

Original article

Peculiarities of CD4⁺ cell signaling in asthma patients exposed to suspended solid particles of atmospheric air

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Abstract: *Objective* — To evaluate the expression of receptors for interleukin-4 (IL-4R), 6 (IL-6R), toll-like receptors 2 (TLR2) and 4 (TLR4) of T helper (Th) cells (CD4⁺), as well as the content of interleukin-4 (IL-4) and 6 (IL-6) in the blood serum of patients with mild and moderate bronchial asthma (BA) exposed to suspended solid particles (SSP).

Methods — The in vitro study included 244 patients with BA and 60 conditionally healthy individuals. Model suspensions (MS) of substances simulating multicomponent air pollution were used as a load. The concentrations of IL-4 and IL-6 were determined by enzyme immunoassay. The CD4⁺ population was analyzed by flow cytometry using monoclonal antibodies, and the expression of IL-4R, IL-6R, TLR2, and TLR4 was assessed. The results of the SSP effect are presented as indices reflecting the values of the indicators with and without MS exposure.

Results — Against the back-ground of well-controlled BA, the most pronounced differences were observed between the groups of patients with mild and moderate BA in the expression of IL-4R and IL-6R: 6.8 times and 1.9 times, respectively. In contrast, TLR2 expression was higher with mild BA. The maximum increase in the level of TLR4 expression (15.5 times) was observed in patients with partially controlled mild BA. When analyzing the indicators of the SSP effect, more pronounced changes were found in patients with moderate BA. In well-controlled BA, the most noticeable differences in the parameters between the groups with mild and moderate BA severity were observed in the IL-4R (1.3-fold) and IL-6R (1.6-fold) expression indices. In patients with partially controlled BA, the most significant changes were found in the TLR2 (1.6-fold) and TLR4 (1.3-fold) expression indices.

Conclusion — Under the influence of SSP, changes in the content of IL-4 and IL-6 cytokines, as well as the expression of specific receptors (IL-4R, IL-6R, TLR2 and TLR4) were noted in BA. As the course of BA worsened, a noticeable deterioration in the cytokine status and the state of the receptor apparatus of CD4⁺ cells was noted, despite the participation of compensatory mechanisms. Our data convincingly indicate the need to monitor patients with bronchopulmonary pathology in conditions of an unfavorable technogenic environment in order to carry out timely corrective measures.

Keywords: asthma, interleukin 4, interleukin 6, T-cell receptor profile, suspended solids particles.

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Introduction

Bronchial asthma (BA) is a chronic pathology that begins with localized inflammation in the airways and progresses to a systemic process involving various immunocompetent cells and regulatory molecules [1]. Systemic inflammation in BA is characterized by impaired intracellular and intercellular signaling, which is evidenced by high levels of proinflammatory cytokines, more severe oxidative stress and increased reactivity of immunocompetent cells [1]. The role of interleukin-4 (IL4), interleukin-6 (IL-6) and their receptors (IL-4R and IL-6R) in the pathogenesis of BA depends on the type of immune response. These molecules are involved in signaling mechanisms that play an important role in the disease process. IL-4 is considered the main cytokine in the Th2 immune response, which also regulates the production of other proallergic cytokines by T helper 2 (Th2) cells.

IL-6 is a pleiotropic cytokine that is produced in response to a variety of inflammatory stimuli [2, 3]. The cytokine response in BA can be mediated by toll-like receptors 2 (TLR2) and 4 (TLR4). These receptors contribute to allergic inflammation by stimulating the Th2 immune response. They are also involved in the initiation of non-Th2 immune responses and stimulation of neutrophilic inflammation [4]. However, the mechanisms by which IL-4R, IL-6R, TLR2 and TLR4 contribute to the pathogenesis of BA remain poorly understood.

Air pollution is an important risk factor for the development and progression of BA [5, 6]. Exposure to particulate matter (PM) in the atmosphere leads to the formation of reactive oxygen species (ROS) and the development of oxidative stress, which in turn activates signaling pathways associated with inflammation and cell damage. Oxidative stress products trigger a cascade of signals regulating the expression of cytokines and their receptors

[7-10]. Therefore, it is extremely important to conduct a comprehensive study of the features of the immune system in patients with BA when exposed to SSP.

Our study aimed at evaluating the expression of IL-4R, IL-6R, TLR2 and TLR4 in CD4⁺ cells and the content of IL-4 and IL-6 in the blood serum of patients with BA when exposed to SSP in the atmospheric air.

Material and Methods

Study participants

The in vitro study involved 244 people with BA, including 131 patients with mild BA (of which 57 had well-controlled BA and 74 had partially controlled BA) and 113 patients with moderate BA (55 with well-controlled BA and 58 with partially controlled BA). The control group consisted of 60 volunteers who were considered practically healthy. The mean age of patients was 42.5±4.4 years. BA was diagnosed in accordance with the Global Strategy for the Treatment and Prevention of Bronchial Asthma (2024), Federal Clinical Guidelines for the Diagnosis and Treatment of Bronchial Asthma (2021) and the International Classification of Diseases, 10th revision. The study was conducted in compliance with the ethical standards set out in the Declaration of Helsinki (2013), approved by the Ethics Committee of the Vladivostok Branch of the Far Eastern Scientific Center for Physiology and Pathology of Respiration, Research Institute of Medical Climatology and Rehabilitation Treatment (protocol No. 9 of November 24, 2021). Voluntary informed consent for the physical examination was obtained from each patient. The criteria for excluding patients from the study were as follows: the presence of acute infectious diseases, chronic diseases of internal organs in the exacerbation phase, and chronic decompensated heart failure.

Model suspension loads

Peripheral blood was collected in glass vials with an anticoagulant, ethylenediaminetetraacetic acid (EDTA). Model suspensions (MS) of substances simulating multicomponent air pollution were used as loads. MS were developed taking into

account preliminary studies of the air in the city of Vladivostok and designed to correspond to the pollution of the ground layer of atmospheric air in an area with a high anthropogenic load [11]. The load was administered at a dose of 1 µg of suspension per 1 ml of blood. The samples were incubated for 1 hr. at a temperature of 37°C. The study was carried out on blood samples subjected to the load of MS, as well as on control samples without MS load.

Instruments

The concentration of IL-4 and IL-6 (Vector-Best, Russia) in blood serum was determined by the enzyme immunoassay method using an automated enzyme immunoassay analyzer, Evolis Twin Plus (Bio-Rad, USA). A suspension of leukocytes was isolated from peripheral blood on a Ficoll-Paque Plus/Ficoll-Verografin gradient. The T helper population (CD4⁺) was analyzed by flow cytometry using monoclonal antibodies (BD, USA) on a FACS Canto II flow cytometer (BD, USA) with an assessment of the expression of IL-4R, IL-6R, TLR2 and TLR4. Data were processed using FACS Diva software. The results of SSP exposure were presented as a total suspended solids (TSS) action index reflecting the ratio of values under the exposure to MS to values without such exposure.

Statistical data processing

Statistical processing of the obtained data was performed using Statistica 10 software (StatSoft Inc., USA). The results were presented as a median (Me) with the lower and upper quartiles (Q25; Q75). Considering that most groups had a non-normal distribution, the Kruskal–Wallis test was employed to test statistical hypotheses. Differences were considered statistically significant at p<0.05.

Results

The results of the calculations performed in the groups of patients with mild and moderate BA without and with exposure to SSP in atmospheric air are presented in [Table 1](#).

Table 1. CD4⁺ cell signaling in bronchial asthma (BA) patients exposed to suspended solid particles (SSP) of atmospheric air

Group	Indicators					
	IL-4, pg/ml	IL-6, pg/ml	IL-4R, %	IL-6R, %	TLR2, %	TLR4, %
Control group n=60	1.16 (1.1; 1.21)	2.12 (2.08; 2.16)	0.93 (0.75; 1.14)	1.75 (1.63; 1.8)	1.31 (1.1; 1.37)	1.02 (0.85; 1.09)
Well-controlled mild BA n=57	1.29*** (1.25; 1.31)	2.9*** (2.86; 2.93)	1.25*** (0.92; 1.41)	2.68*** (2.59; 2.74)	1.99*** (1.91; 2.05)	1.17*** (1.11; 1.19)
Partially controlled mild BA n=74	1.32*** (1.29; 1.34)	3.38*** (3.34; 3.4)	2.48*** (2.11; 2.74)	3.03*** (2.95; 3.11)	2.10*** (2.08; 2.16)	1.49*** (1.43; 1.56)
Well-controlled moderate BA n=55	1.33***# (1.32; 1.35)	4.13***### (4.08; 4.17)	3.02***### (2.89; 3.27)	3.5***### (3.42; 3.58)	2.23***### (2.19; 2.25)	1.23***### (1.2; 1.27)
Partially controlled moderate BA + SSP n=58	1.44***### (1.41; 1.48)	4.60***### (4.55; 4.63)	3.72***### (3.45; 3.91)	3.87***### (3.74; 3.97)	2.30***### (2.28; 2.37)	1.05### (1.01; 1.06)
Well-controlled mild BA + SSP n=57	1.63*** (1.53; 1.74)	5.42*** (5.33; 5.54)	1.69* (1.56; 1.84)	3.16** (2.88; 3.44)	2.39*** (2.32; 2.44)	1.35** (1.24; 1.44)
Partially controlled mild BA + SSP n=74	1.74*** (1.65; 1.82)	7.33*** (7.25; 7.42)	3.39** (3.21; 3.44)	4.85*** (4.73; 4.93)	2.60*** (2.51; 2.68)	2.18*** (2.04; 2.33)
Well-controlled moderate BA + SSP n=55	1.98***### (1.85; 2.11)	9.56***### (9.38; 9.76)	4.12***### (3.97; 4.29)	6.44***### (6.37; 6.52)	2.79***### (2.72; 2.84)	1.49***### (1.41; 1.56)
Partially controlled moderate BA + SSP n=58	2.26***### (2.12; 2.35)	11.41***### (11.36; 11.47)	5.08***### (4.86; 5.22)	8.51***### (8.4; 8.62)	2.97***### (2.9; 3.05)	1.08***### (1.07; 1.1)

IL, interleukin; TLR, toll-like receptor; *, **, ***, statistical significance of differences in patients with BA vs. the control group: p<0.05, p<0.01, *** p<0.001, respectively; #, ##, ### statistical significance of differences in patients with mild severity BA vs. patients with moderate severity BA: p<0.05, p<0.01, *** p<0.001, respectively.

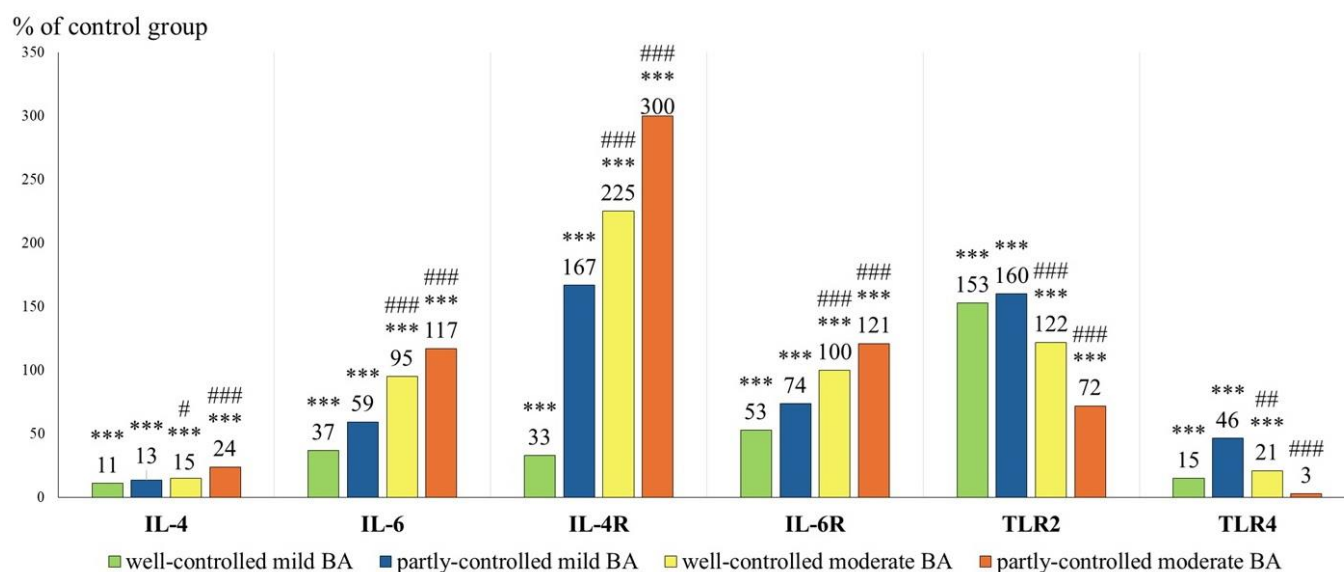


Figure 1. Cytokine levels and receptor expression of CD4⁺ cells in patients with bronchial asthma (BA).

*, **, ***, statistical significance of differences in patients with BA vs. the control group: $p < 0.05$, $p < 0.01$, $p < 0.001$, respectively; #, ##, ### statistical significance of differences in patients with mild severity BA vs. patients with moderate severity BA: $p < 0.05$, $p < 0.01$, $p < 0.001$, respectively.

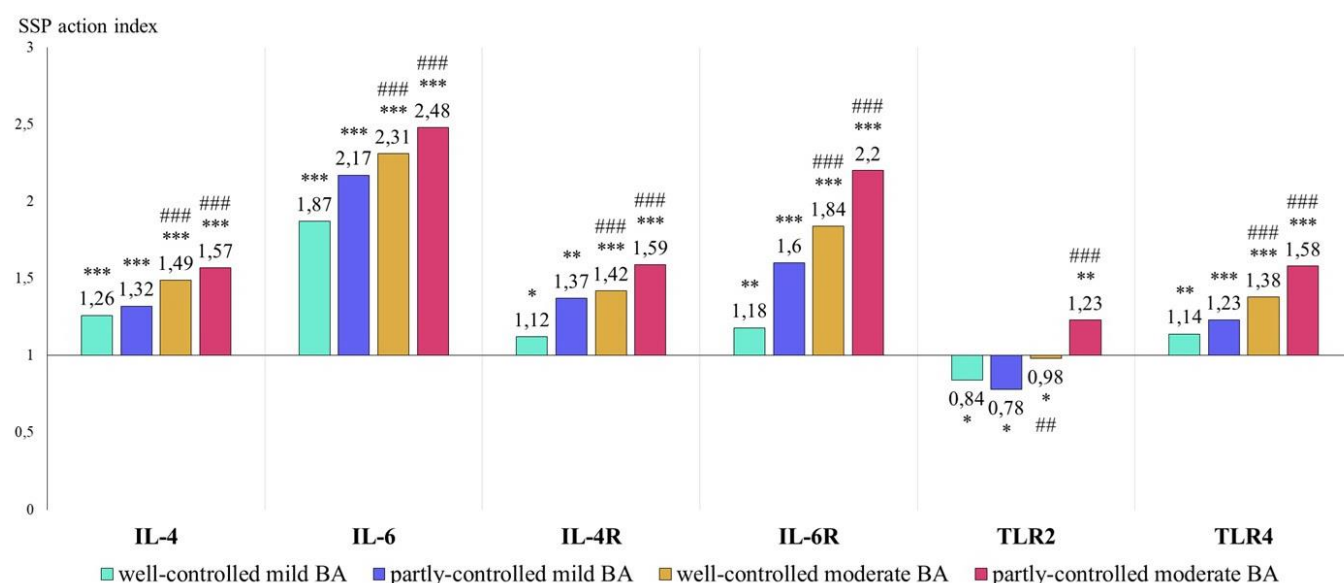


Figure 2. Total suspended solids (TSS) action index values in patients with bronchial asthma (BA) reflecting cytokine levels and receptor expression of CD4⁺ cells with and without TSS exposure in the atmospheric air.

*, **, ***, statistical significance of differences in patients with BA vs. the control group: $p < 0.05$, $p < 0.01$, $p < 0.001$, respectively; #, ##, ### statistical significance of differences in patients with mild severity BA vs. patients with moderate severity BA: $p < 0.05$, $p < 0.01$, $p < 0.001$, respectively. A value of one on the ordinate axis indicates that there is no significant difference between the indices with and without SSP exposure.

The expression levels of IL-4R, IL-6R, TLR2 β and TLR4 on circulating CD4⁺ cells in patients with mild and moderate BA were analyzed to assess their contributions to the pathogenesis of BA. The results for the groups of patients with BA vs. the control group are presented in [Figure 1](#).

Compared with the control group, patients with mild BA exhibited a statistically significant increase in IL-4 levels by 11% ($p < 0.001$) and 13% ($p < 0.001$) in the well-controlled BA and partly controlled BA groups, respectively. Similarly, IL-6 levels were elevated by 37% ($p < 0.001$) and 59% ($p < 0.001$) in these groups. In patients with moderate BA, a statistically significant

increase in the concentration of IL-4 by 15% ($p < 0.001$) and 24% ($p < 0.001$) was observed, along with an increase in the levels of IL-6 by 95% ($p < 0.001$) and 117% ($p < 0.001$) in the groups with well-controlled and partly controlled BA course, respectively.

Relative to the control group, in patients with mild BA, the expression of IL-4R increased by 33% ($p < 0.001$) and 167% ($p < 0.001$) in the well-controlled BA and partly controlled BA groups, respectively. Similar increase was detected for IL-6R: by 53% ($p < 0.001$) and 74% ($p < 0.001$) in the groups with well- and partly controlled BA, correspondingly. Finally, in patients with moderate BA, the expression of IL-4R increased by 225% ($p < 0.001$)

and 300% ($p<0.001$), while the expression of IL-6R was higher by 100% ($p<0.001$) and 121% ($p<0.001$) in groups with well- and partially controlled disease, respectively.

TLR2 expression levels increased by 153% ($p<0.001$) and 160% ($p<0.001$) in patients with mild BA who were classified as well-controlled or partially controlled, respectively. In patients with moderate BA, TLR2 expression levels increased by 122% ($p<0.001$) in well-controlled and 72% ($p<0.001$) in partially controlled BA. Compared with the control group, TLR4 expression increased by 15% ($p<0.001$) and 46% ($p<0.001$) in the well-controlled and partially controlled mild BA groups, respectively. In the well-controlled moderate BA group, an increase of 21% ($p<0.001$) was observed. In partially controlled moderate BA, statistically significant differences in the TLR4 expression level relative to the control group were not detected.

The analysis revealed more pronounced changes in the content of ILs and their corresponding receptors in the group of patients with moderate BA, both with well-controlled and partially controlled disease course. In well-controlled BA, the greatest differences between the mild and moderate severity groups were observed in the level of IL-6 (2.6 times, $p<0.001$), as well as expression of IL-4R (6.8 times, $p<0.001$) and IL-6R (1.9 times, $p<0.001$). In partially controlled BA, the greatest changes were found in the level of IL-4 (1.8 times ($p<0.001$)). In mild asthma, TLR2 expression was 1.3 ($p<0.001$) and 2.2 ($p<0.001$) times higher in the well-controlled and partially controlled groups, respectively. The most pronounced difference in TLR4 expression was observed in the group of partially controlled mild BA (15.5 times ($p<0.001$)).

The results of calculating the TSS action index values for IL levels and IL-R expression in the groups of patients with mild and moderate BA when exposed to SSP in the atmospheric air are presented in [Figure 2](#).

In patients with mild BA, an increase in the TSS action index values for the IL-4 level was observed by 26% ($p<0.001$) and 32% ($p<0.001$); for the IL-6 level, by 87% ($p<0.001$) and 117% ($p<0.001$) in the groups of well-controlled and partially controlled disease, respectively. In moderate BA, an increase in the TSS action index values for the IL-4 level was detected by 49% ($p<0.001$) and 57% ($p<0.001$); and for IL-6 level, by 131% ($p<0.001$) and 148% ($p<0.001$) in the well-controlled and partially controlled groups, respectively.

In the mild BA group, TSS action index values increased for IL-4R expression by 12% ($p<0.05$) and 37% ($p<0.01$); and for IL-6R, by 18% ($p<0.01$) and 60% ($p<0.001$) in the well-controlled and partially controlled groups, correspondingly. In moderate BA, TSS action index values increased for IL-4R by 42% ($p<0.001$) and 59% ($p<0.001$); and for IL-6R, by 84% ($p<0.001$) and 120% ($p<0.001$) in the well-controlled and partially controlled groups.

In both well-controlled and partially controlled mild BA groups, as well as in controlled moderate BA group, a decrease in the TSS action index values for TLR2 expression was observed in the magnitude of 16% ($p<0.05$), 22% ($p<0.05$), and 2% ($p<0.05$), respectively. In contrast, an increase in this parameter was found in partially controlled BA by 23% ($p<0.01$).

TSS action index values in mild BA demonstrated an increase in TLR4 expression of 14% ($p<0.01$) and 23% ($p<0.001$) in the well-controlled and partially controlled clinical groups, respectively. In patients with moderate BA, an increase in TSS action index values for TLR4 levels was observed by 38% ($p<0.001$) and 58% ($p<0.001$)

in well-controlled and partially controlled course of the disease, correspondingly.

Comparison of the TSS action index values in mild and moderate BA yielded maximum changes in IL-6 by 44% ($p<0.001$), in IL-4R by 30% ($p<0.001$), and in IL-6R by 66% ($p<0.001$) with a well-controlled course of moderate BA. Such changes constituted 25% for IL-4 ($p<0.001$), by 45% for TLR2 ($p<0.001$) and by 35% for TLR4 ($p<0.001$) with a partially controlled course of moderate BA.

Discussion

Cytokines play an important role in the pathogenesis of chronic inflammatory processes, affecting the nature of the inflammatory response and the severity of the clinical course of BA. The study confirmed an increase in the level of IL-4 and IL-6 with the severity of BA. It was established that cytokines, acting as regulatory mediators of systemic inflammation, control the processes of immune reactivity, thereby establishing a balance between proinflammatory and anti-inflammatory agents. In the case of the inability of regulatory systems to maintain homeostasis, the destructive effects of inflammatory mediators become dominant, which leads to the development of systemic inflammation [12]. In patients with BA, a multitype Th immune response is observed [13, 14]. Current literature shows the importance of the imbalance of Th immune response types in the pathogenesis of BA and its important role in disease control. IL-4 is the primary mediator of allergic reaction formation in the Th2 response. However, recent studies have shown that elevated IL-4 levels are also a hallmark of non-allergic BA, highlighting its key role as a regulator of inflammatory processes in this condition. Overall, IL-4 can exert pleiotropic effects on a wide range of target cells, including macrophages, hematopoietic progenitor cells, NK cells, and fibroblasts. In addition, it can act as a potent anti-apoptotic factor. IL-4 facilitates the differentiation of naive Th0 cells into Th2 cells, which in turn produce IL-4, IL-13, and IL-5, thereby creating a cyclic effect [15]. IL-4 signaling in T cells is mediated through the type I receptor. The IL-4 receptor alpha (IL-4R α) is a key element in the pathogenesis of allergic asthma. IL-4 is notable for its ability to potently activate STAT6, which then binds to key phosphotyrosines of IL-4R α . IL-4/STAT6 signaling in activated CD4⁺ T cells induces the expression of the master Th2 transcription factor GATA3, which is essential for the function and maintenance of Th2 cells [16]. Thus, IL-4 is able to regulate the polarization of Th2 cells derived from naive CD4⁺ T cells, and, in addition, it induces a Th2 cell phenotype in differentiated Th cells, including Th17 cells [17].

The pleiotropic cytokine IL-6 plays a key role in T cell activation, proliferation, and survival. Therefore, it is a key factor in the formation and maintenance of the systemic inflammatory process observed in BA. IL-6 is responsible for the imbalance between effector T cells and regulatory T cells (Tregs) [18]. In addition, IL-6 is associated with the stimulation of Th2 responses, as it has the ability to interfere with Th1 differentiation by inducing IL-4 expression on activated T cells [19]. According to recent studies, Th17 and Tregs are linked in a reciprocal relationship in which a switching factor such as IL-6 forms a pathway for Treg to Th17 transition. IL-6 signaling can occur in various ways, the least studied of which is classical signaling through the IL-6R receptor. The information presented on its role in the inflammatory process is rather diverse. There is evidence that classical IL-6 signaling controls the polarization of Th2 cells. Based on the above

mechanisms, elevated levels of the proinflammatory cytokine IL-6 contribute to a more severe course of BA [20]. Published data on the concentration of IL-4 [21] and IL-6 [22] in the blood serum correlate with our results, showing an increase in the level of these cytokines in BA. An increase in their content indicates an increase in systemic inflammation in BA with an increase in the severity of the disease.

Analysis of the receptor apparatus revealed an increase in the expression of IL-4R and IL-6R as the severity of BA progresses. Elevated IL-6 levels combined with increased expression of its receptor on CD4⁺ cells aggravate the inflammatory process and redirect the inflammatory response towards the Th2 type, which has an adverse effect on the clinical status of patients with atopic bronchial asthma. In addition, there is evidence to suggest that this receptor plays a role in the activation of Th cells and the formation of Th17 cells, which may contribute to the aggravation of BA. Conversely, IL-4R activates STAT6 transcription, which promotes the release of IL-4 from cells and enhances IL-4R expression in CD4⁺ cells, thereby stimulating their differentiation into the Th2 phenotype. Due to the ability of these cells to independently release IL-4, a positive feedback loop is established [23]. Such changes may worsen the condition of people with BA, gradually weakening the disease control.

TLRs may be associated with aberrant stimulation of immune responses, contributing to the chronic inflammation observed in BA. Our study showed that TLR2 expression increased in BA vs. the control group, with the comparison of groups revealing the maximum increase in mild BA. TLR4 expression increased in mild BA and moderate well-controlled BA. However, we revealed no statistically significant difference between the control group and partially controlled moderate BA. TLRs serve as key costimulatory and regulatory molecules in T cells. By acting directly on T cells, TLR agonists can enhance cytokine production by activated T cells and increase the sensitivity of T cells to stimulation of their receptors. They also promote long-term memory of T cells and reduce the activity of Tregs [24]. TLR stimulation determines the Th1/Th2 balance and Th17 cell differentiation, and also controls eosinophil activation.

The role of TLR2 and TLR4 in the development and progression of BA remains poorly understood due to inconsistent data on the mechanism of their involvement. It has been found that TLR2 and TLR4, which are expressed on the T cell membrane, have a number of effects. They promote the development of allergic inflammation by stimulating the Th2 immune response, while participating in the initiation of non-Th2 immune response and stimulation of neutrophilic inflammation [4, 25]. It has been shown that costimulatory signals produced by TLR2 induce NF- κ B activation, which in turn leads to increased Th1 signaling. It has been suggested that the stimulatory function of TLR2 in BA depends on the activation of the inflammasome-mediated inflammatory response [17, 26]. Recent studies have shown that TLRs expressed in CD4⁺ T cells promote increased functionality and survival of T cells, which is an unfavorable phenomenon in BA [27]. In addition, TLR signaling specific for CD4⁺ T cells promotes the formation of the Th17 response type and significantly contributes to the chronicity of the systemic inflammatory process.

Calculation of TSS action index values allowed evaluating changes in IL-4 and IL-6 levels, as well as the expression of IL-4R, IL-6R, TLR2 and TLR4 receptors in BA under unfavorable anthropogenic conditions. SSP exposure activates a number of

processes associated with the formation of ROS, stimulation of oxidative stress, initiation of cellular signaling cascades and destabilization of antioxidant mechanisms. This leads to activation of systemic inflammation and respiratory disorders [6, 28]. SSPs trigger signaling pathways that in turn lead to the activation of a complex immune system response involving various cell types, with CD4⁺ cells playing an important role in this process [8].

Our study showed that TSS action index values increase with increasing BA severity both in terms of IL-4 and IL-6 levels and in terms of expression of their receptors in CD4⁺ cells. Exposure to small atmospheric toxic particles leads to a significant increase in IL-4 levels [29], as well as to an increase in IL-6 expression, which is regulated by the TLR2 and TLR4/NBAPH oxidase/AFK/NF- κ B signaling pathway. The key process initiating the cascade of reactions is the activation of the NF- κ B pathway [9, 10]. It was found that TSS action index values for TLR4 expression significantly increase. A decrease in the TSS action index values for TLR2 expression is observed in both well-controlled and partially controlled mild BA, as well as in well-controlled moderate BA. However, an increase in this indicator is observed in partially controlled moderate BA. We believe that this finding implies an existence of a compensatory relationship between reparative mechanisms and SSP in the case of BA exacerbation.

Hence, under the influence of the SSP in BA, the content of cytokines (IL-4, IL-6) and the expression of specific receptors (IL-4R, IL-6R, TLR2 and TLR4) change. During an exacerbation of BA, instabilities in the cytokine status and the state of the receptor apparatus of CD4⁺ cells are more pronounced, despite the presence of compensatory mechanisms.

Conclusion

Signaling pathways mediated by IL-4R, IL-6R, TLR2 and TLR4 are involved in modulating the functions of CD4⁺ cells. Therefore, these markers can be considered as a diagnostic test indicating the increasing severity of BA via the reflection of systemic inflammatory processes. In well-controlled BA, the greatest differences between the mild and moderate severity groups were observed in the expression of IL-4R (6.8 times) and the expression of IL-6R (1.9 times) in the case of moderate BA. Expression of TLR2 was higher in mild BA. The greatest increase in the level of TLR4 expression (15.5 times) was observed in partially controlled mild BA. When analyzing the TSS action index values, more pronounced changes were observed in moderate BA. In well-controlled BA, the greatest differences in the TSS action index values between the groups with mild and moderate severity were observed for the IL-4R (1.3-fold) and IL-6R (1.6-fold). In partially controlled BA, the most pronounced changes in the TSS action index values were detected for the TLR2 (1.6-fold) and TLR4 (1.3-fold). Our results convincingly indicate that monitoring patients with bronchopulmonary pathology in conditions of an unfavorable technogenic environment is important for timely correction of disorders.

Limitations

The small sample size is a main limitation of the study.

Funding

The study was not supported by external sources.

Conflict of interest

The authors declare no conflicts of interest.

Ethical approval

All procedures in clinical studies were conducted in accordance with the ethical standards of the institutional and national research committee, as well as the 1964 Declaration of Helsinki and its later amendments.

References

- Novgorodtseva TP, Gvozdenko TA, Vitkina TI, Denisenko YK, Antonyuk MV, Knyshova VV. Regulatory signal mechanisms of systemic inflammation in respiratory pathology. *Russ Open Med J* 2019; 8: 0106. <https://doi.org/10.15275/rusomj.2019.0106>.
- Nur Husna SM, Md Shukri N, Mohd Ashari NS, Wong KK. IL-4/IL-13 axis as therapeutic targets in allergic rhinitis and asthma. *Peer J* 2022; 10: e13444. <https://doi.org/10.7717/peerj.13444>.
- Jevnikar Z, Ostling J, Ax E, Calven J, Thörn K, Israelsson E, et al. Unbiased biomarkers in prediction of respiratory disease outcomes study group. epithelial il-6 trans-signaling defines a new asthma phenotype with increased airway inflammation. *J Allergy Clin Immunol* 2019; 143(2): 577-590. <https://doi.org/10.1016/j.jaci.2018.05.026>.
- Kytikova OYu, Novgorodtseva TP, Denisenko YuK, Antonyuk MV, Gvozdenko T.A. Toll-like receptors in pathophysiology of asthma. *Pulmonologiya* 2021; 31(3): 348-354. Russian. <https://doi.org/10.18093/0869-0189-2021-31-3-348-354>.
- Kondratyeva EV, Veremchuk LV, Vitkina TI. Impact of air dust fractions on the immune system in patients with bronchopulmonary pathology. *Bulletin Physiology and Pathology of Respiration* 2023; (88): 27-34. Russian. <https://doi.org/10.36604/1998-5029-2023-88-27-34>.
- Veremchuk LV, Vitkina TI, Barskova LS, Gvozdenko TA, Mineeva EE. Estimation of the size distribution of suspended particulate matters in the urban atmospheric surface layer and its influence on bronchopulmonary pathology. *Atmosphere* 2021; 12(8): 1010. <https://doi.org/10.3390/atmos12081010>.
- Hou T, Zhu L, Wang Y, Peng L. Oxidative stress is the pivot for PM2.5-induced lung injury. *Food Chem Toxicol* 2024; 184: 114362. <https://doi.org/10.1016/j.fct.2023.114362>.
- Glencross DA, Ho TR, Camina N, Hawrylowicz CM, Pfeffer PE. Air pollution and its effects on the immune system. *Free Radic Biol Med* 2020; 151: 56-68. <https://doi.org/10.1016/j.freeradbiomed.2020.01.179>.
- Vo TTT, Hsu CY, Wee Y, Chen YL, Cheng HC, Wu CZ, et al. Carbon monoxide-releasing molecule-2 ameliorates particulate matter-induced aorta inflammation via Toll-Like receptor/NADPH Oxidase/ROS/NF-κB/IL-6 Inhibition. *Oxid Med Cell Longev* 2021; 2021: 2855042. <https://doi.org/10.1155/2021/2855042>.
- Vo TTT, Wee Y, Chen YL, Cheng HC, Tuan VP, Lee IT. Surfactin attenuates particulate matter-induced COX-2-dependent PGE2 production in human gingival fibroblasts by inhibiting TLR2 and TLR4/MyD88/NADPH oxidase/ROS/PI3K/Akt/NF-κB signaling pathway. *J Periodontal Res* 2021; 56(6): 1185-1199. <https://doi.org/10.1111/jre.12932>.
- Kondratyeva EV, Vitkina TI, Veremchuk LV. Atmospheric ground layer pollution by suspended solid particles in areas with different technogenic loads. *Bulletin Physiology and Pathology of Respiration* 2024; (91): 68-76. Russian. <https://doi.org/10.36604/1998-5029-2024-91-68-76>.
- Antonyuk MV, Gvozdenko TA, Novgorodtseva TP, Vitkina TI, Geltser BI, Yurenko AV, et al. Features of cytokine profile in patients with bronchial asthma in combination with obesity. *Medical Immunology (Russia)* 2018; 20(6): 913-920. Russian. <https://doi.org/10.15789/1563-0625-2018-6-913-920>.
- Vitkina TI, Novgorodtseva TP, Kalinina EP, Lobanova EG, Antonyuk MV. Immune mechanisms for development of controlled and partially controlled asthma. *Medical Immunology (Russia)* 2019; 21(3): 495-502. Russian. <https://doi.org/10.15789/1563-0625-2019-3-495-502>.
- Hammad H, Lambrecht BN. The basic immunology of asthma. *Cell* 2021; 184(6): 1469-1485. <https://doi.org/10.1016/j.cell.2021.02.016>.
- Maspero J, Adir Y, Al-Ahmad M, Celis-Preciado CA, Colodenco FD, Giavina-Bianchi P, et al. Type 2 inflammation in asthma and other airway diseases. *ERJ Open Res* 2022; 8(3): 00576-2021. <https://doi.org/10.1183/23120541.00576-2021>.
- Keegan AD, Leonard WJ, Zhu J. Recent advances in understanding the role of IL-4 signaling. *Fac Rev* 2021; 10: 71. <https://doi.org/10.12703/r/10-71>.
- Fang F, Cao W, Mu Y, Okuyama H, Li L, Qiu J, et al. IL-4 prevents adenosine-mediated immunoregulation by inhibiting CD39 expression. *JCI Insight* 2022; 7(12): e157509. <https://doi.org/10.1172/jci.insight.157509>.
- Schumacher N, Rose-John S. ADAM17 Activity and IL-6 trans-signaling in inflammation and cancer. *Cancers (Basel)* 2019; 11(11): 1736. <https://doi.org/10.3390/cancers11111736>.
- Garbers C, Heink S, Korn T, Rose-John S. Interleukin-6: designing specific therapeutics for a complex cytokine. *Nat Rev Drug Discov* 2018; 17(6): 395-412. <https://doi.org/10.1038/nrd.2018.45>.
- Lambrecht BN, Hammad H, Fahy JV. The cytokines of asthma. *Immunity* 2019; 50(4): 975-991. <https://doi.org/10.1016/j.immuni.2019.03.018>.
- Aghajani M, Rafiei A, Ghaffari J, Valadan R, Kardan M, Soltani M, et al. Immune dysregulation in children with allergic asthma: A close relationship between IL-17 but not IL-4 or IFN-γ. *Research in Molecular Medicine* 2019; 6(1): 16-29. <https://doi.org/10.18502/rmm.v6i1.3926>.
- Pan R, Kuai S, Li Q, Zhu X, Wang T, Cui Y. Diagnostic value of IL-6 for patients with asthma: A meta-analysis. *Allergy Asthma Clin Immunol* 2023; 19(1): 39. <https://doi.org/10.1186/s13223-023-00794-3>.
- Xu E, Pereira MMA, Karakasilioti I, Theurich S, Al-Maarri M, Rappl G, et al. Temporal and tissue-specific requirements for T-lymphocyte IL-6 signalling in obesity-associated inflammation and insulin resistance. *Nat Commun* 2017; 8: 14803. <https://doi.org/10.1038/ncomms14803>.
- Nouri Y, Weinkove R, Perret R. T-cell intrinsic Toll-like receptor signaling: implications for cancer immunotherapy and CAR T-cells. *J Immunother Cancer* 2021; 9(11): e003065. <https://doi.org/10.1136/jitc-2021-003065>.
- Wenger M, Grosse-Kathoefer S, Kraiem A, Pelamatti E, Nunes N, Pointner L, et al. When the allergy alarm bells toll: The role of toll-like receptors in allergic diseases and treatment. *Front Mol Biosci* 2023; 10: 1204025. <https://doi.org/10.3389/fmolb.2023.1204025>.
- Sha JF, Xie QM, Chen N, Song SM, Ruan Y, Zhao CC, et al. TLR2-hif1α-mediated glycolysis contributes to pyroptosis and oxidative stress in allergic airway inflammation. *Free Radic Biol Med* 2023; 200: 102-116. <https://doi.org/10.1016/j.freeradbiomed.2023.03.007>.
- Zhang E, Ma Z, Lu M. Contribution of T- and B-cell intrinsic toll-like receptors to the adaptive immune response in viral infectious diseases. *Cell Mol Life Sci* 2022; 79(11): 547. <https://doi.org/10.1007/s00018-022-04582-x>.
- Sinha A, Pritam JA, Jain HK, Giri S, Pati S, Kshatri JS. Seasonal variations in respiratory morbidity in primary care and its correlation with the quality of air in urban Odisha, India. *PLOS Glob Public Health* 2024; 4(1): e0002313. <https://doi.org/10.1371/journal.pgph.0002313>.
- Zhou J, Geng F, Xu J, Peng L, Ye X, Yang D, et al. PM2.5 exposure and cold stress exacerbates asthma in mice by increasing histone acetylation in IL-4 gene promoter in CD4+ T cells. *Toxicol Lett* 2019; 316: 147-153. <https://doi.org/10.1016/j.toxlet.2019.09.011>.

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