ЭКСПЕРИМЕНТАЛЬНЫЕ ИССЛЕДОВАНИЯ
EXPERIMENTAL RESEARCHES

BLOOD T-CELL SUBPOPULATIONS DYNAMICS IN ASTHMA UNDER SUSPENDED PARTICULATE LOAD *IN VITRO*

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RESUME

Background. *Bronchial asthma (BA) is characterized by dysregulation of the adaptive immune response. A significant contribution to pathological processes in urban environments is made by air pollution with solid suspended particles (HDPE). However, the expression of cytokine (interleukin (IL) 4, 6) and toll-like receptors (TLR) $CD8^+$ cells in BA patients and their dynamics under exposure to atmospheric microtoxicants practically have not been studied.*
The aim. *To determine the features of expression of IL-4R, IL-6R, TLR2, and TLR4 in $CD8^+$ cells in BA of varying severity and under the influence of solid suspended particles of atmospheric air.*
Materials and methods. *The study included 244 patients with asthma, 60 conditionally healthy individuals. Loading with simulated atmospheric suspensions was performed at a dose of 1 microgram (μg) of suspension per 1 ml of blood. The expression of IL-4R, IL-6R, TLR2, and TLR4 on $CD8^+$ cells was analyzed by flow cytofluorometry. Statistical processing of the results was performed in the program "STATISTICA 10.0". The critical significance level (p) for testing statistical hypotheses was assumed at $p < 0.05$.*
Results. *The main differences in cell signaling were observed between the group with partially controlled moderate BA and the control group. The expression of IL-4R is particularly strongly increased – by 217 % ($p < 0.001$), TLR4 – by 103 % ($p < 0.001$). The same group of patients is characterized by the greatest significance of differences in T-cytotoxic cells in comparison with the group of patients with mild bronchial asthma. IL-4 receptor expression on T-cytotoxic cells increased by 160 % ($p < 0.001$), TLR4 – by 108 % ($p < 0.001$).*
Conclusion. *The intensification of receptor expression is observed with an increase in the severity of the disease. The expression of IL-4R and TLR4 changes most intensively in T-cytotoxic cells IL-4R u TLR.*

Keywords: *asthma, T-cytotoxic cells, interleukin receptors, toll-like receptors, suspended solid particles*

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БРОНХИАЛЬНАЯ АСТМА: ОСОБЕННОСТИ СУБПОПУЛЯЦИЙ Т-ЦИТОТОКСИЧЕСКИХ КЛЕТОК КРОВИ ПРИ ИХ НАГРУЗКЕ *IN VITRO* ТВЁРДЫМИ ВЗВЕШЕННЫМИ ЧАСТИЦАМИ

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РЕЗЮМЕ

Актуальность. *Бронхиальная астма (БА) характеризуется нарушениями регуляции адаптивного иммунного ответа. Значительный вклад в патологические процессы в условиях урбанизированной среды вносит загрязнение атмосферного воздуха твердыми взвешенными частицами (ТВЧ). Однако особенности экспрессии цитокиновых (интерлейкин (IL) 4, 6) и толл-лайк рецепторов (TLR) $CD8^+$ клеток у пациентов с БА и их динамика при воздействии микротоксикантов атмосферного воздуха практически не исследованы.*

Цель. *Установить особенности экспрессии IL-4R, IL-6R, TLR2, TLR4 на $CD8^+$ клетках при БА разной степени тяжести и при воздействии твёрдых взвешенных частиц атмосферного воздуха.*

Материалы и методы. *В исследование были включены 244 больных БА, 60 условно здоровых лиц. Нагрузка смоделированными атмосферными взвесями проведена в дозе 1 мкг взвеси на 1 мл крови. Лейкоцитарную взвесь получали методом центрифугирования на фиколл-верографиновом градиенте плотности. Анализ экспрессии IL-4R, IL-6R, TLR2, TLR4 на $CD8^+$ клетках проводился методом проточной цитофлуорометрии. Статистическая обработка результатов производилась в программе «STATISTICA 10.0». Критический уровень значимости (p) при проверке статистических гипотез принимался при $p < 0,05$.*

Результаты. *Наибольшие различия в клеточном сигналинге наблюдаются между группой с частично контролируемой БА средней степени тяжести и группой контроля. Особенно сильно увеличена экспрессия IL-4R – на 217 % ($p<0,001$), TLR4 – на 103 % ($p < 0,001$). При нагрузке ТВЧ эта же группа пациентов характеризуется наибольшей значимостью различий Т-цитотоксических клеток по сравнению с группой больных бронхиальной астмой лёгкой степени тяжести. Экспрессия рецептора к IL-4 на Т-цитотоксических клетках к IL-4 возрастает на 160 % ($p < 0,001$), TLR4 – на 108 % ($p < 0,001$).*

Заключение. *Интенсификация экспрессии рецепторов наблюдается при увеличении тяжести заболевания, ухудшении контроля и воздействии твёрдых взвешенных частиц. Наиболее интенсивно на Т-цитотоксических клеток изменяется экспрессия IL-4R и TLR4.*

Ключевые слова: *бронхиальная астма, Т-цитотоксические клетки, рецепторы к интерлейкинам, толл-лайк рецепторы, твёрдые взвешенные частицы*

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INTRODUCTION

Asthma is one of the key problems in modern pulmonology; this disease was detected in more than 300 million people worldwide [1]. Asthma is a heterogeneous disease; however, regardless of the causes, its development always shows a transition from a local inflammatory process to a systemic one [2]. Recent data indicates an important role of T-cells in asthma development and severity increase [3]. Cytokines and their interaction with cells receptors are key factors in these processes. Main receptors, which importance is confirmed by numerous studies, are interleukin-4 and -6 receptors (IL-4R and IL-6R), toll-like receptors 2 (TLR2) and 4 (TLR4) [4-6]. Involvement of $CD4^+$ cells in a formation and aggravation of asthma is based on the development of Th1, Th2, and Th17 types of immune response [2]. The role of $CD8^+$ cells in asthma pathogenesis is studied less than $CD4^+$. Last researches show that in some cases $CD8^+$ are more associated with asthma severity than $CD4^+$, making this subset an important research topic [7]. $CD8^+$ cells presence can be associated with higher exacerbation frequency and steroids insensitivity in asthma. It is shown that in inflammatory environment cytotoxic cells can be phenotypically shifted from interferon-gamma (IFNγ) production to the synthesis of type 2 or type 17 cytokines [8].

T-cells immune response is affected by many factors, both endogenous and exogenous. Recent researches show that exposure to ambient air's suspended solid particles (SSP) contribute significantly to asthma pathogenesis. SSP drastically increase risk of asthma formation, and almost a third of all asthma cases is associated with a long-term exposure to microscopic air pollutants [9, 10]. It is shown that immunological mechanisms of ambient air's particulate matter influence are closely related to the signaling of adaptive immune cell response [11]. However, by far, there are practically no studies of the response of $CD8^+$ cells to ambient air's SSP impact.

THE AIM

To determine the features of expression of IL-4R, IL- 6R, TLR2, and TLR4 in $CD8^+$ cells in BA of varying severity and under the influence of solid suspended particles of atmospheric air.

MATERIALS AND METHODS

This study was performed in the Vladivostok Branch of the Far Eastern Scientific Center of Physiology and Pathology of Respiration – Research Institute of Medical Climatology and Rehabilitation Treatment. The research was carried out in accordance with the requirements of the Declaration of Helsinki (2013) and rules of clinical practice in the Russian Federation (the order of the Russian Federation ministry № 200н, dated April 1, 2016) with the Vladivostok Branch of the Far Eastern Scientific Center of Physiology and Pathology of Respiration – Research Institute of Medical Climatology and Rehabilitation Treatment local ethics committee approval (Protocol № 9, dated December 22, 2021).

In this experiment, we used model mixtures of microtoxicants created on the basis of studies of air pollution in Vladivostok (from 2017 to 2022). These mixtures simulate the real composition of atmospheric pollutants in the research area. The model suspension used for blood loading included PM 0–0.1 μm (soot and ash – 8.1 %), 0.1–1.0 μm (soot and ash – 19.7 %), 1.0–2.5 μm (soot and ash – 6.3 %), 2.5–10 μm (soot and ash – 5.9 %, minerals (quartz) – 20.4 %, metal particles – 10 %), 10–100 μm (minerals (quartz)) – 19.6 %, organic detritus – 5 %, synthetic particles (plastics, fibers) – 5 % [12].

In the *in vitro* research, biomaterial (peripheral blood) of 304 people was used (average age is 42,5 ± 4,4 years). 60 of them were in the control group (individuals without asthma); 131 had mild asthma (57 – controlled, 74 – partially controlled); 113 had moderate asthma (55 – controlled, 58 – partially controlled). The control and main groups were matched by age and gender. The diagnosis was verified in accordance with the Global Strategy for Asthma Management and Prevention, federal clinical guidelines for diagnosis and treatment of asthma, and international classification of diseases (10^{th} revision). The exclusion criteria were acute infections, chronic diseases in the acute phase, chronic heart failure in the decompensation phase, oncological diseases, diabetes, and contact harmful industrial factors.

Peripheral blood was collected in the morning using tubes with EDTA as an anticoagulant. The mixture of microtoxicants was added at a dose of 1 μg of mixture per 1 ml of blood. Incubation was carried out for 1 hour at 37 °C. The leukocyte suspension was obtained using centrifugation in ficoll-verografine density gradient. Flow cytometry (BD FACSCanto II, USA) was used to evaluate expression of IL-4R ($CD124^+$), IL-6R ($CD126^+$), TLR2 ($CD282^+$) and TLR4 ($CD284^+$) in T-cytotoxic cells ($CD8^+$) (BD, USA). The percentage of subpopulations in the $CD8^+$ population was assessed. 2.5 million events were analyzed in the FACS Diva software (USA).

Statistical processing of the experimental results was performed in «STATISTICA 10.0» software for Windows OS. The results are presented as median values (Me) and quartiles (Q25, Q75). The Kolmogorov – Smirnov criterion was used to verify the coincidence of obtained distribution with a normal one. The analysis revealed a distribution different from normal. The homogeneity of the variance was assessed using Leven's criterion. The statistical significance of differences between independent groups was assessed using the nonparametric Mann-Whitney test, and between dependent groups using the Wilcoxon test. Critical p-value during checking statistical hypotheses was taken as $p < 0.001, < 0.01, < 0.05$.

RESULTS

The analysis of the studied receptors expression revealed the features of cellular signaling in asthma of different severity (Table 1). Significant changes in the parameters compared to the control group were observed

in moderate asthma. $CD8^+CD124^+$ and $CD8^+CD284^+$ cells subsets increased the most.

Patients with controlled moderate asthma have significant differences compared to the control group: $CD8^+$ cells had increased expression of IL-4R – by 113 % ($p < 0.001$), IL-6R – by 89 % ($p < 0.01$), TLR4 – by 22 % ($p < 0.01$), TLR2 – by 13 % ($p < 0.05$). Compared to the group with controlled mild asthma their parameters were also different: expression of IL-4R was increased by 112 % ($p < 0.001$), IL-6R – by 85 % ($p < 0.01$), TLR4 – by 18 % ($p < 0.05$). The most significant differences are between the group with partially controlled moderate asthma and the control group. Expression of IL-4R is increased the most – by 217 % ($p < 0.001$). TLR4 was increased by 103 % ($p < 0.001$), IL-6R – by 96 % ($p < 0.001$), TLR2 – by 23 % ($p < 0.01$). Comparison of groups with asthma of different severity also shows statistically significant differences. In moderate asthma expression of IL-4R was increased the most – by 173 % ($p < 0.001$), level of TLR4 was 83 % higher ($p < 0.001$) and IL-6R – 74 % higher ($p < 0.001$).

Response to the atmospheric particulate matter exposure was characterized by an intensification of signaling processes (Table 2).

In mild controlled asthma after the exposure to SSP, the expression of IL-4R was increased by 23 % ($p < 0.05$), TLR2 – by 29 % ($p < 0,05$) and TLR4 – by 9 % ($p < 0.05$). In patients with mild partially controlled asthma all the studied parameters were increased: TLR4 – by 8 % ($p < 0.05$), TLR2 – by 43 % ($p < 0.05$), IL-6R – by 23 % ($p < 0.05$), IL-4R – by 18 % ($p < 0.01$). In moderate controlled asthma with SSP exposure, the expression of inflammatory markers was higher: TLR4 increased by 22 % ($p < 0.01$), TLR2 – by 62 % ($p < 0.01$),

TABLE 1

PERCENTAGE OF $CD8^+$ CELLS EXPRESSING IL-4R, IL-6R, TLR2, TLR4 IN PATIENTS WITH ASTHMA

Groups			Parameters, % of cells in $CD8^+$ population (Me, (Q25, Q75))			
			$CD8^+CD124^+$	$CD8^+CD126^+$	$CD8^+CD282^+$	$CD8^+CD284^+$
Control group		*n*=60	2.4 (2.11; 2.96)	1.53 (1.27; 1.74)	1.71 (1.56; 1.88)	6.22 (5.89; 6.56)
Mild asthma	controlled	*n*=57	2.42 (2.39; 2.77)	1.56 (1.32; 1.77)	1.75 (1.59; 1.94)	6.4 (6.12; 6.62)
	partially controlled	*n*=74	2.78 (2.35; 2.91)	1.72 (1.5; 1.89)	1.87 (1.75; 2.0)	6.91 (6.75; 7.14)
Moderate asthma	controlled	*n*=55	5.12***### (4.88; 5.36)	2.89**## (2.61; 3.19)	1.93* (1.89; 2.17)	7.56**# (7.14; 7.97)
	partially controlled	*n*=58	7.6***### (7.17; 8.02)	3.0***### (2.97; 3.21)	2.1** (1.93; 2.25)	12.62***### (11.85; 12.9)

Note. * – statistical significance of differences compared to the control group: * – $p < 0.05$; ** – $p < 0.01$; *** – $p < 0.001$; # – statistical significance of differences compared to the group with mild asthma: # – $p < 0.05$; ## – $p < 0.01$; ### – $p < 0.001$.

TABLE 2

PERCENTAGE OF $CD8^+$ CELLS EXPRESSING IL-4R, IL-6R, TLR2, TLR4 IN PATIENTS WITH ASTHMA EXPOSED TO SSP

Groups			Parameters, % of cells in $CD8^+$ population (Me, (Q25, Q75))			
			$CD8^+CD124^+$	$CD8^+CD126^+$	$CD8^+CD282^+$	$CD8^+CD284^+$
Mild asthma + SSP	controlled	*n*=57	2.97* (2.78; 3.37)	1.75 (1.56; 2.29)	2.26* (1.99; 2.47)	6.96* (6.71; 7.32)
	partially controlled	*n*=74	3.28** (2.94; 3.62)	2.11* (1.84; 2.37)	2.68* (2.33; 2.81)	7.49* (7.27; 7.73)
Moderate asthma + SSP	controlled	*n*=55	6.65*### (5.93; 7.15)	3.25*# (3.0; 3.68)	3.12**# (2.94; 3.56)	9.22**## (8.87; 9.64)
	partially controlled	*n*=58	8.54**### (8.21; 9.34)	3.58*## (3.31; 4.11)	3.41***## (3.18; 3.78)	15.6***### (15.21; 16.0)

Note. * – statistical significance of differences compared to the groups without exposure to SSP (Table 1): * – $p < 0.05$; ** – $p < 0.01$; *** – $p < 0.001$; # – statistical significance of differences compared to the group with mild asthma: # – $p < 0.05$; ## – $p < 0.01$; ### – $p < 0.001$.

IL-6R – by 12 % ($p < 0.05$), IL-4R – by 30 % ($p < 0.05$). The most significant differences were observed in patients with moderate partially controlled asthma and SSP exposure: in comparison to the same parameters before contacting with SSP expression of TLR4 was increased by 24 % ($p < 0.001$), TLR2 – by 62 % ($p < 0.001$), IL-4R – by 12 % ($p < 0.01$), and IL-6R – by 19 % ($p < 0.05$).

Comparison of groups with mild and moderate asthma after exposure to SSP showed statistically significant differences. In moderate controlled asthma TLR4 expression was increased by 32 % ($p < 0.01$), TLR2 – by 38 % ($p < 0.05$), IL-6R – by 86 % ($p < 0.05$), IL-4R – by 124 % ($p < 0.001$). Group of moderate partially controlled asthma showed TLR4 expression increased by 108 % ($p < 0.001$), TLR2 – by 27 % ($p < 0.01$), IL-6R – by 70 % ($p < 0.01$), and IL-4R – by 160 % ($p < 0.001$).

DISCUSSION

This study demonstrates the specifics of changes in receptors expression in a T-cytotoxic cells subset in asthma. It is shown that an increase of inflammatory markers expression correlates with asthma severity, its lower control and exposure to SSP. It especially affects IL-4R and TLR4, as their expression changes the most significantly. The importance of toll-like receptors contribution to asthma pathogenesis is convincingly proved in researches [5, 13-15]. The features of the TLR4 functioning in the $CD8^+$ cells subset are partially described in the literature, although not in the context of asthma. In particular, there is evidence of TLR4 activation in T-cytotoxic cells in a mouse model of muscular injury. It can occur under the interaction with interleukins such as IL-12 and IL-23 [15]. Although present information is scattered, it is possible to make an assumption that this aspect is important in asthma, because the increase of IL-12 and IL-23 concentration and their importance for asthma's pathogenesis are described in some phenotypes of this pathology [16, 17]. As present data shows that $CD8^+CD284^+$ interact with asthma's feature cytokines, the tendency of TLR4 expression increase among T-cytotoxic cells may become an important criterion of asthma patients' state assessment.

In asthma, the TLR2 on immune cells is associated with the activation of the NLP3 inflammasome in them, which stimulates the processes of glycolysis, oxidative stress and activation of immune cells. At the moment, the main researches in this field are focused on the study of macrophages, however, such a pattern is described for the $CD8^+$ cells [18]. In addition, there is evidence of increased survival rate, activity and proliferation among the $CD8^+$ cells when the TLR2 is stimulated [19]. Although there is practically no data on $CD8^+CD282^+$ in asthma in the literature, it can be assumed that these signaling relationships can complicate the resolution of the inflammatory process and thereby contribute to the chronization and aggravation of asthma.

The importance of interleukins 4 and 6 in asthma pathogenesis has been revealed in numerous studies. In particular, IL-4 is one of the key cytokines in asthma pathogenesis, as it affects many cell types [4]. This interleukin's interaction with T-cytotoxic cells is noted in allergic diseases, including asthma. An increase of IL-4 level during local inflammation in the airways leads to the formation of the special $CD8^+$ cells phenotype. The presence of T-cytotoxic cells correlates with decreased pulmonary function [20]. IL-6 is also able to modulate T-cytotoxic cells functioning. This cytokine is important for the signaling pathway leading to the expression of IL-21 by the $CD8^+$ cells [21]. IL-21, in turn, is an important cytokine for Th2 and Th17 phenotypes of asthma [22].

There are studies in the modern research field that emphasize the importance of T-cytotoxic cells in asthma. It is primarily due to their resistance to corticosteroid therapy [23]. The pattern we revealed, which shows a higher expression of studied receptors among T-cytotoxic cells, demonstrates the particular vulnerability of cohorts of the population with more severe and less controlled asthma. It is especially important for urbanized areas, where the quality of the environment significantly affects pathologic processes [24]. There is evidence indicating the ability of microscopic SSP to induce the IL-6R gene expression [25]. In the study previously conducted by the authors of this article, experimental evidence was obtained for IL-6 signaling pathway switching under exposure to atmospheric air microtoxicants [26]. The increase of IL-4 production is shown as a response to SSP exposure in mouse model experiments [27]. An increase of IL-4 levels after SSP exposure was also recorded among patients with asthma [28]. Recent data suggest that microtoxicants, triggering a NF-κB signaling pathway, can enhance Th2 and Th17 types of inflammatory responses [29]. TLRs play a significant role in the activation of inflammatory pathways mediated by SSP exposure. There is data on TLR2 and TLR4 activation after SSP exposure, accompanied by Treg/Th17 immune imbalance. There is evidence that SSP exposure triggers TLR4 activation and a signaling pathway that leads to the increase of inflammatory cytokines expression, such as TNF-α, IL-6 и IL-1β. Stimulation of TLR leads to increased production of inflammatory cytokines, which can trigger activation of innate and adaptive immunity [14, 30].

Thus, in asthma there is an intensification of T-cytotoxic cells signaling. The number of $CD8^+CD124^+$ and $CD8^+CD284^+$ cells increased the most. These processes become more active with the aggravation of asthma and a decrease of its control. In the context of the emerging important role of the $CD8^+$ cells in the pathogenesis of asthma, further research of this subset's contribution to the systemic inflammatory processes is required. Exposure to atmospheric air particulate matter additionally burdens the functional activity of adaptive immunity cells. Studied biomarkers can potentially be used as criteria for diagnosing and health monitoring of population, exposed to airborne microtoxicants. Monitoring of these parameters will provide the opportunity to evaluate the immune system response and carry out predictive and preventive events.

The limitation of this study is the relatively small sample size. One of the advantages is the involvement of highly specific markers of the inflammatory process.

CONCLUSION

The study shows the features of receptors expression among the $CD8^+$ cells in asthma, depending on the severity and the level of control of the disease. In the *in vitro* research T-cytotoxic cells subset's response to airborne particulate matter was revealed – expression of IL-4R, IL-6R, TLR2, and TLR4 intensifies. Activation of the $CD8^+$ cells signaling may become an important criterion for assessment the condition of asthma patients and a biomarker of ecology-dependent disorders in urbanized areas.

Conflict of interest

Authors of this article declare no conflict of interest.

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