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Review

Human Acid-Labile Interferon α

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Abstract. In acquired immune deficiency syndrome (AIDS) and autoimmune diseases, like systemic lupus erythematosus (SLE), persisting high levels of interferon (IFN) are detectable in plasma. The IFN has been identified as an unusual human acid-labile IFN-α (al-IFN-α). Its properties are similar to that of the known α interferons except sensitivity to acid treatment (pH 2) which is characteristic for IFN-γ. The nature of al-IFN-α is not known. Four hypotheses have been presented that suggested that: a) al-IFN-α may be a product of a distinct IFN gene; b) or a posttranscriptionally modified IFN-α molecule; c) the phenomenon of al-IFN-α may be an effect of synergistic action of a mixture of acid-stable IFN-α and acid-labile IFN-γ; d) or the effect may be a result of an interaction of acid-stable IFN-α with an unknown factor(s) present in plasma and associated with progression of HIV infection or autoimmune diseases. Neither of the hypotheses have been experimentally proven. To verify the most probable hypothesis of the synergistic interactions between the acid stable and labile IFNs, the experiments with the artificial mixtures of nHuIFN-α and rHuIFN-γ were performed. The synergistic effect was abolished by the treatment either with pH 2 or with anti-IFN-γ antibodies. The residual activity was similar in both cases and corresponded to acid-stable IFN-α. However, al-IFN-γ (AIDS serum with high IFN level) was found to be much more sensitive to acid treatment and only negligible effect of anti-IFN-γ serum was observed. It suggests that the synergistic effect may be only slightly responsible for the phenomenon of acid lability of IFN-α. Foor explanation of the occurrence of al-IFN-α the hypothesis of existence of a factor(s) interacting with IFN-α should be taken into consideration.

Key words: interferon; acid-labile interferon α; synergistic action of IFN-α and IFN-γ; AIDS; HIV infection; systemic lupus erythematosus; autoimmune diseases.

Human Interferons

Four types of human interferons (IFNs) have been identified: IFN-α, IFN-β, IFN-γ and IFN-ω (Table 1) – on the basis of the differences in amino acid sequences and antigenic properties[42, 43]. Interferon α is a family of closely related proteins encoded by 13 genes. In contrast, IFN-ω, IFN-β and IFN-γ are proteins encoded by single genes. Besides, 11 pseudogenes related to IFN-α and IFN-ω have been found in the human genome[5, 21, 22, 56, 57].

In preparations of human virus-induced leukocyte interferon several α interferons have been detected. The main fractions correspond to IFN-α1a and IFN-α2b (ca. 50% of total IFN). The minor components are IFN-α4b, IFN-α7a, IFN-α8b, IFN-α10a, IFN-α14c, IFN-α17b and IFN-α21b[39, 56].

Diversity in the family of IFN-α proteins is even

Abbreviations used: AIDS – acquired immune deficiency syndrome, IFN – interferon, al-IFN-α – acid-labile interferon α, PBMC – peripheral blood mononuclear cells, SLE – systemic lupus erythematosus.

Table 1. Human interferon proteins[5, 21, 22, 56, 57]

Gene	Proteins – sequence variants		Amino acid number	Glycosylation
	found in normal human genome	found in transformed cells		
IFNA1	IFN-α1a	IFN-α1b	166	no
IFNA2	IFN-α2b, IFN-α2c	IFN-α2a	165	O-glycosylation
IFNA4	IFN-α4a, IFN-α4b		166	no
IFNA5	IFN-α5		166	no
IFNA6	IFN-α6		166	no
IFNA7	IFN-α7a	IFN-α7b, IFN-α7c	166	no
IFNA8	IFN-α8b	IFN-α8a, IFN-α8c	166	no
IFNA10	IFN-α10a, IFN-α10b		166	no
IFNA13	IFN-α13[a]		166	no
IFNA14	IFN-α14c	IFN-α14a, IFN-α14b	166	N-glycosylation
IFNA16	IFN-α16		166	no
IFNA17	IFN-α17a, IFN-α17b, IFN-α17c	IFN-α17d	166	no
IFNA21	IFN-α21b	IFN-α21a	166	no
IFNW1	IFN-ω		172	N-glycosylation
IFNB	IFN-β		166	N-glycosylation
IFNG	IFN–γ		143	N-glycosylation

[a] Amino acid sequence identical to IFN-α1a.

larger because many sequence variants of individual genes have been found (Table 1). Some of proteins, coded by these genes, have been identified in normal human cell cultures and therefore may be regarded as the allelic variants. The polymorphism has been observed in cases of IFN-α2[24, 51], IFN-α4[40], IFN-α10[31] and IFN-α17[31, 32]. Alleles of IFN-α4, IFN-α10 and IFN-α17 have been found with high frequencies (more than 10% for each allele). In the case of IFN-α2, which is a predominant subtype in the most of preparations of the leukocyte IFN, IFN-α2b variant was found in more than 99% of individuals tested, whereas IFN-α2a has not been detected in normal population[24, 51]. Thus, the latter IFN belongs to a group of 10 sequence variants found only in transformed cells (Table 1). It is not clear whether these proteins are products of rare alleles or they derived by mutation of the transformed cells.

Various interferon variants may appear after post-translational modifications, namely glycosylation and oligomerization. Glycosylation is characteristic for IFN-ω[4], IFN-β[38] and IFN-γ[10]. Two subtypes of IFN-α are also glycosylated: IFN-α2[3] and IFN-α14[56], whereas molecules of IFN-γ may exist as homodimers[10].

Interferons are often divided into type I and type II. According to this nomenclature system IFN-α, IFN-β and IFN-ω are classified as IFN-type I and IFN-γ as IFN-type II. The reason for such division is a considerable difference between IFN-γ and all other IFNs. On the other hand, two types of IFN receptors exist: type I which can bind IFN-α, IFN-β and IFN-ω, and type II able to bind IFN-γ[46, 53, 58]. Furthermore, type I IFNs are acid-stable whereas type II IFNs are acid-labile after acid treatment at pH 2[42, 43]. Type I and type II IFNs act synergistically when their antiviral or antiproliferative activities are determined[18, 59].

At least 12 different α-IFNs and single IFN-β, IFN-ω and IFN-γ proteins are produced by various human cells. Sequence (allelic) variants of IFN-α increase potential number of different human IFNs up to 30. However, existence of IFN genes or proteins, not recognized as yet, is highly probable. One of the possibilities concern a human equivalent of animal trophoblastic interferons.

Trophoblastic interferons

Two types of trophoblastic interferons designed as IFN-τ and IFN-δ have been found in ruminants and pigs.

IFN-τ (previously named trophoblastin or trophoblast protein-type 1 – TP-1), found in sheep, cows, goats and giraffe, is produced by trophoblast cells during early pregnancy. It exerts antiluteolytic activity and therefore is essential for the maternal recognition of pregnancy. Amino acid sequence of mature IFN-τ consists of 172 residues. It is most closely related to IFN-ω, and to a lesser extent to IFN-α. Like IFN-ω and IFN-α, IFN-τ is stable at pH 2 and represents separate multigene-encoded family of proteins acting through binding to type I IFN receptors. However, unlike other type I interferons, IFN-τ is produces constitutively and is not virally-inducible. Extensive search for IFN-τ genes in mammals, other than ruminants, has not been successful and suggests that this type of IFN was specific only for ruminants[9, 17, 50, 65–67, 73, 75].

The name IFN-δ, that was secreted by pig embryo

trophoblasts, has been recently proposed for a porcine type I interferon (originally called spI-IFN). IFN-δ is antigenically and structurally distinct from other IFNs. Its mature protein, consisted of 149 amino acid residues. It is N-glycosylated and stable at pH 2[52, 53, 55].

Cells of human trophoblast produce IFN-β, IFN-α and IFN-ω[1]. Existence of trophoblastic interferons, different from well-known IFNs (see Table 1) is controversial. For instance, WHALEY et al.[80] described a gene *htIFN* expressed in placenta. It differed from the ruminant and pig trophoblastic IFN genes because its expression was found not only in the peri-implantation period, but also in amniocytes and adult lymphocytes. The gene encoded a protein having 172 amino acid residues and related to IFN-ω and IFN-τ, with a homology to ovine IFN-τ. Although *htIFN* was described in 1994, no more papers on this IFN have been published.

Acid-labile-IFN-α – prevalence and properties

An unusual IFN, having no equivalent in the known human IFNs families (Table 1), has been described. Because it is pH 2 labile (like IFN-γ) but neutralized by anti-IFN-α antibodies, it has been named acid-labile IFN-α (al-IFN-α).

The al-IFN-α is prevalent in plasma or sera of individuals with acquired immune deficiency syndrome (AIDS)[20, 25, 35, 41, 48, 60–62, 76, 77, 79] and several autoimmune diseases such as systemic lupus erythematosus (SLE)[37, 63, 81], rheumatoid arthritis[37, 70] and systemic scleroderma[37, 70]. The levels of al-IFN-α may be as high as 300–1000 antiviral IFN U/ml and persist for months or even years of exacerbation during the course of AIDS[20, 41, 48, 60–62, 76]. Such levels of IFN should be considered as very high in comparison with the physiological levels of the circulating IFN which do not exceed 12–20 U/ml[19, 60, 62]. After i. v. administration of $6–10 \times 10^6$ U of natural or recombinant IFN-α or IFN-β the levels of IFN in plasma were 100–600 U/ml for 10–30 min after injection and then decreased rapidly and returned to baseline by 4–8 h[47, 69, 74]. Hence, the high al-IFN-α levels found in AIDS and some autoimmune diseases may be regarded as pathologically-enhanced.

CAPOBIANCHI et al.[13, 15] found that *in vitro* al-IFN-α was produced by peripheral blood mononuclear cells (PBMC) after stimulation with live or fixed with glutaraldehyde HIV-infected cells (both transformed or normal PBMC infected *in vitro* with HIV were used). CAPOBIANCHI et al.[12] suggested that the viral glycoprotein (gp) 120 is responsible for induction of the endogenous IFN in patients with AIDS. However, only acid-stable IFN-α has been found after stimulation of PBMC with HIV particles as well as the cells infected with other viruses[13]. Relatively low levels of al-IFN-α have been detected after stimulation of PBMC cultures with poly I: C[36], Sendai virus[54], influenza virus[8, 70], *Corynebacterium parvum*[64] and *Staphylococcus aureus*[29]. It was also found that B cell lines, chronically infected with HTLV-I and/or EBV, produced al-IFN-α without any additional inducer[11].

There are several reports describing al-IFN-α-producing cells. CAPOBIANCHI et al.[13] found that al-IFN-α was produced by B lymphocytes. They suggested that interferon synthesis may be due to interaction between circulating B lymphocytes and HIV-infected cells. Large granular lymphocytes (LGL) were also considered to be al-IFN-α producers[29]. There is no evidence what type of cells is responsible for production of al-IFN-α under natural conditions *in vivo*.

The al-IFN-α is active in heterologous cells e. g. in bovine MDBK[25, 63, 76, 79]. Its molecular weight (19-20 kDa)[13, 81], isoelectric point (5.1)[81] and reaction with anti-IFN-α sera[13, 81] resemble that of acid-stable IFN-α. However, affinity chromatography (ConA-Sepharose)[15], the effect of neuraminidase and inhibitory effect of tunicamycin on the al-IFN-α synthesis[14] showed that this IFN was glycosylated (like only two subtypes of IFN-α family, and also IFN-ω, IFN-β and IFN-γ, Table 1). Repeated freezing or thawing had no effect on titer or properties of IFN in samples of sera from AIDS patients[25].

Acid sensitivity is the main property distinguishing al-IFN-α from classic α interferons and resembling IFN-γ. The antiviral activity of al-IFN-α was destroyed when the preparation was acidified below pH 4[13]. However, pH 2 lability of al-IFN-α is less pronounced than that of IFN-γ. Usually 80–90% (range 40–97%) of total IFN activity was found to be pH 2 sensitive[13, 25, 37, 41, 60, 62, 63]. Thus, al-IFN-α may be a mixture of acid-labile and acid-stable IFN-α.

Purification of al-IFN-α by chromatography resulted in detection of acid-stable IFN-α only[15, 76, 81]. CAPOBIANCHI et al.[15] showed that after chromatographical purification (ConA-Sepharose and anti-IFN-α-Sepharose) of *in vitro*-produced al-IFN-α, majority of initial activity was found in acid-stable non-glycosylated IFN-α fraction. Two small fractions contained acid-stable glycosylated IFN-α and acid-labile glycosylated IFN-γ. All obtained IFN fractions had equivalent in known IFN proteins. SWINDELLS et al.[76] showed that al-IFN-α, found in plasma from patients with AIDS, could be bound to anti-IFN-α-Sepharose column. The eluted IFN was acid-stable and formed two electro-

phoretic fractions different from HuIFN-α2. YEE et al.[81] found that ion-exchange chromatography of al-IFN-α preparations (plasma from patients with SLE) resulted in 6-fold purification with 90–95% recovery. However, the partially purified IFN was characterized as acid-stable IFN-α.

The results of measurement and characterization of al-IFN-α activity have been based almost exclusively on biological assays e. g. inhibition of viral cytopathogenic effects. Human WISH[8, 12, 13, 15, 37, 77], A549[60–62], HEp-2[41, 76], HeLa229[76], T98G[48], diploid fibroblasts[70], FS-4[81], T21[41], Gm2504[20, 25, 63], and bovine MDBK cells[8, 20, 25, 63, 76, 77, 79] have been used. The human cells used in the bioassays usually respond to many IFN types and the resulting titers refer to the total IFN activity.

In the experiments the polyclonal antisera of sheep, bovine or rabbit origin against natural human leukocyte IFN have been used[8, 12, 13, 15, 20, 25, 41, 60, 62, 63, 81]. The leukocyte IFN is composed of several subtypes of IFN-α and small amounts of IFN-ω and IFN-β. Thus, there are many possibilities for different reactions. Weaker or stronger reactions with IFN-β, IFN-ω[2], IFN-τ[17, 67] or IFN-δ[55] were shown.

In contrast, immunoassays with the use of monoclonal antibodies and neutralization tests, in which these antibodies were used, failed to detect al-IFN-α[34, 76] or only low levels of the cytokine were found[12, 68]. Furthermore, the immunoassays based on polyclonal antibodies have not shown as high IFN levels as that determined by bioassays[7, 79]. The IFN activity measured by immunoassays may therefore be activity of acid-stable component present in plasma samples together with al-IFN-α. Again, this suggests that al-IFN-α may not be identical to the main subtypes of HuIFN-α family, namely HuIFN-α1 and HuIFN-α2, against which most of the used monoclonal antibodies have been prepared.

Acid-labile IFN-α was described almost 20 years ago, but its nature has not been identified. None of the proposed explanations is consistent with all experimental data. The following hypotheses have been taken into consideration.

– Hypothesis 1: al-IFN-α is encoded by a unique gene[44, 48]. The simplest explanation of the presence of a protein with unusual properties assumes existence of an unknown gene. Human interferon system e. g. genes and proteins have been well described (Table 1). Nevertheless, there is a possibility that more IFN genes may exist. It is not clear whether human trophoblastic interferons are different as it was estimated in ruminants and pigs. The reported sequence of *htIFN*[80] has not been, however, widely accepted[5, 21, 22]. Unique human IFN may be encoded by a gene expressed only in limited periods of life and thus may be difficult to identification.

KONTSEK et al.[44] suggested identity of IFN-ω and al-IFN-α. They found that both IFNs are acid-labile and neutralized by anti-al-IFN-α as well as anti-IFN-ω antisera. However, reactions of al-IFN-α with the sera were weak. This results were not confirmed by others, who detected that human IFN-ω was acid-stable[1, 17] and monoclonal anti-IFN-ω antibodies did not react with al-IFN-α[15].

– Hypothesis 2: al-IFN-α results from posttranscriptional modification of IFN-α[48]. However, up to now no modifications causing acid lability have been identified.

– Hypothesis 3: al-IFN-α results from the measurement of the antiviral activity of a synergistically acting mixture of IFN-α and IFN-γ[15, 47]. This hypothesis is the most frequently accepted explanation of al-IFN-α phenomenon.

CAPOBIANCHI et al.[15] showed that after chromatographical purification of *in vitro*-produced al-IFN-α only fractions corresponding to known human IFN were obtained. Reconstitution experiments, in which IFN-α and IFN-γ fractions were mixed, resulted in development of synergistic effect and acid sensitivity of the total IFN activity. Presence of IFN-γ (determined by immunoassays[12, 15, 16, 28, 68] and mRNA expression[12]) in plasmas with al-IFN-α activity supports above hypothesis.

Synergistic effect may explain the phenomenon of al-IFN-α produced *in vitro*. However, this effect is rather not sufficient for full explanation of the nature of the IFN found in plasmas/sera of individuals suffered from AIDS or autoimmune diseases. Firstly, if the effect of acid lability of IFN-α is caused by the presence of small amounts of IFN-γ, inactivation of the latter IFN should leave only IFN-α to be detected by a bioassay. Different ways leading to such result should give similar effects. However, pH 2 treatment was found to affect the al-IFN-α activity far more than anti-IFN-γ antibodies[12]. Secondly, IFN-α and IFN-γ in plasma or serum were concomitantly observed also in healthy people[16, 23], in early stages of HIV infection[68] or in other diseases[45] where al-IFN-α was not observed. Nevertheless, the possibility that in plasma/serum of patients with AIDS or autoimmune diseases synergistic action of IFN-α and IFN-γ takes place in atypical way cannot also be excluded.

In order to explain experimental data with synergistic model it should be assumed that larger amounts of IFN-α and smaller amounts of IFN-γ (because total activity of al-IFN-α was not affected by anti-IFN-γ

antiserum, but completely or almost completely inactivated by anti-IFN-α antibodies) led to obtain considerable increase (potentiation factor 5–10) of detectable IFN activity. However, experimental data showed that in cytophatic effect inhibition assays (used as the bioassay for determination of IFN activity in studies on al-IFN-α) the potentiation factor was in range of 2 to 6[15, 27]. The experiments presented in Table 2 failed to simulate the al-IFN-α phenomenon by mixing IFN-α and IFN-γ. The potentiation factor not exceeded 2.5. The similarity of acid and anti-IFN-γ treatments was observed when mixtures of classical IFNs were applied. In the case of AIDS sera (i. e. preparations of al-IFN-α) significant differences resulted from such treatments were found.

– Hypothesis 4: al-IFN-α is caused by a factor present in plasma during onset of autoimmune diseases or AIDS[48, 81]. YEE et al.[81] found that chromatography of al-IFN-α-containing SLE plasma led to obtaining only acid-stable IFN-α. They suggested that a factor(s) causing acid lability was removed during purification. To support the conclusion they showed that dilution of natural lymphoblastoid IFN-α in plasma of individuals with SLE resulted in acid lability of this IFN. Similar results were obtained when acid-stable rIFN-α was added to AIDS sera[48].

The nature of proposed factor has not been established. The hypothetical factor should permanently destroy IFN-α activity at low pH. Therefore, an acid-activated protease was taken into consideration[81]. The role of interferon inhibitory activity connected with the increased circulating soluble interferon α/β receptors present in AIDS and SLE sera was also discussed[6].

Acid-Labile IFN-α in AIDS

High levels of al-IFN-α, persistently found in plasma of patients with AIDS, may origin either from continuous production connected with persistent stimulation e. g. HIV-1[78], viral gp120[12, 30] and HIV-infected cells[13, 15] were able to induce IFNs. On the other hand, down-regulation of IFN-receptors was observed during the progression of AIDS resulting in accumulation of IFNs[49].

In HIV infection, presence of al-IFN-α have been

Table 2. Effect of neutralizing antibodies and acid treatment on IFN activity in sera of AIDS patients (al-IFN-α) and mixtures of IFN-α and IFN-γ

Preparation (U/ml)	IFN activity (U/ml) after treatment:				
	none	anti-HuIFN-α	anti-HuIFN-γ	dialysis at pH 2 and re-dialysis at pH 7	dialysis at pH 7
AIDS serum No. 1	16	<8	16	<6	18
AIDS serum No. 2	384	<8	192	48	192
AIDS serum No. 3	576	8	576	72	576
AIDS serum No. 4	36	<12	36	6	48
AIDS serum No. 5	144	<12	144	48	144
Experiment 1					
nHuIFN-α (72)	72	<12	72	60	60
rHuIFN-γ (4)	<6	<12	<12	<6	<6
nHuIFN-α (72) + rHuIFN-γ (4)	192	<12	72	72	144
Experiment 2					
nHuIFN-α (384)	384	<12	384	384	384
rHuIFN-γ (4)	<6	<12	<12	<6	<6
nHuIFN-α (384) + rHuIFN-γ (4)	768	<12	384	384	768
Experiment 3					
nHuIFN-α (384)	384	<12	384	288	288
rHuIFN-γ (24)	24	24	<12	<6	18
nHuIFN-α (384) + rHuIFN-γ (24)	768	36	288	384	384

Results of measurements of IFN activities in AIDS sera were taken from PIASECKI et al.[60]

nHuIFN-α – natural leukocyte interferon. Human peripheral blood leukocytes (whole blood from HIV-negative individuals) were stimulated with Newcastle disease virus. The culture supernatants were dialyzed against pH 2 and checked with neutralizing antibodies. The final preparation was characterized as acid-stable IFN-α. The presence of small amounts of IFN-ω or IFN-β could not be excluded.

rHuIFN-γ – recombinant protein (Genentech Inc., USA).

nHuIFN-α and rHuIFN-γ were diluted in calf serum to the final concentration as stated in the table. After appropriate treatment IFN activity was determined.

IFN activity was determined by cytopathic effect inhibition antiviral assay on A549 cells with the use of EMC virus. Detailed description of the methods was published elsewhere[60, 61].

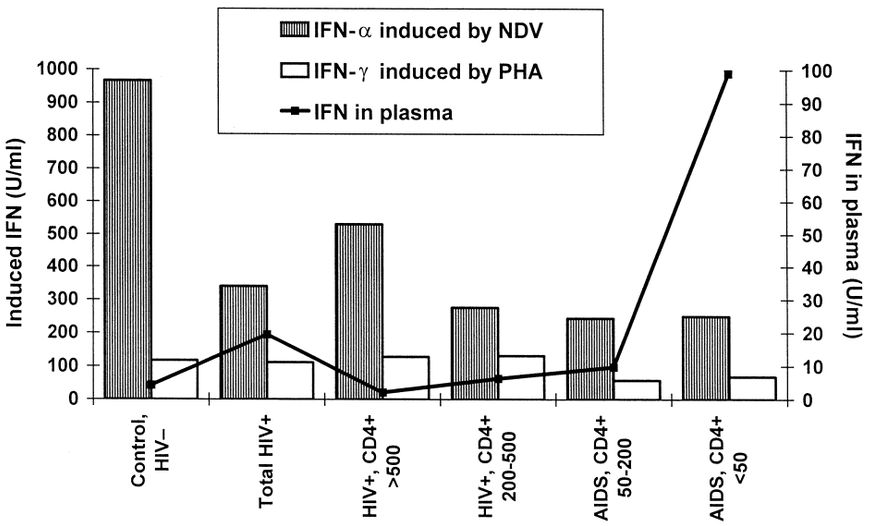

Fig. 1. Effect of HIV infection on IFN responses (according to PIASECKI et al.[62]). Mean IFNs levels in HIV^- and HIV^+ patients are shown. HIV^+ group was divided into subgroups depending on $CD4^+$ lymphocytes count to show changes in IFN responses during progression of HIV infection. IFN levels in plasma (line, right scale), and IFN-α and IFN-γ production by whole blood leukocytes induced *ex vivo* with Newcastle disease virus (NDV) or phytohemagglutinin (PHA), respectively (columns, left scale), were measured

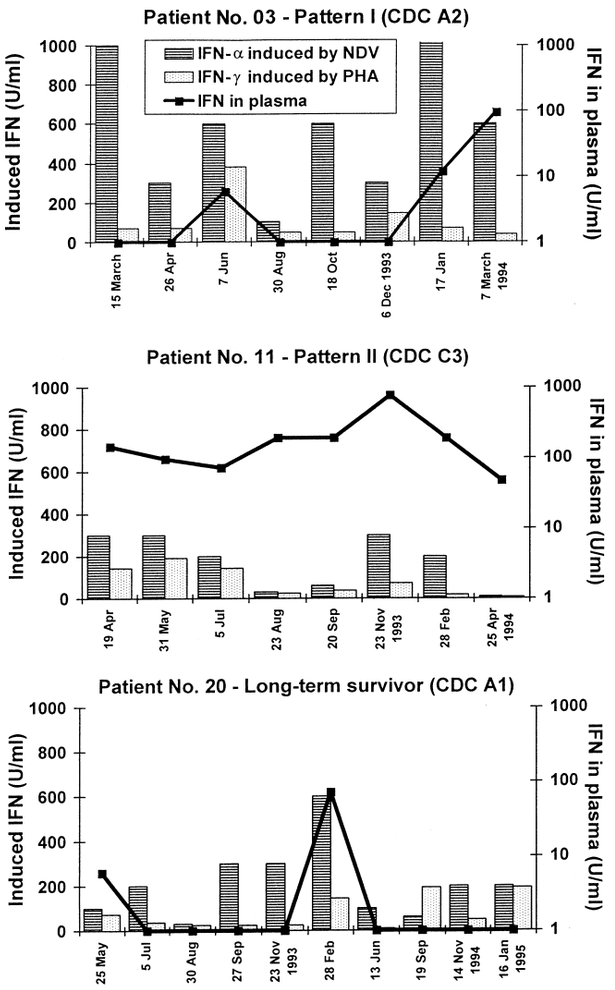

Fig. 2. Patterns of interferon responses in HIV^+ patients. The examples are taken from PIASECKI et al.[61]. Pattern I – characteristic for patients in good clinical condition, pattern II – found in patients with AIDS, long-term survivor – long-surviving and asymptomatic. IFN levels in plasma (line, right scale), and IFN-α and IFN-γ production by whole blood leukocytes induced *ex vivo* with Newcastle disease virus (NDV) or phytohemagglutinin (PHA), respectively (columns, left scale), were measured

associated with progression to AIDS and it was an unfavorable prognostic factor[35, 61, 62]. Blood leukocytes of HIV^+ patients produced significantly less IFN-α after stimulation with Newcastle disease virus than HIV^- individuals. On the other hand, IFN-γ production in response to phytohemagglutinin was impaired only in AIDS patients with $CD4^+$ cell count below 200/μl (Fig. 1)[62].

Long-term investigations of HIV^+ patients with at least 4 successively taken blood samples for IFN determinations showed two different patterns of IFN responses. In pattern I, characteristic for patients in good clinical condition, low levels of IFN in plasma and hig levels of induced IFN-α and IFN-γ were observed. On the contrary, high levels of al-IFN-α in plasma and low levels of induced IFNs were found in pattern II characteristic for AIDS patients. A variation of pattern I was found in the case of the patient defined as long-term survivor having relatively low levels of all IFN tested (Fig. 2)[61].

The findings show the usefulness of the IFN levels determinations, which may become a useful marker for monitoring the progression of HIV infection and results of therapy. The improvement of the clinical status of the patients with AIDS, as a result of applied combined antiretroviral therapy (2–3 reverse transcriptase inhibi-

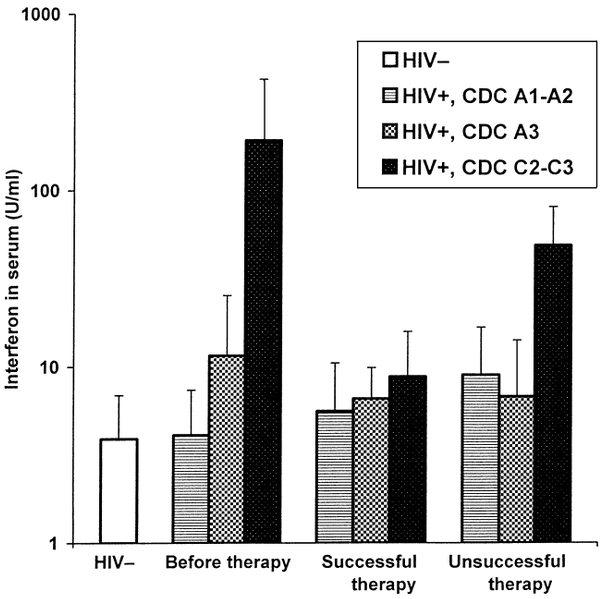

Fig. 3. Effects of the combined antiretroviral therapy on serum IFN level in HIV^+ patients (according to PIASECKI et al.[60]). Mean IFNs levels and standard deviations are shown. The patients were divided into groups depending on their clinical status (from A1 – asymptomatic with high $CD4^+$ count, to C3 – AIDS with low $CD4^+$ count). The therapy was considered to be successful when the clinical improvement was observed. In the other cases unsuccessful effect was stated

tors plus 1–2 viral protease inhibitors), was found to be associated with the decrease of al-IFN-α levels in sera (Fig. 3)[60].

On the other hand, increase of al-IFN-α levels was a significant factor responsible for disease progression[72, 76]. Therefore, attempts to deplete IFN-α from plasma of HIV-infected subjects by using anti-IFN-α antibodies[26, 33] and apheresis technique with immunoaffinity column containing polyclonal antibodies against IFN-α[76] have been applied. However, the therapy was not successful because IFN-α levels were rapidly reconstituted[76]. This suggests that the presence of al-IFN-α may be a consequence but not the cause of the disease progression.

Acid-Labile IFN-α in Autoimmune Diseases

The origin and persistence of al-IFN-α in AIDS and in the autoimmune diseases may be analogous. The pathogenic relationship of HIV infection and SLE have been emphasized[71]. In the case of HIV infection, the virus may trigger off the autoimmune reactions[72], including high levels of unusual al-IFN-α which correlated with severity of the diseases. IFN was found to be elevated in about 50% of all SLE patients and was more prevalent in patients with active SLE[63].

In conclusion, the measurements of al-IFN-α level in plasma or sera may be useful for monitoring the progression and therapy of various infectious and non-infectious diseases. However, none of the discussed hypotheses is able to explain the nature of the phenomenon of al-IFN-α. A part of acid-labile effect is probably due to presence of IFN-γ acting synergistically with IFN-α. However, unusual properties of acid-labile IFN activity detectable in plasma or sera of AIDS and SLE patients cannot be explained by synergistic effect only. Since IFN levels are correlated with progression of the diseases, it is likely that during development of pathological changes a factor(s) interacting with IFN-α is produced. It would be also important to find whether this hypothetical factor play role in persistence of high IFN levels in plasma.

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