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Correlation between miR-146a and miR-155 levels and concentration of cytokines in patients with allergopathy in chronic persistence of Epstein-Barr virus infection

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Abstract

Analysis of correlation between miR-146a and miR-155 levels and concentration of antiviral cytokines in patients with allergopathy in active and latent phases of chronic persistence of Epstein-Barr virus infection (EBV) has been conducted. Thus, 38 patients with allergopathy and chronic persistence of EBV of different genders, age 32.7±3.2 years have been examined, who were divided into groups depending on the phases of virus persistence. Control group included 20 healthy individuals. Reliable changes in IL12, IL33, IL1ß and IFN-γ were revealed in patients of both groups. The results: reliably higher levels of miR-146a expression, by 2.9 times (p=8.0E-04) and by 2.25 times (p=0.011), respectively, compared with control group; reliable difference in miR-155 levels in patients with EBV-infection in active and latent forms of virus persistence (p=1.0E-07) and significant decrease in the indicated miRNA (p=1.0E-07) by 55.8 times in patients with latent course of EBV-infection compared with control. A reliable reverse correlation of various intensities was detected between IL12, IL1ß, IFN-γ and miR-146a; absence of correlation between TNF-α, IL33 and miR-146a was observed. A direct correlation was revealed between all investigated cytokines IL12, TNF-α, IL33, IL1ß, IFN-γ and miR-155. the results of investigation showed that elevation of miR-146a can prognostically indicate inhibition

of pro-inflammatory activity of cytokines and anti-inflammatory protection with the formation of pathological disorders, including allergopathy. Meanwhile, the presence of chronic persistence of EBV demonstrates an opposite direction of correlations between miR-155 and cytokines with pro-inflammatory properties, which confirms the ability of opportunistic infections to modulate immune response toward allergopathy.

Key words: **cytokines; miR-146a; miR-155; chronic Epstein-Barr virus infection; allergopathy.**

ВЗАИМОСВЯЗЬ УРОВНЕЙ miR-146a И miR-155 С КОНЦЕНТРАЦИЕЙ ЦИТОКИНОВ У БОЛЬНЫХ С АЛЛЕРГОПАТОЛОГИЕЙ ПРИ ХРОНИЧЕСКОЙ ПЕРСИСТЕНЦИИ ЭПШТЕЙНА-БАРР ВИРУСНОЙ ИНФЕКЦИИ

Резюме

Проведен анализ взаимосвязи уровней miR-146a и miR-155 с концентрацией противовирусных цитокинов у больных с аллергопатологией в активной и латентной фазах хронической персистенции Эпштейна-Барр вируса (EBV). Обследовано 38 больных с аллергопатологией и хронической персистенцией EBV, разного пола в возрасте 32,7±3,2 лет, которые были разделены на группы в зависимости от фаз вирусной персистенции. Контрольную группу составили 20 здоровых лиц. Выявлены достоверные изменения IL12, IL33, IL1ß и IFN-γ у пациентов обеих групп. Показано: достоверно более высокие уровни экспрессии miR-146a, соответственно 2,9 раза (p=8,0E-04) и в 2,25 раза (p=0,011) по сравнению с контрольной группой; достоверная разница уровней miR-155 у пациентов с EBV-инфекцией в активной и латентной фазах персистенции вируса (p=1,0E-07) и значительное снижение в 55,8 раз указанной miRNA (p=1,0E-07) у пациентов при латентном течении EBV-инфекции по сравнению с контролем. Определена достоверная обратная корреляционная связь различной силы между IL12, IL1ß, IFN-γ и miR-146a; отсутствие корреляционных связей между TNF-α, IL33 и miR-146a. Обнаружена прямая корреляционноя связь между всеми исследованными цитокинами IL12, TNF-α, IL33, IL1ß, IFN-γ и miR-155. Результаты исследования показали, что повышение miR-146a может прогностически указывать на подавление провоспалительной активности цитокинов, ингибирование противоинфекционной защиты с формированием патологических

нарушений, в т.ч. аллергопатологии. Наличие же хронической персистенции EBV демонстрирует кардинально противоположное направление корреляционных взаимосвязей miR-155 и цитокинов с провоспалительными свойствами, подтверждает свойство оппортунистических инфекций модулировать иммунный ответ в направлении аллергопатологии.

Ключевые слова: цитокины, miR-146a, miR-155, хроническая Эпштейна-Барр вирусная инфекция, аллергопатология.

Introduction. MiR-146a and miR-155 have a lot in common in a large spectrum of their biological activity in normal and pathological conditions; they are expressed and function in various immunocompetent cells and control specificity of immune response. At present, the role of microRNA data in pathogenesis of many infectious, autoimmune, oncological and other diseases has been confirmed [3, 10, 18]. However, there are little data about association of miR-146a and miR-155 with allergopathy, and the results of some of them are controversial.

One of the potential causes of impairment of the body's immunological tolerance is the presence of chronic infectious process, caused, primarily, by intracellular agents, among which Epstein-Barr virus (EBV) is common. EBV is characterized by lifelong persistence in the human body, direct infecting of immunocompetent cells and multiorgan tropism [8]. Persistence of viruses in the body promotes mobilization of cell-mediated and humoral factors of antiviral protection in obligatory involvement of cytokines [16, 20]. According to literature data, the level of miR-146a and miR-155 expression influences the production of cytokines with anti- and pro-inflammatory properties [11]. Thus, imbalance of cytokines with various functional properties is observed in different allergic diseases, especially due to persistence of immunotropic virus.

Aim of the research: to investigate correlation of miR-146a and miR-155 levels with concentration of antiviral cytokines in patients with allergopathy in active and latent phases of chronic persistence of Epstein-Barr virus.

Materials and methods of investigation.

The research was conducted according to the 7th amendment to the principles of Declaration of Helsinki involving human rights (2013) and corresponding laws of Ukraine. Clinical diagnosis of allergic rhinitis (AR) and/or bronchial asthma (BA) was determined by criteria Allergic Rhinitis and its Impact on Asthma (ARIA, 2016), Global initiative for asthma

(GINA, 2016-2017), atopic dermatitis (AD) – by criteria of unified clinical protocol "Atopic dermatitis" (2006).

Determination of total IgE and specific sIgE to allergens, specific IgG to antigens of EBV (EBNA-IgG, VCA-IgG) was performed by ELISA method using test systems "Euroimmun" (Germany) according of manufacturer's instructions. Detection of DNA EBV in the blood, saliva and mucosa of the posterior pharyngeal wall was conducted by polymerase chain reaction (PCR) method on diagnostic preparations "AmpliSens" (RF) using "Rotor-Gene 6000" (Corbett Research, Australia). Active phase of chronic EBV-infection was determined by the presence of DNA EBV (simultaneously or separately) – in the blood, saliva and mucosa of the posterior pharyngeal wall (amount of DNA EBV copies – 10^3-10^7/ml) and increased titres of specific antibodies – EBV-VCA-IgG and EBNA-IgG by 5-10 times. Latent phase of chronic EBV-infection was determined by the absence of DNA virus combined with elevated titres of specific EBNA-IgG and EBV-VCA-IgG. Chosen groups included patients only with mono-EBV infection.

Based on obtained data, patients were divided into two groups: 1st group – 20 individuals with allergic diseases and chronic persistence of EBV in active phase (EBV "+"); 2nd group – 18 individuals with allergic diseases and chronic persistence of EBV in latent phase (EBV "-").

Skin prick-tests were performed with extracts of respiratory allergens (Inmunotek, Spain), the process and assessment of results was conducted according to European requirements [5].

Determination of miR-146a and miR-155 expression in samples of blood serum was conducted by reverse transcription and real time PCR from total RNA, isolated using mirVana™PARIS™ (Ambion, USA). Reverse transcription was performed using High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, USA), specific primers for each miRNAs and 10 ng of total RNA. Quantitative real time PCR was performed using TaqMan MicroRNA Assays (Applied Biosystems, USA): U6 snRNA (as endogenous control). Amplification was performed on 7500 Fast Real_time PCR (Applied Biosystems, USA). The obtained data were analyzed with database 7500 Fast Real_time PCR and presented in a chart (Fig.1).

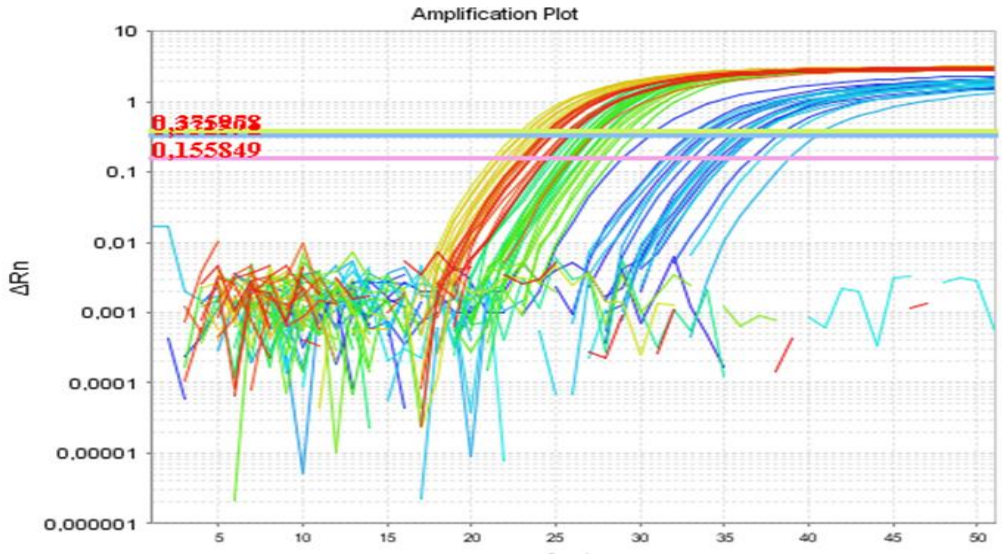

Fig.1. A chart of intensification of fluorescence in real time PCR

Determination of cytokines IL1b, IFN-γ, IL12 (p70), TNF-α, IL33 was conducted in two samples of blood serum by PCR method using magnetic microspheres, conjugated with monoclonal antibodies, using platform BioPlex 200 with HRF (Bio-Rad, USA), which included Luminex xMAP®. Standard curves were drawn using logistic regression 4- or 5-PL, the obtained results were analyzed by means of the program BioPlex Manager 6.0 (Bio-Rad, USA).

The results of investigations were analyzed with statistical set IBM SPSS Statistics v.21. For primary analysis and drawing of charts, Microsoft Excel was used. Reliability of difference between samplings was assessed by Student's t-criterion, differences were considered reliable at $p<0.05$. All quantitative indices are presented as x±SD, where x – is mean arithmetic, SD – standard deviation. Correlation analysis was performed by means of Pearson's coefficient of correlation.

Results of investigation

Based on conducted investigations, the following diagnoses were established: 1) persistent (year-round) or intermittent (seasonal) AR – in 26 (68.4%) patients; persistent, of mild degree, controlled BA – in 3 (7.9%); atopic dermatitis of adult type, localized erythematous squamous form of mild degree (SCORAD from 10.0% to 18.0%) – in 8 individuals (21.1%). Mild degree eosinophilia was detected in the blood – in 5 (13.2%) patients; in nasal cytogram – in 10 (26.31%), increased level of total serum IgE – in 22 (57.9%) individuals. Sensitization to

various groups of respiratory allergens was revealed in all patients by the results of skin prick tests. Polysensitization was detected in 26 (68.4%) patients.

Conducted anamnestic, clinical and laboratory analysis of these data showed that the symptoms of atopic dermatitis, pollinosis with polysensitization, high level of total IgE were more frequently observed in a group of patients with active form of chronic EBV persistence. However, in patients with latent form of chronic EBV persistence, bronchial obstructive syndrome and eosinophilia in the blood and nasal cytogram were more common.

Comparative analysis of cytokine profile was performed in investigated groups and control group (table 1).

Table 1

Comparative analysis of cytokine profile in patients with allergic diseases and chronic EBV-infection in different phases of persistence (M±sD)

Cytokines (pg/ml)	**1st group** (EBV+) (n=20)	**2nd group** (EBV-) (n=18)	**3rd group** control (n=20)	**P(1-3)**	**P(2-3)**	**P(1-2)**
	1	**2**	**3**			
IL1ß	3.48±1.03	2.55±0.30	2.76±0.45	0.093	**0.007**	**0.0001**
IFN-γ	0.98±0.42	0.84±0.23	1.11±0.29	0.095	**0.012**	0.334
TNF-α	5.76±1.67	5.98±2.74	6.02±2.75	0.111	0.190	0.762
IL 12	2.88±0.42	3.89±1.74	3.65±1.26	**0.013**	0.618	**0.016**
IL33	2.87±1.79	5.55±1.79	4.69±3.10	0.120	0.127	0.647

Analysis of results showed that various changes in cytokine profile were detected in patients with allergic diseases and chronic EBV persistence in different forms compared with control. In patients with active form of chronic EBV persistence, a reliable decrease or tendency to reduction of IL12, IL33 was verified with simultaneous increase in IL1ß level and normal concentration of IFN-γ, TNF-α. In patients with latent form of chronic EBV persistence, a reliable decrease in IL1ß and IFN-γ concentration and increase in IL12 and IL33 was established. The level of pro-inflammatory cytokine TNF-α in both investigated groups did not change considerably.

A comparative analysis of miR-146a and miR-155 expression in patients of investigated groups and individuals of control group was performed (table 2).

Table 2

Levels of miR-146a and miR-155 expression in patients of investigated groups

microRNA (ng)	**1st group** (EBV+) (n=20)	**2nd group** (EBV-) (n=18)	**3rd group** control (n=20)	**P (1-2)**	**P (1-3)**	**P (2-3)**
miR-146a	0.19±0.29	0.15±0.26	0.07±0.10	0.91	**8.0E-04**	**0.011**
miR-155	6.6E-04 ± 1.9E-03	8.0E-06± 8.0E-07	4.3E-04 ± 8.0E-04	**1.0E-07**	**2.5E-03**	**1.0E-07**

As it is seen in table 2, in patients of both groups with allergopathy and chronic EBV infection in active and latent forms, reliably higher levels of anti-inflammatory miR-146a expression were observed, by 2.9 times (p=8.0E-04) and 2.25 times (p=0.011), respectively, compared with control group. Though the level of miR-146a in patients of the 1st group was by 1.3 times higher than in the 2nd group of patients, reliable difference was not observed (p>0.91) (fig. 2).

Concerning the level of miR-155 expression, in patients with allergopathy and active phase of EBV infection, expression of this miRNA was reliably higher by 1.5 times compared with control group (p=2.5E-03). It should be emphasized that a considerable decrease in this miRNA by 55.8 times (p=1.0E-07) was noticed in patients of the second group in latent course of EBV infection compared with control group (fig. 3).

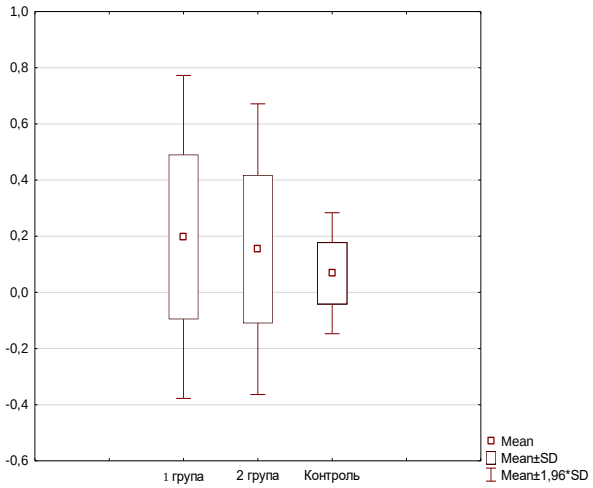

Fig.2. Levels of miR-146a expression in investigated groups

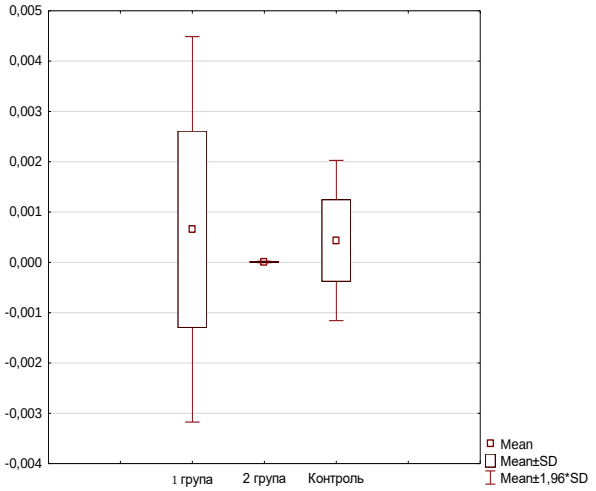

Fig.3. Levels of miR-155 expression in investigated groups

According to the obtained results, a reliable difference of miR-155 level was established in patients with EBV infection in active and latent forms of virus persistence (p=1.0E-07).

Thus, in patients with allergopathy in active phase of chronic EBV persistence, a reliable activation of miR-146a and miR-155 expression was revealed compared with control. However, in latent form of EBV infection, a reliably high level of expression of anti-inflammatory miR-146 and a significant inhibition of pro-inflammatory miR-155 was detected. In particular, the degree of miR-155 expression in latent phase was by 81.3 times lower than in active form of chronic persistence of EBV infection.

Correlation analysis of interaction of miR-146a and miR-155 levels with the concentration of antiviral cytokines in patients with allergopathy in chronic persistence of EBV demonstrated a reliable reverse correlation of various intensities between TNF-α, IL33 and miR-146a (fig. 5a, 6a). Besides, a direct correlation was revealed between all investigated cytokines IL12, TNF-α, IL33, IL1ß, IFN-γ and miR-155 (fig. 4b, 5b, 6b, 7b, 8b).

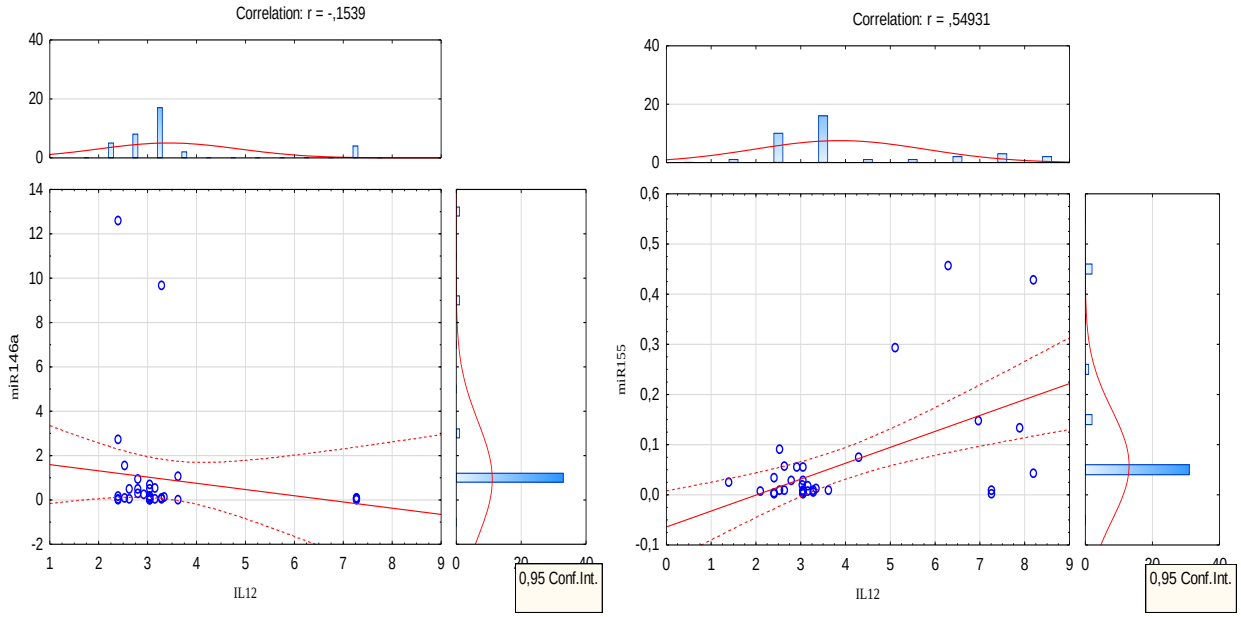

Fig. 4 a, b. Investigation of correlation between IL12, miR-146a and miR-155

Discussion of the research results

In infected patients, EBV induces expression of miR-155 and miR-146a on different immunocompetent cells (monocytes, macrophages, dendrites, natural killer cells (NK), T- and B-

lymphocytes etc.), defining a type of control of immune mechanisms. Usually, these two miRNAs demonstrate antagonistic direction of action [2, 11]. MiR-155 and miR-146a are especially sensitive to many inflammatory stimuli, particularly cytokines (TNF-α, IFN types I and II), Toll-like receptors etc. [13, 19].

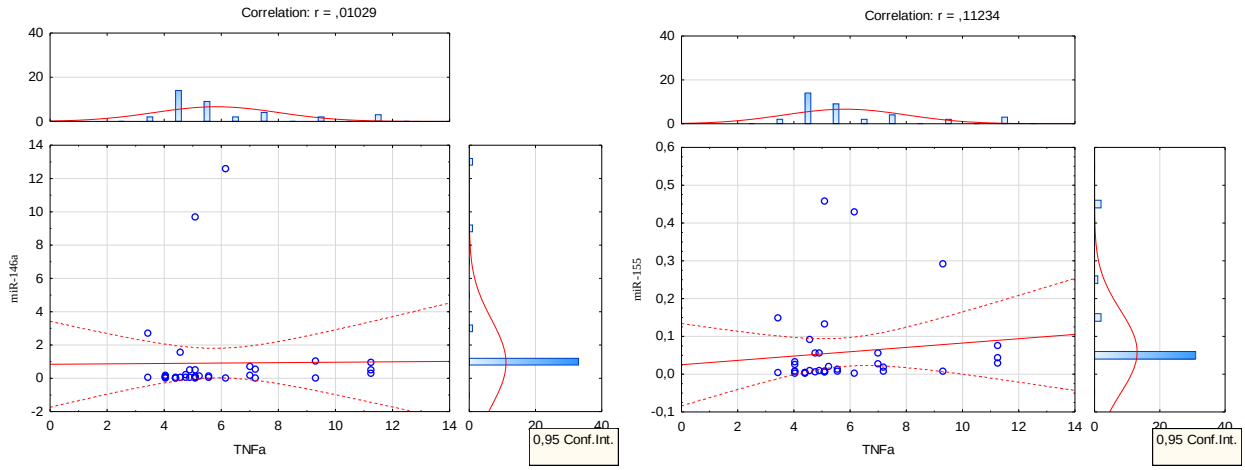

Fig. 5 a, b. Investigation of correlation between TNFα, miR-146a and miR-155

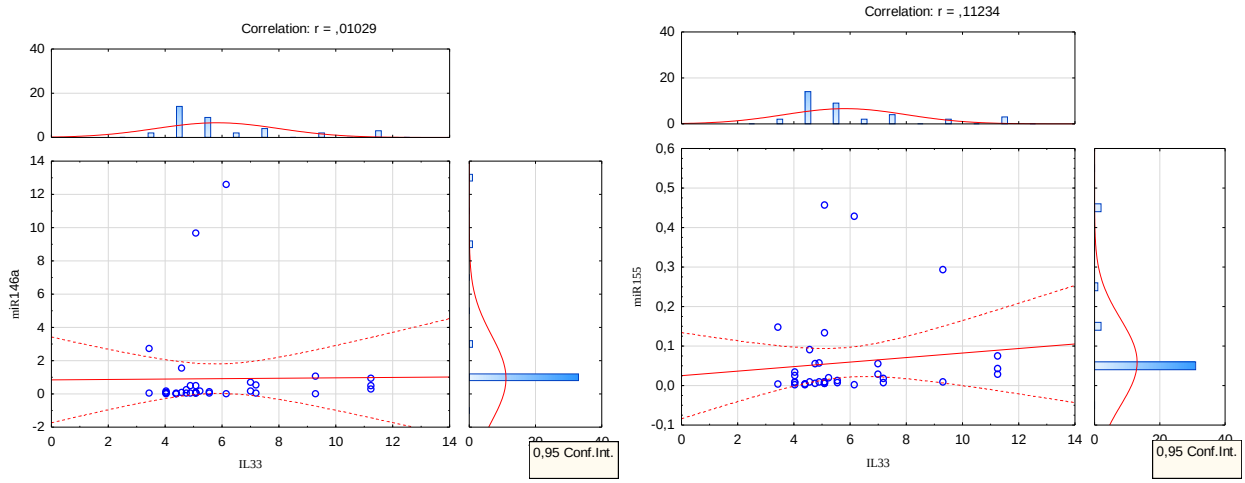

Fig. 6 a, b. Investigation of correlation between IL33, miR-146a and miR-155

The majority of EBV-infected cells in latent condition express six nuclear antigens (EBNA 1-6), three membrane proteins (LMP1, LMP2A, LMP2B) and non-coding antigens (EBER-1, EBER-2 RNA) [4, 17].

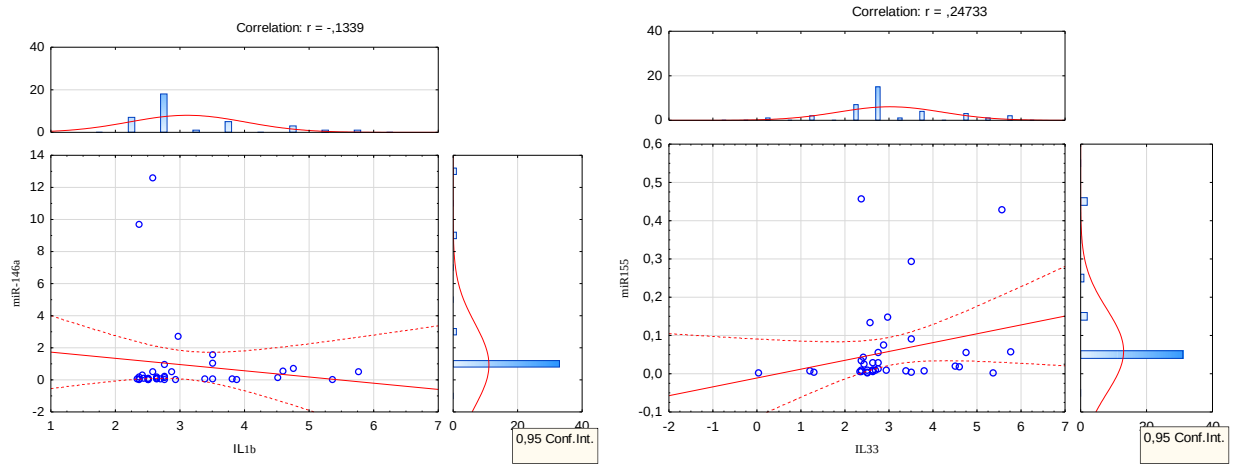

Fig. 7 a, b. Investigation of correlation between IL1ß, miR-146a and miR-155

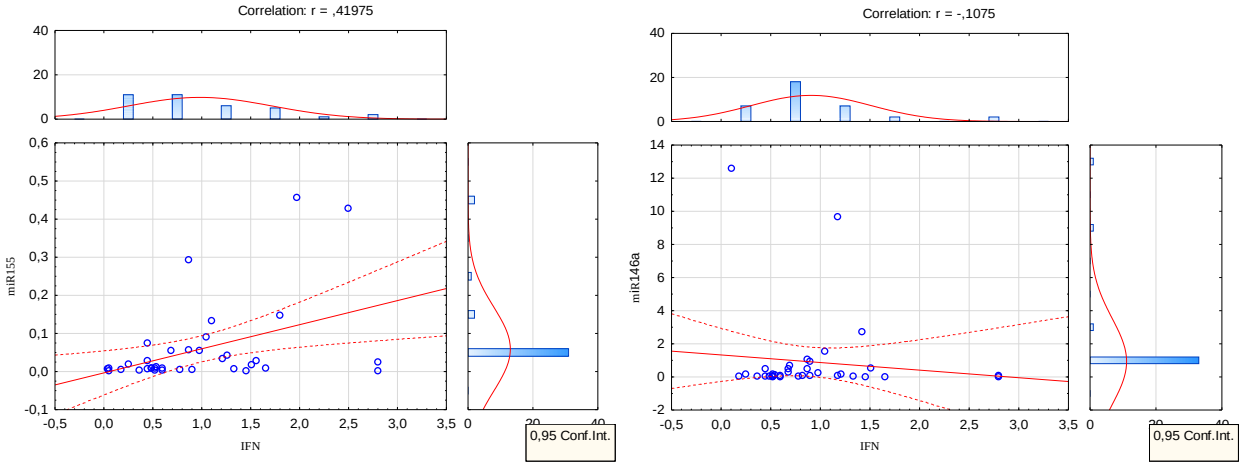

Fig. 8 a, b. Investigation of correlation between IFN-γ, miR-146a and miR-155

Natalie Motcsh and co-authors proved that LMP1 stimulates expression of miR-146a via NF-kB-dependent way. LMP1 is known to launch a signal cascade, which activates cell factors of transcription (NF-kB and AP-1), promoting survival and proliferation of EBV-infected cells; maintenance of chronic EBV persistence in the human body by modulation of congenital immune

factors on virus-infected host's cells. In this work, it is shown that stimulation of miR-155 expression in EBV-infection, except for LMP1, can occur under the influence of other viral gene products [5, 13]. The obtained data coincide with the results of our investigations. The degree of miR-146a expression, compared with control group, was higher in patients with allergopathy and chronic EBV persistence, especially in active form of infection.

STAT1 (member of the family of transcription factors) participates in a positive regulation of genes by the signal of I-III type interferons and is an important target of miR-146a on $CD8^+$-cells, which produce antiviral cytokines, including TNF-α and IFN-γ. Blockage in vitro of miR-146a in $CD8^+$-cells significantly increased their virus-specificity [18]. Overexpression of miR-155 intensified antiviral $CD8^+$-T-cell mechanisms in vivo [3, 9]. As the results of our investigations showed – increased level of miR-146a in patients of the 1st group correlated with normal level of TNF-α and IFN-γ, which resulted in reduction of intensity of antiviral protection and promoted replication of the virus and was confirmed by PCR method. Thus, under conditions of active EBV replication, functional ability of miR-146a towards inhibition of antiviral factors dominated over the ability of miR-155 to their stimulation. In patients with latent phase of chronic persistence of EBV, elevated miR-146a and decreased level of miR-155 logically promoted a reliable decrease in IFN-γ concentration, and, as a result, promoted virus persistence [14]. Instead, in patients of the 1st group a reliably increased expression of miR-146a correlated with such level of TNF-α, IFN-γ and IL-1β, that reliably did not differ from the indices of individuals in control group. A reliably high anti-inflammatory influence of miR-146a was verified in patients with latent form of chronic persistence of EBV, where concentration of IL-1β and IFN-γ was reliably lower than in healthy individuals. The content of TNF-α in the blood of this group of patients reliably did not differ from individuals of the control group. These data show that modulation of miR-146a demonstrates anti-inflammatory action. In opposite, insufficiently effective influence of TNF-α and IFN-γ on cell-mediated and humoral antiviral mechanisms in these patients could be the cause of long-lasting virus circulation with its significant replication in individuals with active form of infection. Since IFN-γ belongs to important mediators, which influence IgE synthesis, decrease in the level of the cytokine in patients of both groups promoted the formation of IgE-dependent allergic processes. According to literature data, investigation of knockout of miR-146a gene showed that deficiency of this miRNA leads to excessive production of IL-6 and TNF-α, loss of suppressive effects of T-regular

cells (T-reg), reduction of IFN-γ secretion [10, 15]. Conclusions of these investigations are confirmed by the results of our analysis, particularly: high expression of miR-146a did not influence TNF-α and IFN-γ concentrations in patients with active form and promoted reduction (primarily of IFN-γ level) in patients with latent form of chronic persistence of EBV.

In opposite, miR-155 is regarded as a positive modulator of immune response due to production of pro-inflammatory cytokines [10]. It has been proved that the role of miR-155 implies programming of macrophages as to their conversion into pro-inflammatory macrophages [7]. Since IL-1β and TNF-α are predominantly synthesized by antigen-presenting cells (APC), in our case, the presence of a direct correlation between low expression of miR-155 and reduction of IL-1β and TNF-α levels could be expected. However, by obtained results, concentration of IL-1β and TNF-α did not reliably differ from the norm in patients with active phase of chronic persistence of EBV and a reliably high expression of miR-155. In patients with latent form and a reliably low level of miR-155 – the level of IL-1β proved reliably reduced, and TNF-α did not differ from the indices of healthy individuals. It can be assumed that it is also associated with a low level of IFN-γ, which is able to induce miR-155 expression.

Thus, oversuppression of miR-155 level in patients with latent form of chronic EBV persistence promoted a reliable decrease in concentration of pro-inflammatory cytokines IL-1β i IFN-γ, however, did not influence TNF-α level, the value of which did not reliably differ from control indices. Impairment of these mechanisms can promote intensification of a negative influence of EBV on a patient's body, which is confirmed by the results of our investigations.

It is known that IL-33 belongs to the family IL-1 with pro-inflammatory properties, it is able to mobilize APC, NK and T-lymphocytes, and in the process of immunological inflammation – eosinophils, labrocytes, IgE production [1]. Concerning IL-12, it is synthesized by APC and induces production of IFN-γ, IL-2 and TNF-α, acts as a growth factor for NK and T-cells, intensifies their cytotoxicity [6]. In patients with active form of chronic EBV persistence, level of IL-33 and IL-12 proved to be decreased with simultaneous increase in miR-146a and miR-155 expression. In patients with latent form, concentration of these interleukines was within normal ranges with simultaneous increase in miR-146a expression and significantly decreased miR-155.

It has been established that expression of miR-146a and miR-155 does not influence maturation of APC (primarily of dendrites), but modulates the production of pro-inflammatory

cytokines [11, 19]. High expression of miR-146a is likely associated with low migration ability of dendrites originating from monocytes [18], which can become the cause of non-effective formation of antiviral immunity with further activation of EBV. This assumption is confirmed by the obtained results, which show more manifested expression of miR-146a in patients with active phase of infection. Experiments on neutralization of miR-155 expression in monocytes, which mature to dendrite cells showed that miR-155 is not involved in the processes of differentiation of dendrites, however, it participates in IL-12 expression [3, 10]. Besides, absence of miR-155 expression on dendrites impair the ability of the cells to influence immune tolerance, increasing the risk of development of autiummune and allergic reactions [11]. The results of our investigations demonstrated that different association interrelations of miR-146a, miR-155 expression and content of IL-12 in patients in both phases of chronic EBV persistence resulted in reduction of activity of pro-inflammatory cytokines, impairment of APC function, including their ability to form tolerance, which promoted inhibition of antiviral protection and intensified replication of EBV, the risk of development of immunopathologic diseases, including allergopathy.

Perspectives of further investigations. Revealed interrelations of miR-146a i miR-155 levels with concentration of antiviral cytokines in patients with allergopathy indicated various roles of these miRNAs in immunopathogenesis of allergic diseases in the presence of chronic persistence of EBV in active and latent phases of infection, which in the future can be investigated in the context of targeted personified therapy of patients.

Conclusions. Thus, elevation of miR-146a can prognostically indicate inhibition of pro-inflammatory activity of cytokines, inhibition of anti-infectious protection with the formation of pathological disorders, including allergopathy. At the same time, the presence of chronic EBV persistence demonstrates a completely opposite direction of correlations between miR-155 and cytokines with pro-inflammatory properties, which confirms the property of opportunistic infections to modulate immune response towards allergopathy.

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