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S.O. Zubchenko, V.V. Chopyak, A.M. Havrylyuk, G.O. Potemkina, M.P. Lomikovska
Danylo Halytsky Lviv National Medical University, Lviv

INVESTIGATION OF MIR-BART 13 AND 15 IN PATIENTS WITH ALLERGOPATHY IN COMBINATION WITH CHRONIC EPSTEIN-BARR VIRAL INFECTION

e-mail: svitlana_zu@meta.ua

Epstein-Barr (EBV) virus initiates a wide spectrum of immunomodulating effects in the human body. EBV is one of the first viruses, in which expression of miRNAs has been revealed, that are used as targets for detection of the virus in clinical investigations. To investigate association relationships of miR-BART 13 and 15 in patients with allergopathy and chronic EBV-infection in active and latent phases. In general, 46 patients with chronic EBV-infection in active/latent phases have been examined, age 18-59 years, 65% of females, 37% of males. Clinical, general laboratory, instrumental, specific allergological, molecular genetic, and cytological investigations were performed. High levels of miR-BART 13 expression were detected in patients with allergopathy in combination with chronic EBV-infection in active ($p<0.01$) and latent ($p<0.05$) phases compared to healthy individuals. The difference in miRNAs 13, 15 expression levels depending on the medium of virus replication was not found. Investigation of miRNAs 13, 15 in the groups, formed according to verified allergic diseases, showed that higher levels of miRNAs 13 were observed in the group of patients with bronchial asthma (BA) in combination with an active phase of EBV-infection ($p<0.01$). Reverse correlation between miR-BART-13 and FEV1 and direct correlation with levels of total IgE were also detected in this group of patients. Higher indices of miR-BART 15 were recorded in patients with BA and active EBV-infection compared to control group ($p<0.05$). In patients with BA and active phase of chronic EBV-infection, elevation of the levels of miR-BART-13 expression can be a biomarker of the severity of allergic inflammatory process due to amplification of bronchial obstruction level and formation of hyper-IgE syndrome.

Key words. Chronic Epstein-Barr viral infection, allergic diseases, miR-BART 13, miR-BART 15.

The study is a fragment of the research project "Forecasting the development of virus-induced phenotypes of allergic diseases with personification of their diagnosis and treatment", state registration No. 0118U000110.

One of the urgent problems in modern medicine is high infection level with Epstein-Barr virus (EBV) in the population, which constitutes over 98% in adults [15]. EBV has a wide spectrum of immunomodulating effects – thus, there are numerous data about a significant role of the virus in pathogenesis of many diseases, including allergic ones [2, 7]. It should be noted that unlike α- and β-herpes viruses, which can cause the disease in their lytic form, EBV, as well as γ-herpes virus, could be a trigger of pathologic disorders even in latent phase [12, 13]. Besides, EBV became one of the first human viruses, in which miRNAs expression was detected, that are used as targets for detection of virus in clinical investigations by means of in situ hybridization (ISH) [4].

MiRNAs are small non-coding double-stranded RNA molecules, with the length approximately 22 pairs of nucleotides. By means of consecutive and multicomponent regulation of gene expression, miRNAs provide control over many metabolic processes and modulate gene expression at post-transcription level [6]. The obtained data indicate miRNA ability with gene regulatory mechanism, similar to RNA-interference, to participate in body response to viral infection. Thus, an important function of miRNAs is the control of virus replication during cell infecting and its persistence. However, some viruses express own miRNAs. At present, 502 of them have been identified, 44 of which belong to EBV. Functions of these miRNAs are being studied.

The purpose of our research was to investigate association relationships of miR-BART 13 and 15 in patients with allergopathy, sensitized to pollen allergens in combination with chronic EBV-infection in active and latent phases.

Materials and methods. This prospective investigation was conducted at the department of clinical immunology and allergology of Danylo Halytsky Lviv national medical university and Lviv regional medical centre of clinical immunology and allergology, Ukraine. In general, 228 patients were observed, who visited doctors in 2016-2018 years and were diagnosed as having bronchial asthma (BA) and / or allergic rhinitis (AR), sensitization to pollen allergens. Among them, an investigation group included 46 patients with allergopathy and chronic EBV-infection in active/latent phases, aged 18-59 years, 63% of females (29 individuals), and 37% of males (17 individuals).

The patients were undergoing clinical, general laboratory, instrumental, specific allergological, molecular genetic, and cytological investigations of an impression smear from nasal mucosa. Skin prick tests (SPT) were performed with allergen extracts (Diater, Spain); assessment of the results was done according to European requirements. Assessment of the functional condition of lungs was performed based

on spirography (Vitalograf ALPHA № AL011734, Germany). Clinical diagnosis of AR and / or BA was made by ARIA (2016), GINA (2016-2017) criteria.

To determine general and specific IgE (sIgE) to allergens and specific antibodies to EBV (EBNA-IgG, EBV-VCA-IgG), the method of immunoenzymatic analysis was used, involving test systems "Euroimmun", Germany according to a manufacturer's instruction. Detection of EBV in blood, saliva and mucosa of the posterior pharyngeal walls was performed by the method of polymerase chain reaction on diagnostic agents "AmpliSens" (RF) using "Rotor Gene 6000" (Corbett Research, Australia).

Determination of miR-BART 13, 15 expressions in serum samples was performed as follows: total RNA was isolated using mirVana^{TM}PARIS^{TM} (Ambion, USA); miRNAs were determined by the method of reverse transcription and PCR in real time. Reverse transcription was performed using High Capacity cDNA Reverse Transcription Kit (Applied Byosystems, USA), specific primers for each miRNAs and 10 ng of total RNA. Quantitative PCR in real time was conducted using TaqMan MicroRNA Assays (Applied Biosystems, USA): U6 snRNA (as endogenous control). Temperature regime: initial denaturation 95°C - 10 minutes; 45 cycles 95°C - 15 seconds and 60°C - 60 seconds. Level of miRNA was calculated by the formula 2ΔCt*100), normalized to U6 snRNA and presented in conditional units (CU). Amplification was performed by 7500 Fast Real_time PCR (Applied Biosystems, USA). The obtained data were analyzed by means of database 7500 Fast Real_time PCR and presented in charts (fig.1). The investigation was performed at the department of general and molecular pathophysiology, Institute of physiology named after O.O. Bohomolets of the National Academy of Sciences of Ukraine.

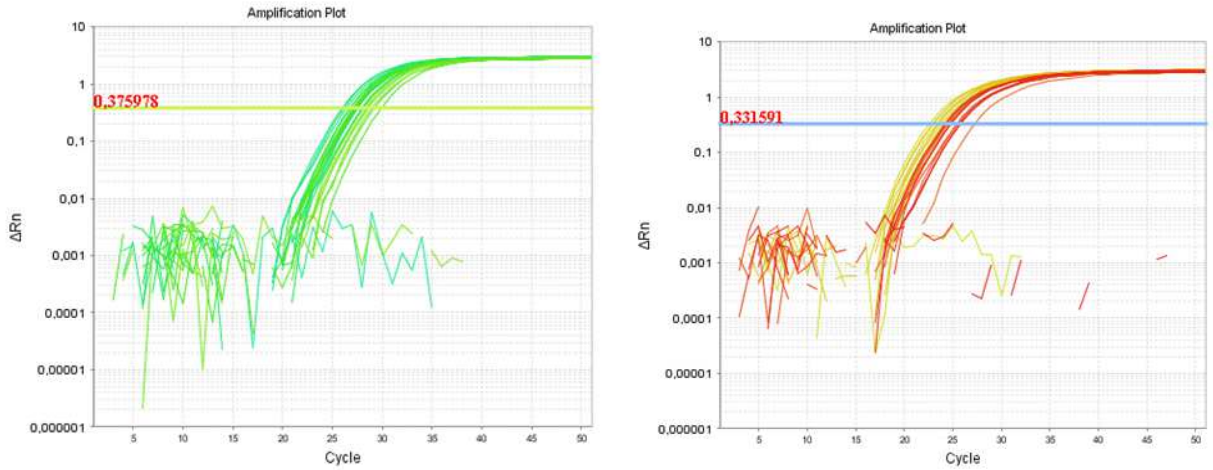

Fig.1. A chart of increase in fluorescence amplification in the process of PCR in real time

Results of investigation were analyzed using statistic set IBM SPSS Statistics v.21. A set Microsoft Excel was used for primary analysis and drawing charts. Reliability of the difference between samples was assessed by Student's t-criterion, the differences were considered reliable at $p<0.05$. All quantitative indices are presented in the form x±SD, where x – is mean arithmetic, SD – standard deviation. Correlation analysis was performed by Pearson's correlation coefficient.

The investigation was conducted according to the 7th amendments to the principles of the Declaration of Helsinki – ethical principles for medical research involving human subjects (2013), the European Convention on Human Rights and corresponding Laws of Ukraine.

A control group included 20 healthy individuals of respective age and gender.

Results of the study and their discussion. Based on conducted clinical, general laboratory, instrumental, specific allergological and molecular genetic investigations, 46 patients were selected to achieve a stated goal – 27 individuals with allergopathy in combination with an active phase of chronic EBV-infection (PCR "+" saliva and / or mucosa) and 19 individuals with allergopathy and latent form of EBV-infection, defined due to the presence of specific EBNA-IgG$^+$ and EBV-VCA-IgG$^+$ antibodies and negative PCR data.

Determination of miR-BART 13, 15 was performed for all patients. As the results of investigation showed, expression of miR-BART 13 was higher among the patients with allergopathy both in active ($p<0.01$) and latent ($p<0.05$) phases of chronic EBV-infection compared to control. Concerning expression of miR-BART 15, no differences between the results depending on EBV persistence phase were detected ($p>0.05$) (fig. 2).

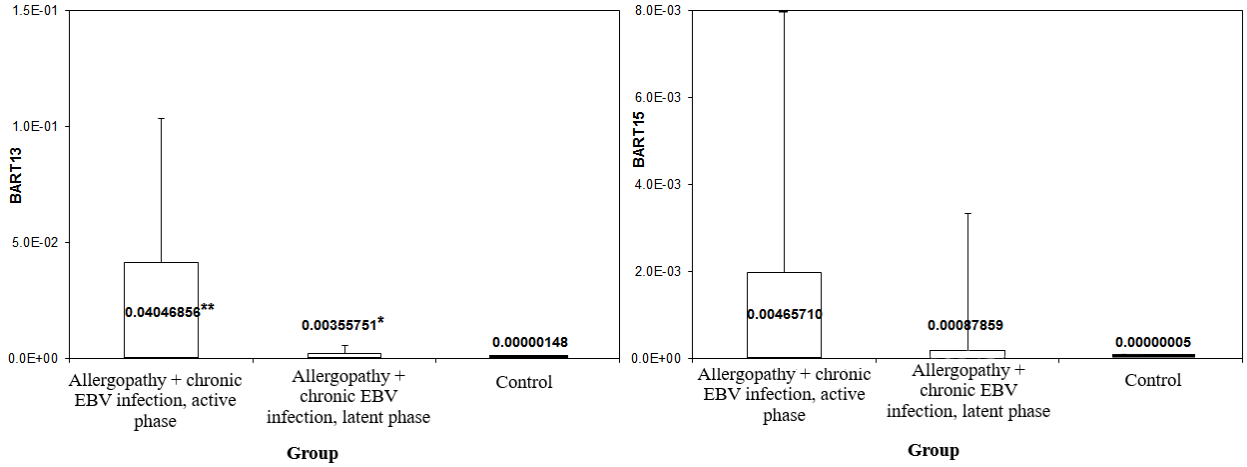

Fig 2. Comparative analysis of miR-BART 13, 15 levels in patients with allergopathy in different phases of chronic EBV-infection and control group

A comparative analysis of miR-BART 13, 15 levels was conducted in patients with allergopathy in combination with an active phase of EBV depending on the medium of virus replication. Thus, the patients with PCR EBV "+" were divided into 3 subgroups: 10 individuals – PCR EBV "+" saliva, 6 individuals – PCR EBV "+" mucosa, 11 individuals – PCR EBV "+" saliva + mucosa. It was detected that there was no reliable difference between the levels of miR-BART-13 and miR-BART-15 expressions depending on the medium of virus replication ($p>0.05$) (Fig. 3).

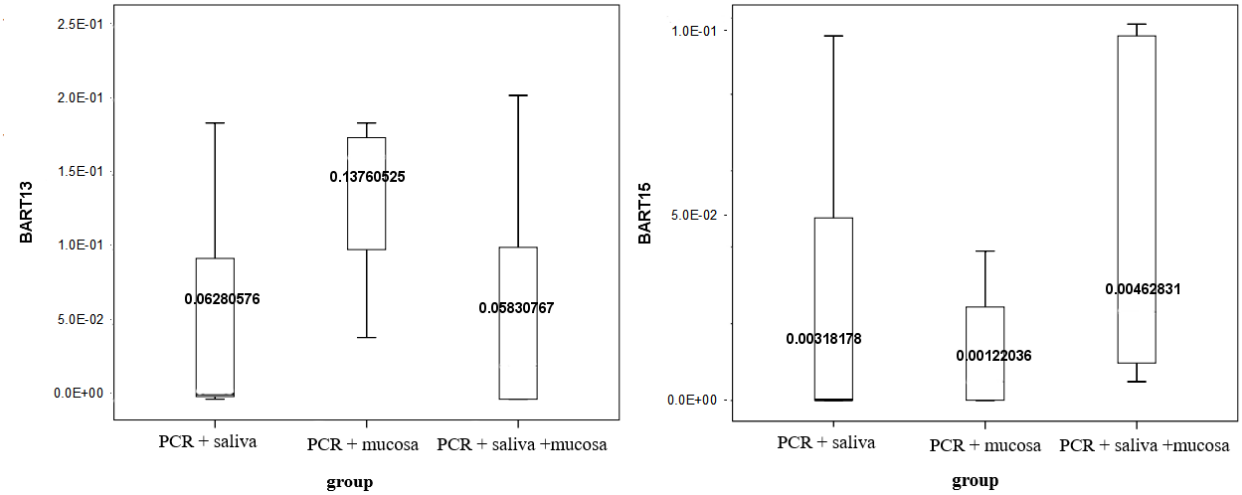

Fig3. Comparative analysis of the levels of BART-13 and 15 expressions depending on the medium of EBV replication

Since different allergic diseases were verified in these patients, we decided to divide them into the groups depending on diagnosed allergopathy and phases of EBV persistence and to investigate a possible association with miR-BART 13, 15 in these groups: 1st group (14 individuals) – patients with intermittent AR (pollinosis) and chronic EBV-infection in active phase (PCR "+" saliva and/or mucosa); 2nd group (13 individuals) – patients with intermittent or mild persistent, controlled BA and chronic EBV-infection in active phase (PCR "+" saliva and/or mucosa); 3rd group (10 individuals) – patients with intermittent AR (pollinosis) and chronic EBV-infection in latent phase (PCR "-"); 4th group (9 individuals) – patients with intermittent or mild persistent, controlled BA and chronic EBV-infection in latent phase (PCR "-"); 5th group (20 individuals) – control (PCR EBV "-").

Detailed description of the groups is given in table 1.

Table 1

Characteristics of investigated groups

Characteristics of the groups	1st group (n=14)	2nd group (n=13)	3rd group (n=9)	4th group (n=10)	4th group (n=20)
Gender, n (%) males females	 6 42.9%) 8 (57.1%)	 5 (38.5%) 8 (61.5%)	 3 (33.3%) 6 (66.7%)	 5 (50.0%) 5 (50.0%)	 7 (35.0%) 13 (65.0%)
Age (M±m), years	34.5±4.2	31.7±3.8	36.8±5.1	34.6±4.3	31.6±5.3
Clinical symptoms, n (%)* Rhinorrhea	 14 (100.0%)	 12 (92.3%)	 9 (100.0%)	 9 (90.0%)	 0

Rhinoconjunctivitis	11 (78.6%)	9 (69.2%)	7 (77.8%)	7 (70.0%)	0
Itching of the nose/eyes	10 (71.4%)	9 (69.2%)	6 (66.7%)	6 (60.0%)	0
Difficulty breathing	2 (14.3%)	13 (100.0%)	1 (11.1%)	10 (100.0%)	0
Cough	2 (14.3%)	12 (92.3%)	2 (22.2%)	8 (80.0%)	0
Sneezing	10 (71.4%)	7 (53.8%)	6 (66.7%)	5 (50.0%)	0
SPT (Ø papules, mm):					
Mixture of herbs	10.4±3.9	8.7±2.8	9.2±2.5	6.2±2.5	0
Mixture of trees	4.2±2.7	5.2±2.1	6.4±2.3	6.4±2.3	0
Mixture of weeds	6.4±2.4	6.7±2.6	8.1±2.0	9,1±2.0	0
Results of spirometry:					
FEV1,%	98.8±2.8	81.1±1.4	97.9±2.7	86.1±1.3	98.8±1.2
Reverse FEV1, % (salbutamol, 200 mg)	2.7±1.2	13.5±0.6	3.2±1.1	13.8±0.4	2.5±1.1
Number of individuals with polysensitization	10 (71.4%)	9 (69.2%)	7 (77.8%)	7 (70.0%)	0
PCR results, * from 10^3 to 10^6:					
blood	0	0	0	0	0
saliva	2.1±1.5	3.1±1.2	0	0	0
mucosa	3.4±1.1	3.2±1.3	0	0	0
Number of individuals with hyper-IgE syndrome	8 (57.1%)	7 (53.8%)	5 (55.6%)	5 (50.0%)	0
Level of tIgE, IU/ml	185.0 ±7.5	192.8±17.2	143.0±5.7	190.9±7.1	31.0±9.7
Presence of allergopathy in relatives	6 (42.8%)	6 (46.1%)	4 (44.4%)	4 (40.0%)	0

* combination of symptoms is possible

Comparative analysis of the levels of miR-BART-13 and miR-BART-15 expressions in investigated groups showed that there is higher ($p<0.01$) level of miR-BART-13 expression in the second group of individuals compared to the first, third, fourth and control groups. On investigation of miR-BART-15, statistically reliable difference was detected only between the second ($p<0.05$) and control groups of investigation (Fig. 4). It should be noted that in the previous research, no difference in BART-15 expression was detected.

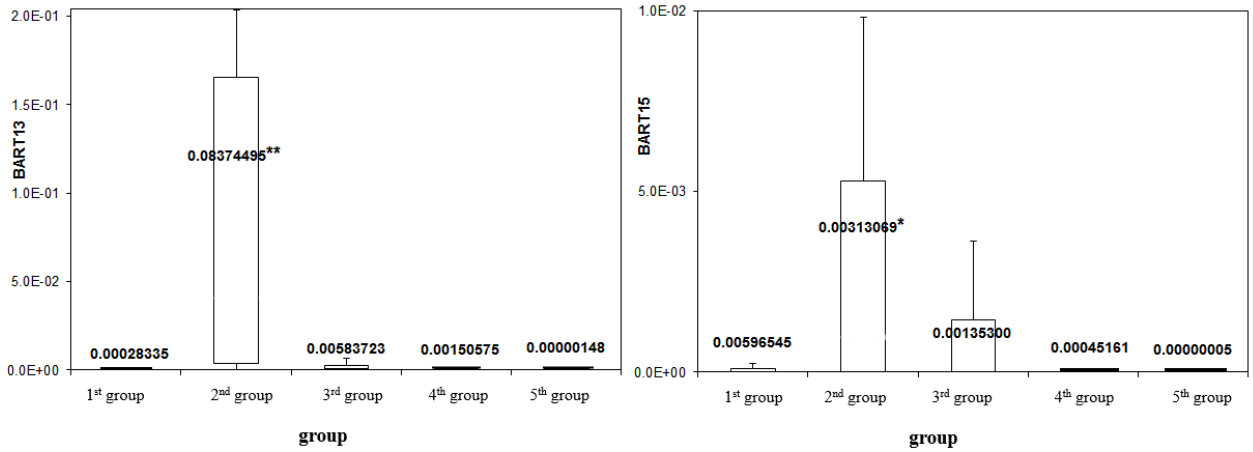

Fig. 4. Comparative analysis of the levels of BART-13 and 15 expressions depending on verified allergopathy in combination with chronic EBV-infection in active, latent phases and control group

Thus, expression of miR-BART- 13 and 15 was higher in patients of the second group with BA in combination with active phase of EBV infection.

Since patients with BA in combination with latent phase of EBV infection also constituted the fourth group of investigation, we decided to conduct a comparative analysis of the indices of external respiration and peculiarities of IgE synthesis in patients of the second and fourth groups and explore possible relationships of these indices with miR-BART-13 і 15 levels.

Table 2

Comparative analysis of indices of external respiration and total serum IgE in patients of the second and fourth groups

Indices	Groups of comparison	
	second group (n=13)	fourth group (n=10)
FEV1, %	81.1±1.4*	86.1±1.3
Reverse FEV1,%	13.5±0.6	13.8±0.4
Number of individuals with hyper IgE	7 (53.8%)	5 (50.0%)
Level of tIgE, IU/ml	192.0±17.2	190.9±7.1

* reliability of difference between groups of investigation, $p<0.05$

As it is seen from table 2, lower levels of FEV1 were detected in patients of the second group ($p<0.05$) compared to the fourth group, whereas statistical difference in the indices of reverse FEV1 was not observed. Concerning IgE investigation, the number of individuals with hyper-IgE syndrome did not differ statistically in groups as well as mean value of the levels of this immunoglobulin. Association analysis of miR-BART-13 with the mentioned indices demonstrated that there is a correlation with the levels of total serum IgE in patients with BA in combination with active phase of EBV (2^{nd} group) (Fig. 5). In patients of the fourth group in combination with latent phase of EBV, correlations between miR-BART-13 and indices of comparison were not detected. Conducted association analysis of miR-BART-15 with indices of FEV1 and levels of total serum IgE demonstrated that no correlation connections were observed between compared indices in both the second group and the fourth group.

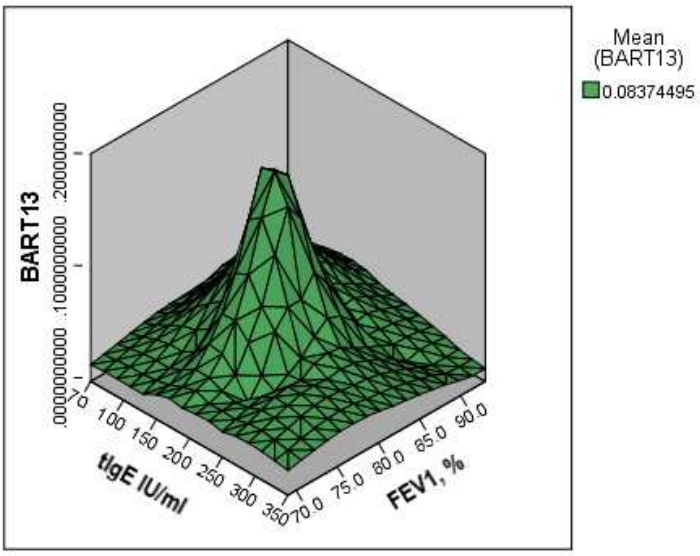

Fig. 5. Association relationships between miR-BART 13 and indices of serum IgE and FEV1 in patients of the second group

Thus, miR-BART-13 was higher in the group of patients with BA in combination with chronic EBV-infection in active phase. At the same time, reverse correlation between miR-BART-13 and FEV1 and direct correlation with levels of total serum IgE were observed in this group of patients. Concerning miR-BART-15, there was no difference in comparison of groups depending on replication stage of EBV. It should be mentioned that a reliably higher level of miR-BART-15 expression was also in the group of patients with BA in combination with chronic EBV-infection in active phase, however, only compared to control group. We did not reveal any correlations between miR-BART-15, indices of FEV1 and total serum IgE.

It is known that clinically manifested forms of primary EBV-infection in the form of acute respiratory infection (over 40 % of cases) or infectious mononucleosis (approximately 18% of cases) usually have a benign course and end in recovery with permanent EBV persistence in the body [7, 15]. Latent condition enables the virus to remain in the host's cells actually inactive and preserve different models of gene expression (known as programs of latency), which, first of all, help to avoid the action of a host's immune system [11]. Under "favorable" conditions, the virus activates and changes its condition to lytic phase (activation), while using the host's cell for production of viral offspring. Thus, horizontal infecting of other cells occurs with related negative consequences for the body [8; 10].

In addition, EBV became one of the first viruses in humans, in which expression of miRNAs was detected [14]. It has been investigated that miRNAs expression occurs in two regions of EBV (BamHI-A left transcript, or BART and BamHI-H right transcript, or BHRF1). EBV-transformed cells express viral miRNAs, directed at viral genes and genes of host's cells. Encoded EBV miRNAs can modulate latent/ lytic phases of EBV life cycle, as well as interfere with basic cell mechanisms involved in fundamental cancerous processes such as apoptosis, proliferation, progression of cell cycle, transformation ability and other mechanisms related to tumor. In particular, it has been shown that EBV-encoded BART-miRNAs and deregulated cellular miRNAs participate in the formation of nasopharyngeal carcinoma (NPC), interfering with an expression of viral genes and host's genes. At the same time, they transform immune reactions, stimulate signal ways to proliferation, development of metastases and, even inhibit sensitivity to radiochemotherapy [5, 7]. At present, it has been established that miRNAs, obtained from BHRF1, are highly expressed only in EBV-positive lymphoblast cells, whereas miRNAs BART were detected in all EBV-infected cell lines, in particular, lymphoblast cells, Burkitt's lymphoma, Hodgkin's disease, nasopharyngeal carcinoma etc. According to the obtained results, it is seen that miRNA, encoded EBV play significant roles in pathobiology of EBV life cycle and associated types of cancer [1]. In researches of Y. Kawano and co-authors, it was shown that the levels of miR-BART2-5p, 4, 7, 13, 15 and 22 were considerably elevated in patients with systemic signs of chronic EBV-infection in active phase compared to patients with infectious mononucleosis. In addition, the levels of expression of miR-BART2-5p 13 and

15 demonstrated direct correlations with specific clinical symptoms of chronic active EBV-infection, which did not depend on the level of viral load in plasma. Thus, authors concluded that miR-BART2-5p 13 and 15 are potential biomarkers of severity and prognosis of chronic activated EBV-infection [3]. Since miRNAs have high stability and are relatively easy to detect quantitatively, nowadays, issues concerning their use as EBV biomarkers of associated diseases are being actively discussed [4].

According to our data, an active phase of chronic EBV infection is often revealed in patients with allergopathy, namely, with seasonal rhinitis, sensitization to pollen allergens. By the concept of atopic march, it is known that approximately in 23-28% of patients, allergic rhinitis can be transformed into BA, and in 11.5% comorbid pathology is lifelong (AR+BA) [9]. In addition, without early start of specific allergen immunotherapy (AIT), BA progresses from mild form to moderate and severe. Thus, for patients and practical doctors, the issue of early diagnosis of allergopathy complications is significant, as well as decisions as to AIT conduction and prognosis of the disease course.

Conducted investigations demonstrated that higher level of miR-BART 13 expressions was in patients with allergopathy in combination with chronic EBV infection in active and latent phases compared to control, which obviously indicated the presence of virus in the body. Differences in the levels of miRNAs expression depending on the medium of virus replication were not found. However, having divided patients into groups depending on verified allergic diseases, we detected that the highest levels of miR-BART 13 were observed in the group of patients with BA in combination with active phase of EBV infection. In this group of patients, a reverse correlation between the levels of miR-BART-13 and FEV1 and direct correlation with the levels of IgE was also detected. Respective correlations were not found in patients with BA in combination with latent phase of chronic EBV-infection. Thus, in patients with BA and active phase of chronic EBV infection, increase in the levels of miR-BART-13 expression can be a biomarker of the severity of allergic inflammatory process due to increased level of bronchial obstruction and formation of hyper-IgE syndrome.

At the same time, the level of miR-BART 15 expression did not have a reliable difference in patients with allergopathy in combination with active and latent phases of chronic EBV-infection and control group. However, after division of patients into groups depending on verified allergopathy, we received higher miR-BART 15 indices in patients with BA and active EBV infection compared to control group of individuals. The obtained results are interesting and do not require additional investigations.

Conclusions

1. High levels of miR-BART 13 expression were detected in patients with allergopathy in combination with chronic EBV infection in active ($p<0.01$) and latent ($p<0.05$) phases compared to healthy individuals.

2. The levels of miR-BART 13 and 15 expressions in patients with allergopathy in combination with chronic EBV infection in active phase did not depend on the medium of virus replication.

3. In patients with BA and active phase of EBV infection, reverse correlation between the levels of miR-BART-13 and FEV1 and direct correlation with the levels of total serum IgE was detected.

4. Increased level of miR-BART 13 expression can be a biomarker of formation of severe allergological inflammatory process due to impairment of airway conductance and formation of hyper-IgE syndrome in individuals with BA in combination with EBV-infection in active phase.

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Реферати

ДОСЛІДЖЕННЯ MIR-BART 13 І 15 У ПАЦІЄНТІВ З АЛЕРГОПАТОЛОГІЄЮ НА ТЛІ ХРОНІЧНОЇ ЕПШТЕЙНА-БАРР ВІРУСНОЇ ІНФЕКЦІЇ

Зубченко С.О., Чоп'як В.В., Гаврилюк А.М., Потьомкіна Г.О., Ломіковська М.П.

Вірус Епштейна-Барр (EBV) ініціює широкий спектр імуномодулюючих ефектів в організмі людини. EBV - один із перших вірусів, у якому виявлена експресія miRNAs, які використовуються як мішені для виявлення вірусу в клінічних дослідженнях. Метою роботи було дослідити асоціативні зв'язки miR-BART 13 і 15 у пацієнтів з алергопатологією і хронічною EBV-інфекцією в активній і латентній фазах. Обстежено 46 пацієнтів з хронічною EBV - інфекцією в активній/латентній фазах, вік 18-59 років, 63% жінок, 37% чоловіків. Виконували клінічні, загальні лабораторні, інструментальні, специфічні алергологічні, молекулярно-генетичні, цитологічні дослідження. Високі рівні експресії miR-BART 13 виявлені у пацієнтів з алергопатологією на тлі хронічної EBV-інфекції в активній ($p<0,01$) і латентній ($p<0,05$) фазах порівняно зі здоровими особами. Різниці у рівнях експресії miRNAs 13, 15 залежно від середовища реплікації вірусу не виявлено. Дослідження miRNAs 13, 15 у групах, сформованих залежно від верифікованих алергічних хвороб, показало, що вищі рівні miR-BART 13 спостерігалась серед групи пацієнтів з бронхіальною астмою (БА) на тлі активної фази EBV-інфекції ($p<0,01$). У даній групі пацієнтів також виявлений зворотній кореляційний зв'язок між рівнями miR-BART-13 та ОФВ1 і прямий кореляційний зв'язок з рівнями загального IgE. Вищі показники miR-BART 15 були у пацієнтів з БА і активною EBV-інфекцією порівняно з контрольною групою осіб ($p<0,05$). У пацієнтів з БА і активною фазою хронічної EBV-інфекції підвищення рівнів експресії miR-BART-13 може виступати біомаркером тяжкості алергічного запального процесу на підставі збільшення рівня бронхіальної обструкції і формування гіпер-IgE синдрому.

Ключові слова. Хронічна Епштейна-Барр вірусна інфекція, алергічні хвороби, miR-BART 13, miR-BART 15.

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ИССЛЕДОВАНИЕ MIR-BART 13 И 15 У ПАЦИЕНТОВ С АЛЛЕРГОПАТОЛОГИЕЙ НА ФОНЕ ХРОНИЧЕСКОЙ ЭПШТЕЙНА-БАРР ВИРУСНОЙ ИНФЕКЦИИ

Зубченко С.А., Чопяк В.В., Гаврилюк А.М., Потемкина Г.А., Ломиковская М.П.

Вирус Эпштейна-Барр (EBV) инициирует широкий спектр иммуномодулирующих эффектов в организме человека. EBV является одним из первых вирусов, в котором обнаружена экспрессия miRNAs, которые используются в качестве мишеней для выявления вируса в клинических исследованиях. Целью работы было исследовать ассоциированные связи miR-BART 13 и 15 у пациентов с аллергопатологией и хронической EBV-инфекцией в активной и латентной фазах. Обследовано 46 пациентов с хронической EBV - инфекцией в активной / латентной фазах, возраст 18-59 лет, 63% женщин, 37% мужчин. Проводили клинические, общие лабораторные, инструментальные, специальные аллергологические, молекулярно-генетические, цитологические исследования. Высокие уровни экспрессии miR-BART 13 обнаружены у пациентов с аллергопатологией на фоне хронической EBV-инфекции в активной ($p<0,01$) и латентной ($p<0,05$) фазах по сравнению со здоровыми лицами. Разницы в уровнях экспрессии miRNAs 13, 15 в зависимости от среды репликации вируса не обнаружено. Исследование miRNAs 13, 15 в группах, сформированных в зависимости от верифицированных аллергических болезней, показало, что высокие уровни miR-BART 13 наблюдалась среди группы пациентов с бронхиальной астмой (БА) на фоне активной фазы EBV-инфекции ($p<0,01$). В данной группе пациентов также обнаружена обратная корреляционная связь между уровнями miR-BART-13 и ОФВ1 и прямая корреляционная связь с уровнями общего IgE. Показатели miR-BART 15 у пациентов с БА и активной EBV-инфекцией были выше по сравнению с контрольной группой лиц ($p<0,05$). У пациентов с БА и активной фазой хронической EBV-инфекции повышение уровня экспрессии miR-BART-13 может выступать биомаркером тяжести аллергического воспалительного процесса на основании увеличения уровня бронхиальной обструкции и формирования гипер-IgE синдрома.

Ключевые слова. Хроническая Эпштейна-Барр вирусная инфекция, аллергические болезни, miR-BART 13 miR-BART 15.

Рецензент Костенко В.О.