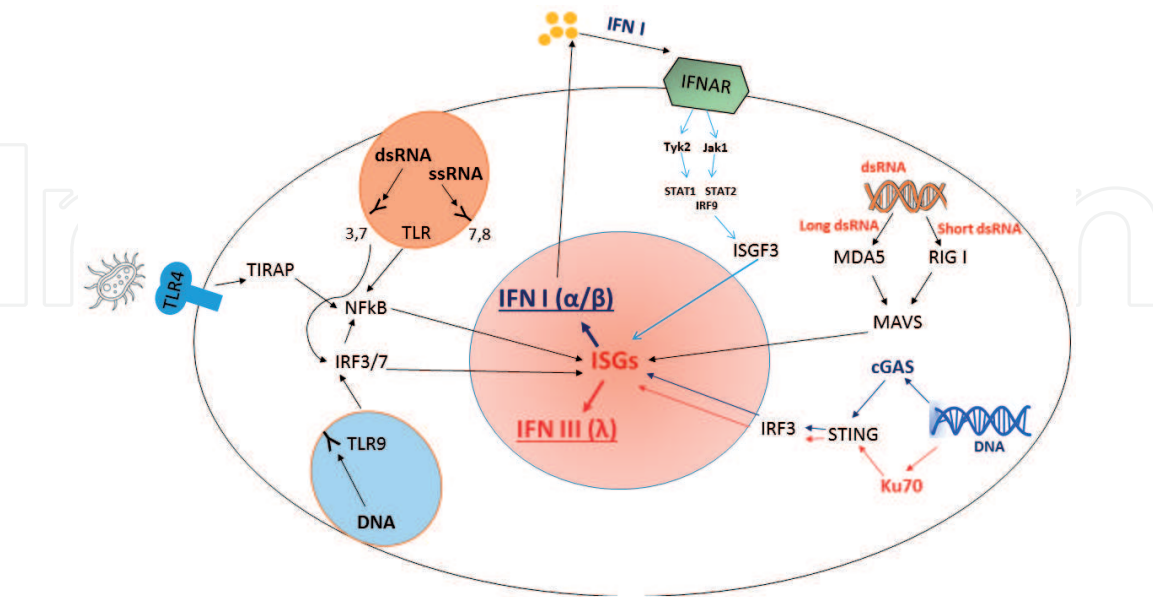


Figure 1. Molecular mechanisms of the induction of type I and III interferon synthesis. PAMPs: dsRNA, double-stranded RNA; ssRNA, single-stranded RNA. Nucleic acid sensors: cGAS, cyclic GMP-AMP synthase; MDA5, melanoma differentiation-associated protein 5; RIG-I, RIG-I-like receptor dsRNA helicase enzyme. Adaptor proteins: TIRAP, toll-interleukin 1 receptor (TIR) domain-containing adaptor protein; MAVS, mitochondrial antiviral-signaling protein; STAT, signal transducer and activator of transcription. Nuclear factors: IRF, IFN regulatory factor; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; IFNAR, IFN α receptor; ISGs, interferon-stimulated genes; Tyk, tyrosine kinase; Jak, Janus kinase.

receptors located on the cell membrane, which leads to the activation of Tyk2 and Jak1 kinases, which undergo phosphorylation and activate signal transduction and transcription activation proteins (STAT1 and STAT2). As a result, a heterotrimeric complex is formed, known as IFN-stimulating gene factor-3 (ISGF3), which includes IFN regulatory factor 9 (IRF9). Janus kinase (Jak) activation is negatively regulated by IFN α -inducible proteins SOCS1 and SOCS3. The binding of ISGF3 promotes interferon-stimulated genes (ISGs), which leads to their transcriptional activation and the collective actions of hundreds of ISGs, resulting in the production of a large number of induced IFN, which inhibits both viral replication and the spread of viruses. Rapid type I IFN secretion and then rapid synthesis induce activity of congenital and adaptive immunity cells by activation of pro-inflammatory cytokines that activate cellular and humoral antiviral immune response [9] (**Figure 1**).

3. Interferonopathies classification

During acute viral infection, IFN level is significantly elevated, and more than 70% of cells acquire antiviral status, i.e., they are protected against virus penetration and are able to efficiently neutralize them. Type I IFN has several very important positive effects: direct and indirect antiviral effect, protective antiviral effect, antitumor effect, and immunomodulatory effect. At the same time, it was shown that increased production of IFN can lead to negative consequences similar to autoimmune reactions.

The information presented by several authors about interferon system pathologies is vast and diverse but is not well-systematized. All known defects of IFN system, including type I and II IFN, whether congenital or acquired, including various disorders (deficiency; inadequate response to contact with viruses, bacteria, and mutated or tumor cells; IFN system paralysis; IFN overexpression), are pathologies of IFN system. All those defects of IFN system are collectively known as interferonopathies. There is an urgent need to create a classification of congenital and acquired disorders of the IFN system. We believe that the classification of IFN pathology would help in determining the correct approaches to the differentiated choice of adequate treatment tactics.

Based on our own and others' experience, we have developed the interferonopathies classification as per the following table [1–3, 10–15] (**Table 1**).

3.1 Congenital type I interferonopathies associated with IFN α overexpression

Recently several studies have presented genetic and molecular disorders accompanying rare Mendelian diseases that are associated with type I IFN overexpression resulting from defects in intracellular nucleic acid metabolism, DNase deficiency, or defects in sensor nucleic acid recognition. Genetic disorders—Mendelian diseases (Aicardi-Goutières syndrome, familial chilblain lupus, spondyenchondromatosis, proteasome-associated autoinflammatory syndrome, Singleton-Merten syndrome)—resulting in inadequately high type I IFN overexpression accompanied by a certain range of clinical disorders are called type I interferonopathies. Interferonopathies have rare pathology; their occurrence varies from 1:10,000 to 1:1,000,000 people. According to the literature, the most common syndrome is Aicardi-Goutières [16]. The frequency of some recently described genetic disorders (e.g., PRAAS2) cannot be counted [17]. Such disorders cause a great number of own nucleic acids in cell cytoplasm to appear. It results in active DNA recognition and pathological overexpression of type I IFN which launch autoimmunity hyperactivation, thus leading to autoimmune inflammation affecting the central and peripheral nervous system. It also results to skin and vessel damage (vasculitis), lung damage, etc. Therefore rapid

I. Congenital interferonopathies	II. Acquired—secondary interferonopathies
1. IFN deficiency 1.1 Interferon α deficiency (IFN α) 1.2 Interferon β deficiency (IFN β) 1.3 Interferon γ deficiency (IFN γ) 2. Interferon overexpression 2.1 IFN α overexpression 2.1.1 Autoinflammatory syndromes and autoimmune diseases (systemic lupus erythematosus (SLE), systemic angiitis, dermatomyositis), Down syndrome 2.1.2 Type I interferonopathies: Aicardi-Goutières syndrome (AGS), familial chilblain lupus (FCL), spondyenchondromatosis, proteasome-associated autoinflammatory syndrome (PRAAS), Singleton-Merten syndrome (SMS)	1. IFN deficiency 1.1 IFN α deficiency 1.2 IFN β deficiency 1.3 IFN γ deficiency 2. Interferon system paralysis 2.1 Blockage IFN α adequate response 2.2 Blockage IFN β adequate response 2.3 Blockage IFN γ adequate response 3. IFN overexpression 3.1 Cytokine storm

Table 1.
Classification of interferonopathies.

and efficient immune reaction to alien nucleic acids is positive when it causes type I IFN activation during pathogen invasion and antimicrobial protection. It becomes deleterious when it responds to own DNA which is due to the defect of own nucleic acid metabolism. Some neurological, vascular, and skin symptoms which are typical for type I interferonopathies are reviewed in such multifactorial diseases as exanthematous lupus erythematosus, widespread vasculitis, and autoimmune multiple myositis [6, 7, 18] (**Table 2**).

3.1.1 Target therapy by biologics in the treatment associated with type I IFN overexpression of type I IFN hyperproduction

Data available on genetic defects of intracellular nucleic acid metabolism greatly facilitate understanding of the mechanisms of insufficient immune activation, which can help in the development of new therapeutic approaches to the treatment of autoinflammatory and autoimmune diseases [1–3]. The progress in understanding immunopathogenesis mechanism makes it possible to set the exact targets for new therapeutic strategy development [1, 2]. The immune dysregulation syndrome is characterized by a high level of IFN α , a deficiency of regulatory T-lymphocytes, impaired functioning of B cells, and low content of low-density neutrophils. These neutrophils easily form neutrophilic extracellular traps (NET), and the resulting DNA complexes provoke an increase in IFN α synthesis, and then pDC recognizes autoDNA and produces IFN α [10, 11, 19]. These disorders are observed primarily in systemic lupus erythematosus. New approaches in treatment of SLE and other type I interferonopathies have been developed. Monoclonal antibody therapy in type I interferonopathies treatment with SLE is sifalimumab, rontalizumab against IFN α , and anifrolumab against IFN α receptor (IFNAR). Baricitinib (JAK1/JAK2 inhibitor) is currently at clinical studies (phases 2 and 3) in small cohort of patients with interferonopathies [20–22]. It is also known that treatment with baricitinib decreased disease signs and symptoms and allowed a significant reduction of corticosteroid treatment in patients with CANDLE and SAVI [23] (**Figure 2**).

3.2 Congenital interferonopathies associated with type I IFN deficiency

There are genetic defects in the synthesis of IFN α /IFN β and IFN γ and defects in the receptors for IFN α and IFN γ (IFNAR and IFNGR) including genetic disorders associated with low IFN production according to recent studies. Those genetic

Syndrome	Responsible gene	Phenotypes
Aicardi-Goutières syndrome	TREX1, RNASEH2B, RNASEH2C, RNASEH2A, SANHD, ADAR, IFIH1	Encephalopathy, muscular dystonia, microcephaly, calcification of the basal ganglia in the substance of the brain, cramps, fever, increased acute phase blood markers, cytopenia, increased levels of interferon in the cerebrospinal fluid
Singleton-Merten syndrome	IFIH1 DDX58 RIG-I	Cardiovascular diseases with aortic calcification, osteoporotic manifestations, dental and skeletal abnormalities, psoriatic skin lesions
Proteasome-associated autoinflammatory syndromes Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)	PSMB4 PSMB3 PSMB8 PSMB9 POMP	Erythematous skin lesions, panniculitis, lipodystrophy, arthritis with the development of joint contractures, myalgia, hepatomegaly, splenomegaly, calcification of the basal ganglia in the brain, fever, increased acute phase blood markers Recurrent fevers in the first months of life, along with characteristic skin lesions, lipodystrophy, violaceous swollen eyelids, arthralgias, extremity contractures, and delayed physical development as well as systemic inflammation markers have been identified as CANDLE-related clinical manifestations
STING-associated vasculopathy with onset in infancy (SAVI)	TMEM173	Vasculopathy with the formation of distal gangrene; necrosis; erythematous rash on the face, tip of the nose, and auricles; interstitial lung disease, arthralgia, fever
Spondyloenchondrodysplasia (SPENCD)	ACP5	Spondylometaphyseal dysplasia, stunting, calcification of the basal ganglia in the substance of the brain, arthropathy, thrombocytopenia, deficiency of cellular and humoral immunity
ISG15 deficiency	ISG15	Calcification of the basal ganglia in the substance of the brain, convulsions, mycobacterial infections
USP18 deficiency (pseudo-TORCH syndrome)	USP18	Cerebral hemorrhage and calcification, hepatomegaly, thrombocytopenia
Trichohepatoenteric syndrome 2	SKIV2L	Watery diarrhea, brittle and tangled hair, liver damage, mental retardation
Retinal vasculopathy with cerebral leukodystrophy (RVCL)	TREX1	The main characteristics of RVCL include the middle-age onset, the progressive visual loss due to retinal vasculopathy (telangiectasias, microaneurysms, and retinal capillary obliteration around the macula), and variable neurological manifestations such as dementia or migraine

Syndrome	Responsible gene	Phenotypes
Familial chilblain lupus	TREX1	Rare monogenic form of cutaneous lupus erythematosus; partly ulcerating acral lesions or painful bluish-red papules located in the fingers, toes, nose, and ears; arthralgias, affecting mainly large joints, without evidence of true arthritis; photosensitivity; or mouth ulcers
X-linked reticulate pigmentary disorder (XLPDR)	POLA1	Generalized hyperpigmentation intermingled with small hypomelanotic macules during early childhood, a distinctive face characterized by an upswept frontal hairline and arched eyebrows, as well as severe photophobia, recurrent respiratory infections, and severe gastrointestinal disorders

Table 2.
Genetic disorders associated with immune dysregulations and clinical characteristics of interferonopathies associated with type I IFN overexpression.

defects of IFNs are accompanied by clinical signs of severe recurrent viral and/or mycobacterial infection.

Congenital defects of type I IFN are associated with mutation of genes participating in synthesis of IFN α /IFN β resulting to deficiency of various molecules (STAT1, UNC93B1, MCM4, TLR3, TRAF3, TRIF, TBK1) and decline level of IFN α /IFN β . Deficiency of IFN γ , its receptor IFNGR (IFN γ R1), and IL-12 plays an important role in IFN γ regulation [12, 24, 25]. Congenital defects of type I IFN have been globally systematized in 2015 by Bousfiha et al. [24]. It has been proven that it causes severe viral and bacterial intracellular infections which are the cause of deaths. Such patients are needed in replacement therapy with recombinant IFN α 2b in complex

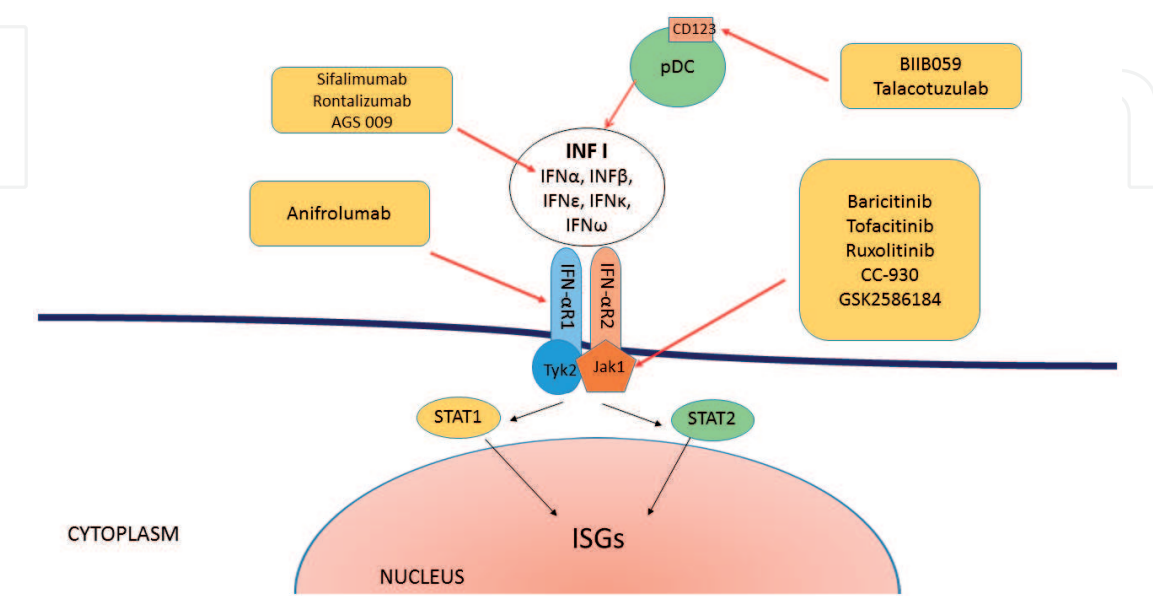


Figure 2.
Target therapies by biologics in the treatment of type I IFN overproduction. IFNAR, IFN α receptor; ISGs, interferon-stimulated genes; Tyk, tyrosine kinase; Jak, Janus kinase; pDC, plasmacytoid dendritic cell; STAT, signal transducer and activator of transcription.

with antioxidants. Congenital defects of IFN γ R1 receptor are associated with severe intracellular mycobacterial infections. Combined genetic defects leading to deficiency of IFN α and IFN γ are associated with an autosomal recessive mutation in the STAT1 gene, which causes severe viral and mycobacterial infections [12, 24, 25] (**Table 3**).

3.3 Acquired: secondary interferonopathies

There are secondary acquired disorders in the IFN system, which cause a weakening of antiviral resistance in adults and children [12]. Different viruses can damage synthesis and production of IFN at various interferonogenesis stages. These secondary defects of the type I IFN lead to the occurrence of severe viral infections

Predominant susceptibility to viral infection		
Syndrome	Responsible gene	Phenotypes
Herpes simplex encephalitis (HSE)	AR (autosomal recessive inheritance): UNC 9381 TLR3 TRIF AD (autosomal dominant inheritance): TLR3 TRIF TRAF3 TBK1	Dominant clinical phenotype is HSE during primary infection with HSV1, usually between 3 months and 6 years of age Specific tests examining the TLR3 pathway marked decrease on the ability of patient's fibroblasts to produce IFN β /IFN λ in response to TLR3 agonists and HSV1 infection
Warts, hypogammaglobulinemia, infection, myelokathexis (WHIM) syndrome	AD: CCXR4	Warts/human papilloma virus infection Neutropenia, reduced B cell numbers
Epidermodysplasia verruciformis	EVER1/TMC6, EVER2/TMC8	Human papilloma virus (group B1) infection and skin cancer
STAT1 deficiency STAT2 deficiency		Viral infections
CD16 deficiency		Severe viral infections
IRF7 deficiency		Severe influenza disease
Susceptibility to mycobacteria		
Syndrome	Responsible gene	Phenotypes
IRF8 deficiency	AR: IRF8	Susceptibility to mycobacteria, <i>Candida</i> , myeloproliferation
RORc deficiency	RORc	Susceptibility to mycobacteria, <i>Candida</i>
MSMD IL-12-IFN γ axis deficiency	AD: IFNGR1 Complete AR IFNGR1 and AR IFNGR2 Partial STAT1 LOF (AD), partial IFNGR1, partial IFNGR2, complete IL-12R1, complete IL-12B, complete ISG15, XL CYBB, IRF8, Tyk2, XL NEMO	Mycobacterial osteomyelitis Serious disseminated BCG and environmental mycobacteria infections (soft tissue, bone marrow, lungs, skin, bones, and lymph nodes), <i>Salmonella</i> spp., <i>Listeria monocytogenes</i> , and viruses Usually less severe

Table 3.
 Genetic disorders and clinical characteristics of interferonopathies associated with type I IFN deficiency.

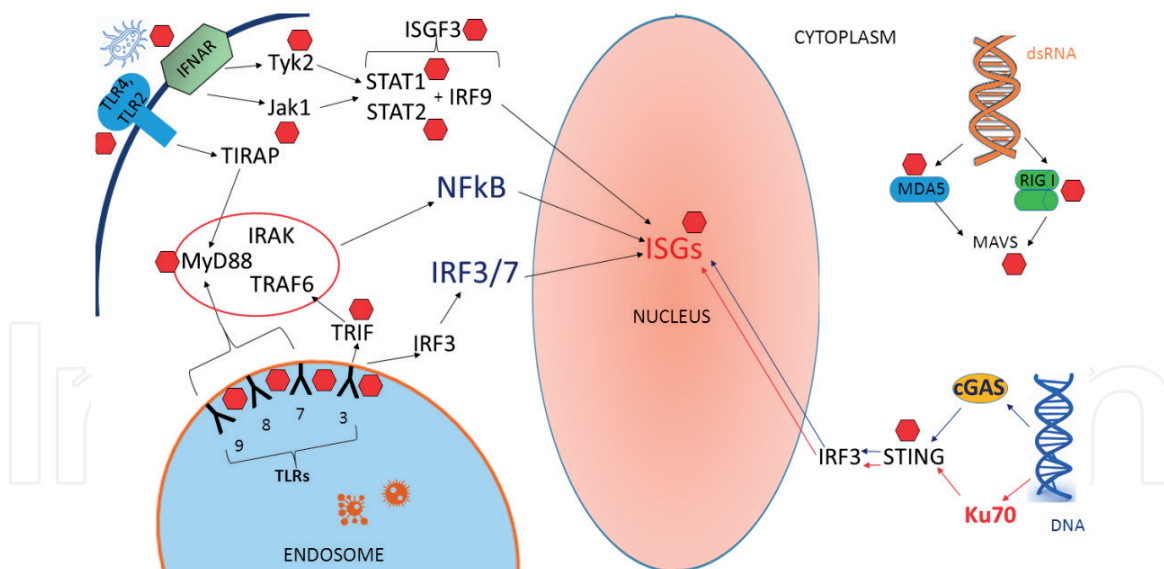


Figure 3.

Blockage of signaling pathways for the induction of interferon by viruses (red hexagons indicate the points of application of all herpesviruses, majority of respiratory viruses, chronic hepatitis B and C viruses, etc.). dsRNA, double-stranded RNA; IRF, IFN regulatory factor; IFNAR, IFN α receptor; ISGs, interferon-stimulated genes; Tyk, tyrosine kinase; Jak, Janus kinase; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; cGAS, cyclic GMP-AMP synthase; MAVS, mitochondrial antiviral-signaling protein; MDA5, melanoma differentiation-associated protein 5; STAT, signal transducer and activator of transcription; TRIF, TIR domain-containing adaptor inducing interferon-beta; Ku70, component of the nonhomologous end-joining pathway that repairs DNA double-stranded breaks.

(herpesviral encephalitis), recurrent acute respiratory viral infections (recARVI), chronic recurrent HSV1 infection, atypical chronic EBV infections, and other atypical cases of virus infection. It was shown that viruses can avoid the effects of IFN and inhibit the action and synthesis of IFN using various molecular mechanisms. Numerous studies demonstrated that a lot of viruses (all herpesviruses, majority of respiratory viruses, hepatitis B and C viruses, etc.) produce proteins capable of inhibiting synthesis and production of IFN α /IFN β and IFN γ . Viruses can damage each stage of the expression of ISGs [9] (**Figure 3**).

Patients with recurrent acute respiratory viral infections and various chronic herpesvirus infections including recurrent herpes viral infections have secondary defects of IFN system. Immunocompromised children of various ages and adults may suffer from recARVI with the frequency of 10 to 16–24 and more times annually; almost in 100% of cases, it is associated with the presence of mono and mixed herpes viral infection. The frequency of recurrent chronic HSV1/HSV2 infection of facial and/or genital location in those patients may reach 16–24 times per year. Epstein-Barr virus may cause atypical virus infection associated with chronic fatigue syndrome [12].

3.3.1 Differentiated approaches to interferon therapy in patients with secondary interferonopathies

The problem of developing new approaches to the treatment of congenital and acquired defects of the IFN system is very acute [12, 26–28]. Acquired defects in the IFN system (93–96%) and impaired functioning of neutrophilic granulocytes (NG) are most often detected in patients with recurrent chronic herpes virus infections.

We conducted experiment in vitro to study the effect of recombinant IFN α 2b (rIFN α 2b) on NG in viral (cells from patients with HSV1/HSV2 infection) and bacterial (model infection by fMLP) infections. The study showed positive regulation of the negatively charged IFN α β R1⁺IFN γ R⁺TLR4⁺NG phenotype in patients with various chronic herpesvirus infections under the influence of rIFN α 2b in vitro.

It was noted that the number of NGs carrying IFN α β R1 and IFN γ R and expression density of IFN α β R1 is increasing, wherein expression density of IFN γ R and TLR4 is decreased [29]. rIFN α 2b modulating effects on CD16⁺CD66b⁺CD33⁺CD11b⁺NG phenotype transformed by fMLP in experimental model of bacterial process in vitro, to promote remodeling of the pro-inflammatory NG phenotype into anti-inflammatory, have been shown [30]. Thus rIFN α 2b has a protective effect on the NG phenotype according to experimental data.

In clinical practice, the use of parenteral IFN to correct disorders in the IFN system is very difficult due to the presence of numerous side effects. One should also bear in mind the inefficiency of short courses of IFN therapy for restoration of the normal IFN system functioning in recARVI, recurrent chronic herpes viral infection of facial or genital location, and papilloma virus infection of the skin and mucosa characterized by recurrent episodes when the frequency of recARVI and/or recurrent attacks of HSV1/HSV2 infection may reach 14–24 and more per year. For over 20 years, we have been developing interferon therapy programs using drugs in Russian production—rectal suppositories and gel of recombinant human IFN α 2b (rIFN α 2b+aox) in combination with antioxidants (vitamins E and C) (Viferon) [12–15, 26, 27]. During that period, we managed to demonstrate safety, antiviral, and immunomodulatory efficiency of this kind of IFN therapy, total absence of any side effects that are typical for parenteral IFN therapy, and total absence of antibodies against IFN α 2b. Replacement therapy with rIFN α 2b + aox is prescribed to patients with primary, genetically preconditioned, congenital or acquired IFN system disorders. In case of primary IFN system disorders, patients need a basic recovery therapy making it possible to eliminate viral antigens as much as possible; and then it is required to select dosage for permanent replacement therapy with rIFN α 2b+aox. In case of acquired interferon deficiency, patients are prescribed with differentiated therapy with high, medium, and low doses of rIFN α 2b+aox (Figure 4).

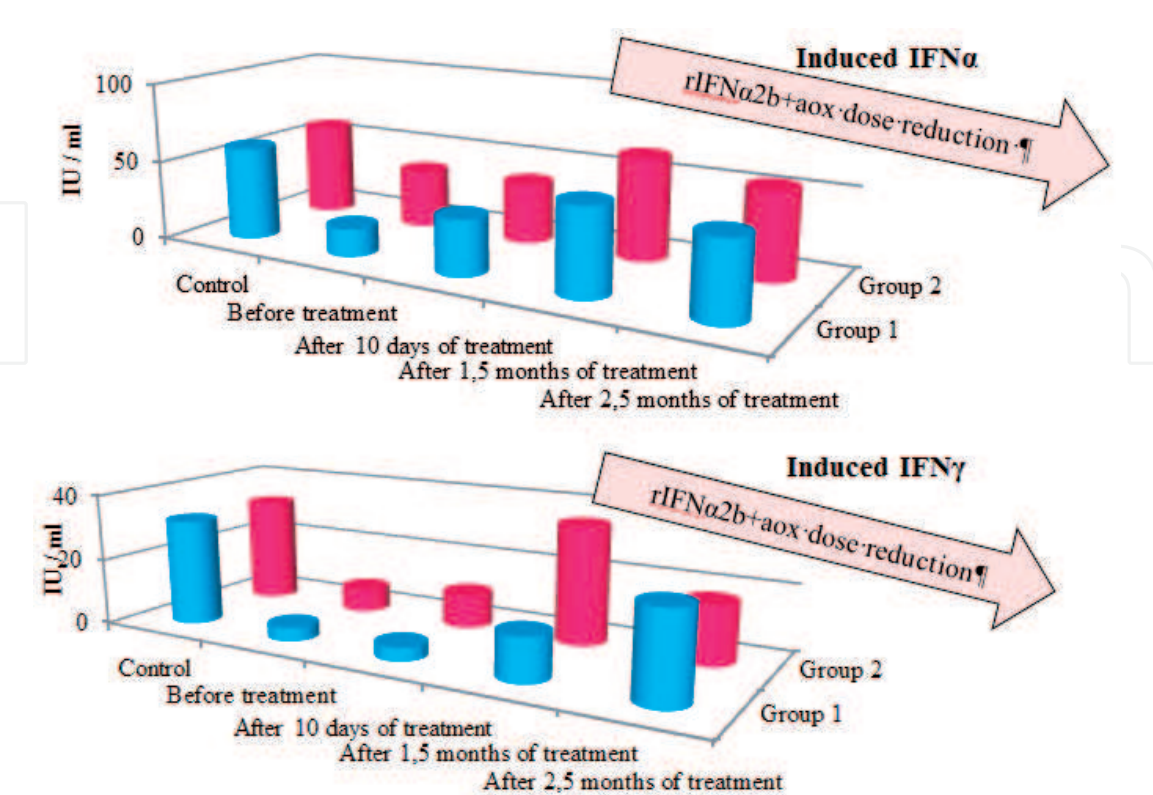


Figure 4.
Dynamics of changes in the system of IFN in immunocompromised children against the background of therapy with rIFN α 2b+aox (Viferon).

At the same time, in case when we had treated the group of patients with combined immunodeficiency (defects of induced production of IFN α and IFN γ and dysfunctions of phagocytic and microbicidal activities of neutrophilic granulocytes) that was associated with recurrent acute respiratory viral infection and different chronic herpes viral coinfections, combined interferon and immunomodulatory therapy was used. The aim was to restore the levels of induced production of IFN α and IFN γ and to reconstruct dysfunctions of phagocytic and microbicidal activities of neutrophilic granulocytes and other deficient chains in antiviral immunity. One group of children, group 1, received an interferon therapy program (rIFN α 2b+aox), and patients in group 2 received a program of combined interferon therapy (rIFN α 2b+aox) and immunotherapy (glucosaminylmuramyl dipeptide). The use of replacement and immunomodulatory mono-rIFN α 2b+aox or in combination with immunotherapy (glucosaminylmuramyl dipeptide) has helped us to receive very good clinical efficacies and has reached restoration of interferon status and normal functioning of neutrophilic granulocytes ($p < 0.05$) (**Figure 5**). At the same time, it is required to take into account both uneven viral infection syndrome manifestation and the rate of IFN α deficiency as well as peculiarities of immune system disorders in case of secondary immune deficiency [12–15, 27].

Here is an example illustrating the change in clinical, immune, and interferon status in immunocompromised children with recurrent acute respiratory viral infections under the influence of interferonotherapy.

Clinical case. Patient X, 3 years old. The child suffers from repeated acute respiratory viral infections 1–2 times per month (14–16 episodes per year); the duration of the acute period of respiratory viral infection is 7–10 days. The clinical symptoms of the disease were acute rhinitis, acute pharyngitis, acute laryngitis, acute tracheitis, febrile and subfebrile body temperature for 2–4 days, and severe symptoms of intoxication. The duration of the frequent incidence of acute respiratory viral infections is 2 years. The defects of the immune system are a decrease of CD3⁺CD4⁺ lymphocytes and CD3⁺CD8⁺ lymphocytes; a decrease of immunoregulatory index; neutropenia; a decrease of bacteria absorption and digestion processes by neutrophils; and a decrease of microbicidal activity of neutrophils. We tested spontaneous and Newcastle disease virus-induced IFN production during the incubation of peripheral blood (24 h, $t\ 37^{\circ}\text{C}$ in 5% CO₂). The level of induced IFN α in the patient was 4 IU/ml versus 58 IU/ml in control. The patient was prescribed rIFN α 2b+aox therapy with a total duration of 2.5 months.

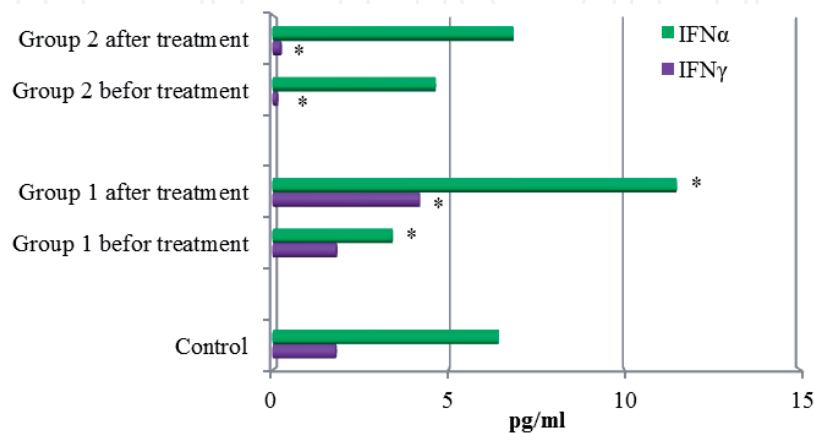


Figure 5. The state of the interferon system in immunocompromised children with recurrent respiratory infections on the background of differentiated programs interferon and immunotherapy. Note: group 1 received an interferon therapy program (rIFN α 2b+aox); group 2 received a program of combined interferon therapy (rIFN α 2b+aox) and immunotherapy (glucosaminylmuramyl dipeptide); (* $p < 0.05$, reliability in relation to control).

Treatment program:

- Local intranasal use of rIFN α 2b+aox (Viferon gel, 36,000 IU/g), two to three times a day, 6 weeks.
- Systemic rectal application of rIFN α 2b+aox suppositories according to a “step-by-step” scheme:

300,000 IU per day, 10 days.

300,000 IU per day three times a week, 2 weeks.

300,000 IU per day two times a week, 2 weeks.

150,000 IU per day two times a week, 2 weeks.

150,000 IU per day once a week, 2 weeks.

Conducted local and systemic interferon therapy led to a reduction in the frequency of acute respiratory viral infections to three episodes per year lasting 5–7 days, proceeding in a milder form. Rehabilitation of immunity parameters occurred after 2.5 months of interferonotherapy, and the level of induced IFN α was normalized to 64 IU/ml.

4. Conclusion

Summing up the above information, we may conclude that new biological drugs based on mAb are effective and safe, and they are able to neutralize IFN α overexpression in type I interferonopathies, both in Mendelian's diseases and in autoimmune disorders. At the same time, local and system use of rIFN α 2b+aox (Viferon) in congenital and acquired IFN system defects associated with viral infection syndrome, where a differential dosage is selected individually taking into account the rate of deficiency and an adequate, extended course of therapy is optimal because it is associated with positive clinical and immunological effects without any negative and side effects. Our more than 20-year experience has shown that using rIFN α 2b+aox in patients with congenital or acquired IFN system defects had demonstrated positive clinical effect and is safe [31]. IFN (rIFN α 2b+aox) therapy can be used with very good clinical efficacy in cases of primary or secondary defects of induced production of IFN α and IFN γ . From the other side, it is very important that in patients with a genetic predisposition to the manifestation of autoimmune diseases, primarily vasculitis and systemic lupus erythematosus, we do not recommend to use IFN therapy.

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