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ПОПУЛЯЦИОННЫЙ СОСТАВ CD4⁺5RA/CD4⁺5RO ПОЗИТИВНЫХ Т-ЛИМФОЦИТОВ И ЦИТОКИНОВЫЙ ПРОФИЛЬ У ДЕТЕЙ С АЛЛЕРГИЧЕСКИМИ РЕСПИРАТОРНЫМИ ЗАБОЛЕВАНИЯМИ

Турянская А.И., Плехова Н.Г., Сабыныч В.А., Просекова Е.В.

ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ, г. Владивосток, Россия

Резюме. Изменения Т-клеточных популяций, ответственных за хроническое течение аллергического воспаления и заболеваний, в том числе бронхиальной астмы, пока еще недостаточно изучены. Целью этого исследования было выявление фенотипических изменений в популяциях CD45RA/CD45RO позитивных Т-лимфоцитах и уровней регуляторных цитокинов (TNFα, IFNγ, IL-4, IL-6, IL-8, IL-10, IL-13, IL-17A, IL-17F) при аллергических респираторных заболеваниях (АЗ) у детей. В образцах крови у 90 детей в возрасте от 3 до 11 лет (60 больных с АЗ и 30 здоровых ровесников) исследовали иммунные клеточные популяции и показатели цитокинов. Уровни IL-4, IL-8, IL-10, IL-13, IL-17A и IL-17F в сыворотке крови детей с бронхиальной астмой и аллергическим ринитом отличались от соответствующих показателей в контрольной группе ($p = 0,001$). Содержание $CD3^+CD8^+CD45RACD45RO^+$ клеток, Т-хелперов ($p < 0,05$) и Th-эффекторов, одновременно экспрессирующих обе изоформы $CD45RA^+$ и CD45RO рецептора в периферической крови детей с АЗ, значительно превышало таковые показатели в контрольной группе ($p < 0,001$). У здоровых детей популяция Th17 (лимфоциты фенотипа $CD3^+CD4^+CD196$) составляла 9,49±1,6% $CD3^+CD4^+$ клеток; число таких лимфоцитов значительно повышалось (до 14,5±0,77%) у детей с АЗ ($p < 0,001$). Абсолютное содержание $Th17^+$ клеток составляло 93,0±9,30 и 127,0±72,0 клеток/мкл соответственно ($p = 0,002$). Показатели CD4CD45RO позитивных клеток памяти у детей с АЗ оказалось значительно ниже ($p < 0,001$), тогда как количество $CD3^+CD19^+$ клеток было повышенным по сравнению со здоровыми ровесниками ($p < 0,05$). Абсолютное содержание этих клеток не различалось между этими группами. Число $CD8^+CD45RO^+$Т-лимфоцитов было значительно выше у детей с аллергическими заболеваниями ($p < 0,025$). Данное исследование показывает, что количественное соотношение $CD3^+CD8^+CD45RA^+$ и $CD3^+CD8^+CD45RO^+$Т-клеточных популяций, а также повышение уровней цитокинов, синтезируемых по Th2-, Th17-пути, в периферической крови может быть полезным для понимания генеза респираторных аллергий, и эти данные расширяют наше знание об иммунных механизмах аллергических расстройств с целью индивидуализации терапевтических программ.

Ключевые слова: Т-лимфоциты, Т-хелперы, цитокины, аллергический ринит, атопическая бронхиальная астма, дети

Адрес для переписки:

Плехова Наталья Геннадьевна
ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ
690002, Россия, г. Владивосток, пр. Острякова, 2.
Тел./факс: 8 (423) 242-97-78.
E-mail: pl_nat@hotmail.com

Address for correspondence:

Plekhova Natalia G.
Pacific State Medical University
690002, Russian Federation, Vladivostok, Ostryakov ave., 2.
Phone/fax: 7 (423) 242-97-78.
E-mail: pl_nat@hotmail.com

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POPULATIONAL COMPOSITION OF CD4+5RA/CD4+5RO POSITIVE T LYMPHOCYTES AND CYTOKINE PROFILE IN CHILDREN WITH ALLERGIC RESPIRATORY DISEASES

Turyanskaya A.I., Plekhova N.G., Sabynych V.A., Prosekova E.V.

Pacific State Medical University, Vladivostok, Russian Federation

Abstract. The changing states of T cell populations responsible for the chronic course of allergic inflammation and diseases, including allergic bronchial asthma, are not yet sufficiently characterized. The aim of this study was to detect phenotypic changes in the CD45RA/CD45RO positive T lymphocytes and the level of regulatory cytokines (TNFα, IFNγ, IL-4, IL-6, IL-8, IL-10, IL-13, IL-17A, IL-17F) in allergic respiratory diseases (ARD) in children. In blood of 90 children aged 3-11 (60 children with ARD and 30 healthy peers) were studied of the immune cellular populations and cytokine indices.

The levels of IL-4, IL-8, IL-10, IL-13, IL-17A and IL-17F in blood serum of children with bronchial asthma and allergic rhinitis differed from appropriate indices in control group ($p = 0.001$). The quantity of $CD3^+CD8^+CD45RACD45RO^+$ cells, T helpers ($p < 0.05$) and Th effectors simultaneously expressing both isoforms of the $CD45RA^+$ and CD45RO receptor in peripheral blood of children with ARD significantly exceeded those in control group ($p < 0.001$). In healthy children, Th17 population ($CD3^+CD4^+CD196$ lymphocytes) comprised 9.49±1.6% of $CD3^+CD4^+$ of cells, the number of such lymphocytes was significantly increased to 14.5±0.77 in children with allergic diseases ($p < 0.001$). Absolute numbers of $Th17^+$ cells were 93.0±9.30 and 127,0±72.0 cells/μl respectively ($p = 0.002$). Indicators of CD4CD45RO positive memory cells in children with ARD was determined as significantly lower ($p < 0.001$), whereas quantity of $CD3^+CD19^+$ proved to be higher ($p < 0.05$) than in healthy peers. Absolute counts of these cells did not differ between the groups. The number of $CD8^+CD45RO^+$T lymphocytes was significantly higher in children with allergic diseases ($p < 0.025$). This research shows that the quantitative ratio of $CD3^+CD8^+CD45RA^+$ and $CD3^+CD8^+CD45RO^+$ populations of T cells, and increased levels of cytokines, synthesizable *via* Th2 and Th17, in peripheral blood may be helpful for understanding genesis of allergic respiratory diseases, and extends our knowledge on immune mechanisms of allergic disorders for individualization of therapeutic programs.

Keywords: T lymphocytes, T helpers, cytokine, allergic rhinitis, atopic bronchial asthma, children

Introduction

In case of allergic diseases, imbalance in regulation of immune response to antigen is accompanied by decrease of suppressive activity of regulatory T cells, production of specific immunoglobulin antibodies IgE or implementation of delayed-type hypersensitivity reaction and allergic inflammation. The role of activated $CD4^+$T cells of memory as the main producer of cytokines of activated T helpers of type 2 (Th2) in allergic bronchial asthma and a number of other atopic diseases has been proven. Cytokines of Th2 profile – IL-4 and IL-13 interact with resident cells of pulmonary tract, including epithelium, myofibroblasts and smooth muscle cells, as a consequence affects pathophysiological features of implementation of inflammation in bronchial asthma [3, 15]. Originally was considered that the specified Th2 cytokine generally were produced by $CD3^+CD4^+$T cells, the ability to synthesize them and $CD3^+CD8^+$T cells is currently shown, were found allergen – specific $CD3^+CD8^+$ of the T cell [7]. Suggested, that an increase in the number of activated T cells of memory (CD54RO/CD25) in the lungs or peripheral blood indicated chronic inflammation in asthma. $CD3^+CD4^+$ populations (Th1, Th2, Th9, Th17, Th22, Treg and Tfh), $CD3^+CD8^+$ of memory and effector subpopulations differ on extracellular (CD25, CD45RO, CD45RA, CCR-7, L-Selectin [CD62L], etc.) and intracellular to markers (FOXP3), epigenetic and genetic programs and metabolic ways (catabolic or anabolic) that defines their pathogenic value in development of allergic inflammation.

Differentiation of naive T cells into functionally complete effectors is accompanied by acquisition of a characteristic cytokine profile, which, as a result, determines their functional activity. Thus, subpopulations $CD4^+$T lymphocytes – T helpers (Th) are responsible for the formation of cell-mediated and acquired types of immune response and these cells are phenotypically highly heterogenic. Under the influence of the various cytokine produced by $CD3^+$

CD4+ lymphocytes various subpopulations of T helpers (Th) are formed: Th1 are the cells synthesizing interferon – gamma (IFNγ), Th2 – the producing IL-4, IL-5 and IL-13, regulatory T cells, Treg capable to synthesis of TGF-β and expression of a transcription factor of FoxP3 [12, 15]. Antigen expressed T cells by phenotypic characteristics are divided into populations of effector and T cells of memory, the latest are divided into T cells with effector memory by expression of CCR7 receptor (Tem) and central memory of CCR7 (Tcm) [6]. It has been previously reported that memory T cells are associated with chronic inflammatory diseases [8]. However, specific subpopulations of human memory T cells, which are responsible for the chronic course of allergic inflammation and diseases, including allergic bronchial asthma, are not yet sufficiently characterized.

Correlation of plasticity of T subpopulations and possibility of cell transition from one population to another depending on microenvironment, type of obtained cytokine signals and other factors are shown [9]. Development of inflammatory process in respiratory tract in case of allergic diseases is accompanied by participation of different populations of immunocompetent cells and mediators of inflammation. Among pathogenetic mechanisms of bronchial hyperreactivity the dysregulation of the immune answer with changes of activity and a ratio of subpopulations of Th1, Th2, Th9 and Treg is noted. Locally, numerous extracellular messengers are contained in the focus of allergic inflammation in addition to activated immune cells, which act as the main initiators of T helper cell plasticity. Polarization of cells of Th2 in Th0 is initiated by IL-4 and the main effector cytokine of Th2 of cells IL-4, IL-5 and IL-13. Th17 after stimulation of TGF, IL-6 and IL-21 produce IL-17A, IL-17F, IL-22 and IL-26 and also IL-6 and IL-21 as positive loopback cytokine with feedback [13, 15].

The aim of the study is to detect phenotypic changes in the CD45RA/CD45RO of positive T lymphocytes and the level of regulatory cytokines (TNFα, IFNγ, IL-4, IL-6, IL-8, IL-10, IL-13, IL-17A, IL-17F) in allergic respiratory diseases in children.

Materials and methods

The study included 90 children aged 3-11, among them 60 children with a verified diagnosis of allergen-induced bronchial asthma phenotype with mild (11.67%) and moderate severity (88.33%) clinical course of disease (44 (73.33%) bronchial asthma children combined with allergic rhinitis) and 30 healthy peers who made up the comparison (control) group. All children were observed in RSBHI "Vladivostok Clinical and Diagnostic Center". Verification of the disease phenotype was carried out in accordance with the recommendations of the international conciliation documents PRACTICAL (2008), European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Global Strategy for Asthma Management and Prevention (2018) and ARIA (2016). The criteria for exclusion from the study were up to 3 years of age and older than 11 years, virus-induced phenotype, severe course of bronchial asthma and use of immunocorrective drugs in the previous six months. The design of the study was approved by the Interdisciplinary Ethics Committee of Pacific State Medical University 23.06.2014, Protocol No. 7.

Immunophenotyping of the cells was carried out using human-specific mouse monoclonal antibodies conjugated with FITC, phycoerythrin (PE), allophycocyanin (APC) and VioBlue (Miltenyi Biotec GmbH, Germany). Immunological study included determination of T lymphocyte ($CD3^+$) populations, T helpers ($CD3^+CD4^+$), cytotoxic T cells ($CD3^+CD8^+$), B lymphocytes ($CD19^+$)As well as determining the expression of the differentiation antigen CD45 with the RA and RO isoforms (Clone T6D11 and REA611 respectively, Miltenyi Biotec GmbH, Germany) on subpopulations of naive T lymphocytes ($CD3^+CD4^+CD45RA^+$), "terminally differentiated" CD45RO – positive Th-cells memories ($CD3^+CD4^+CD45RA$ $CD45RO^+$) and also the bearing two isoforms a double – positive transitional Th-cells ($CD3^+CD4^+CD45RA$ $CD45RO^+$). Th17 cells were identified as $CD3^+CD4^+$ positive events with an additional signal for receptor expression to Th17 cell-specific chemokine CCR6 (CD196 (CCR6) -APC clone REA277; Miltenyi Biotec GmbH, Germany). For determination of intracellular content of cytokine of IL-17 used monoclonal antibodies against IL-17A (REA1063 clone), marked PE-Vio770, isotypic control of an antibody against REA (Miltenyi Biotec GmbH, Germany). Lymphocyte subpopulation was determined by multicolor flow cytometry using MACSQuant TM Analyzer 10 (Miltenyi Biotec GmbH, Germany). The data were analyzed by gaining at least 30,000 leukocytes in the sample. The population of $CD3^+$ PE-labeled lymphocytes was gated using fluorescent channel (FL3) and lateral light scattering parameter (SSC). Respectively, two-parameter a pillbox rafts $CD3^+CD4^+CD45RA^+CD4^+5RO^+$ (Th eff), $CD3^+CD4^+CD196^+$ (Th17 $CD196^+$) and $CD3^+CD4^+IL\text{-}17A^+$ (Th IL-17A) were created for assessment of percentage of $CD3^+CD4^+CD45RA^+$ (Th naive), $CD3^+CD4^+CD45RA$ $CD45RO^+$ (Th em, effector T cells of memory) [5].

Concentration of interleukins (TNFα, IFNγ, IL-4, IL-6, IL-8, IL-10, IL-13, IL-17A, IL-17F) and IgE in serum of blood determined by method of the

solid-phase enzyme immunodetection with use of sets of reactants according to the enclosed instruction (interleukins in pg/ml, reactants of eBiociens, Bender Medsystems GmbH, Austria, IgE in IU/ml, LLC Alcor Company of Biot, St. Petersburg).

For statistical processing of digital data used methods parametrical (at normal distribution of indicators and coefficient of a variation of CV ≤ 30%) and nonparametric (at distribution, other than normal, and coefficient of a variation of CV > 30%) statistics with use of the Statistica 10 program. The arithmetic mean (M), median (Me), quadratic mean deviation ([alpha]), arithmetic mean error (± m), upper and lower quartile ($Q_{0.25}$-$Q_{0.75}$), confidence interval (CI), index validity factor (t) and differences (t and p) were counted. Correlation analysis techniques were used in calculating the Spirman rank correlation coefficient with checking the normality of the characteristic value distribution (Shapiro–Wilk). The scope of the studies carried out and the use of the corresponding statistical methods allowed to estimate the results with reliability and critical level of significance $p < 0.05$.

Results and discussion

In children with allergic respiratory diseases compared to healthy peers, there was an increase in the specific weight and absolute amount of eosinophils in peripheral blood ($p < 0.01$) and serum total IgE content (318, 20±25.23 IU/ml (CI 306.69-443.89 IU/ml and 51, 80±14.19 IU/ml (CI 25.95-79.96 IU/ml respectively $p < 0.01$). At bronchial asthma and allergic rhinitis at children indicators of IL-4, IL-8, IL-10, IL-13, IL-17A and IL-17F in serum of blood differed with indicators of group of control (Figure 1). The serum IL-17A content of children with allergic diseases ranged from 89.8 to 365.5 pg/ml (123.7 [107-139]) and was significantly higher ($p = 0.0001$) in the group of healthy children (from 23.8 to 97.9 pg/ml (68.7 [47.4-83.3]), Figure 1G). Serum IL-17F levels in children with allergic diseases ranged from 19.2 to 76.0 pg/ml (28.6 [25.2-36.5]) and did not differ significantly with those of healthy peers (21.6-76.0 pg/ml (27.7 [25.3-35.0]). In the isolated course of bronchial asthma and in combination with allergic rhinitis, an increase in the concentration of interleukins 4,8,13

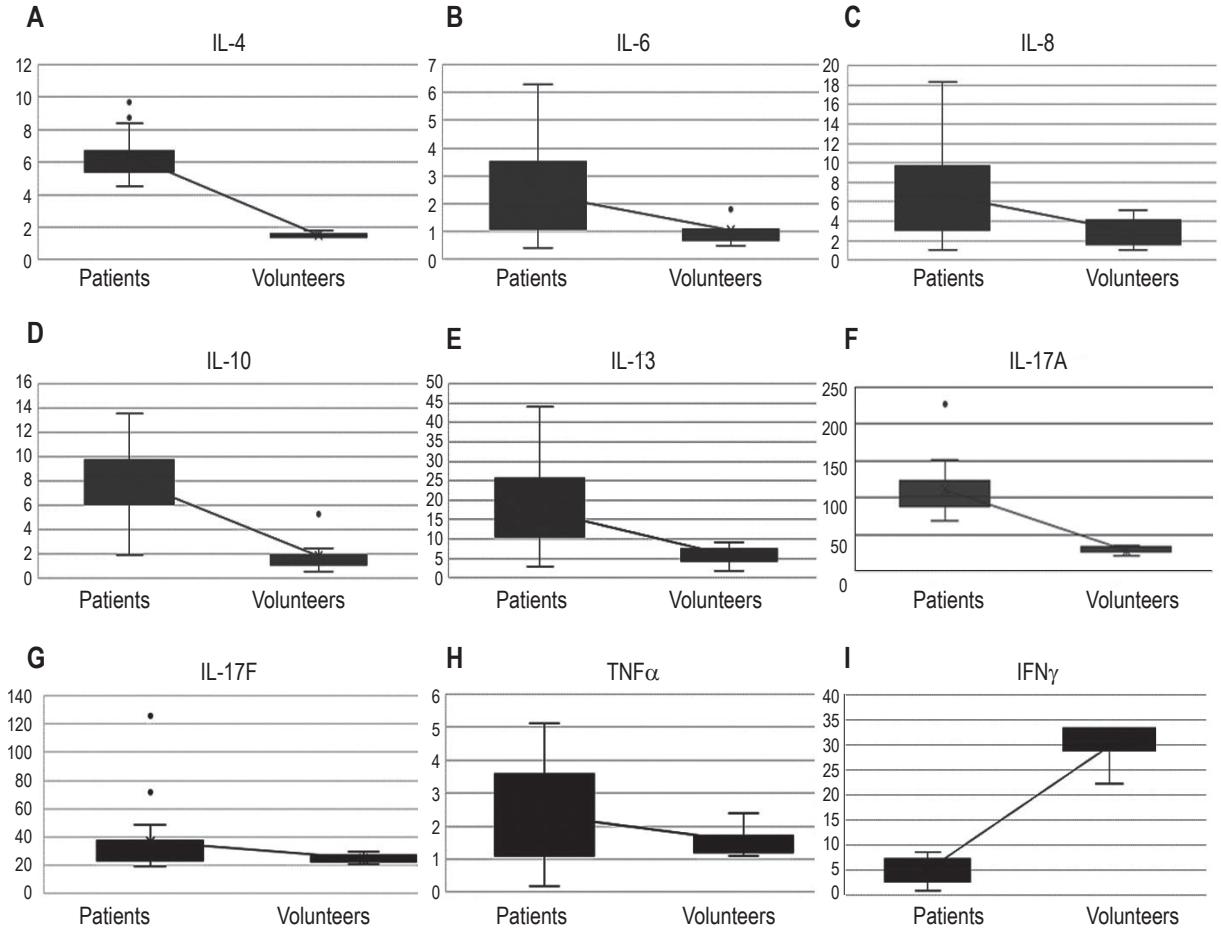

Figure 1. Cytokine content in the blood serum of children with allergic respiratory diseases and healthy peers

and 17A was detected with a decrease in the production of interferon gamma without significant differences depending on the prevalence of allergic inflammation. At healthy children indicators of interleukins in serum of blood varied in the range from several units of (IL-4, IL-8, IL-13) up to several tens (IL-17A, IL-17F, IFNγ) picograms in a milliliter with the confidential intervals (CI) of IL-4 – 1.44-1.54 pg/ml; IL-8 – 2.41-3.18 pg/ml; IL-13 – 4.34-5.78 pg/ml; IL-17A – 21.78-25.69 pg/ml; IL-17F – 24.51-26.89 pg/ml; IFNγ – 28.62-30.58 pg/ml. At children with allergic diseases straight lines of weak force of correlation between indicators of IL-17A and IL-17F, IL-13 and IL-4 and the return orientation of interrelation are noted IL-8 with IL-17A and IFNγ, IL-13 with IL-17F and IFNγ are revealed between IL-4 with IL-8 and IL-17F, at reliability of negative correlation of indicators of IL-17F with IL-4 and IFNγ.

The primary contact of naive T cells with the antigen is accompanied by their clonal expansion and differentiation into different subpopulations of effector cells. Phenotypical sign of a differentiation of naive T lymphocytes is the expression on a CD45RO isoform surface instead of the CD45RA isoform [4, 11]. The cytometric analysis at healthy and children with allergic diseases of respiratory organs did not reveal statistically significant differences in the percentage of populations of $CD3^+$, $CD8^+$, $CD8^+CD45RA$ and $CD4^+CD45RA$ $CD45RO^-$ (Figure 2). The specific gravity and absolute number of $CD3^+CD8^+CD45RA^-$ $CD45RO^+$ cells in the peripheral blood of children with allergic diseases significantly ($p < 0.001$) exceeded those in the control group (Figure 2B). Decrease in percent of CD3CD45RA of positive cells and CD3CD45RO indicates increase in a pool of the differentiated cells which are not bearing an isoforms

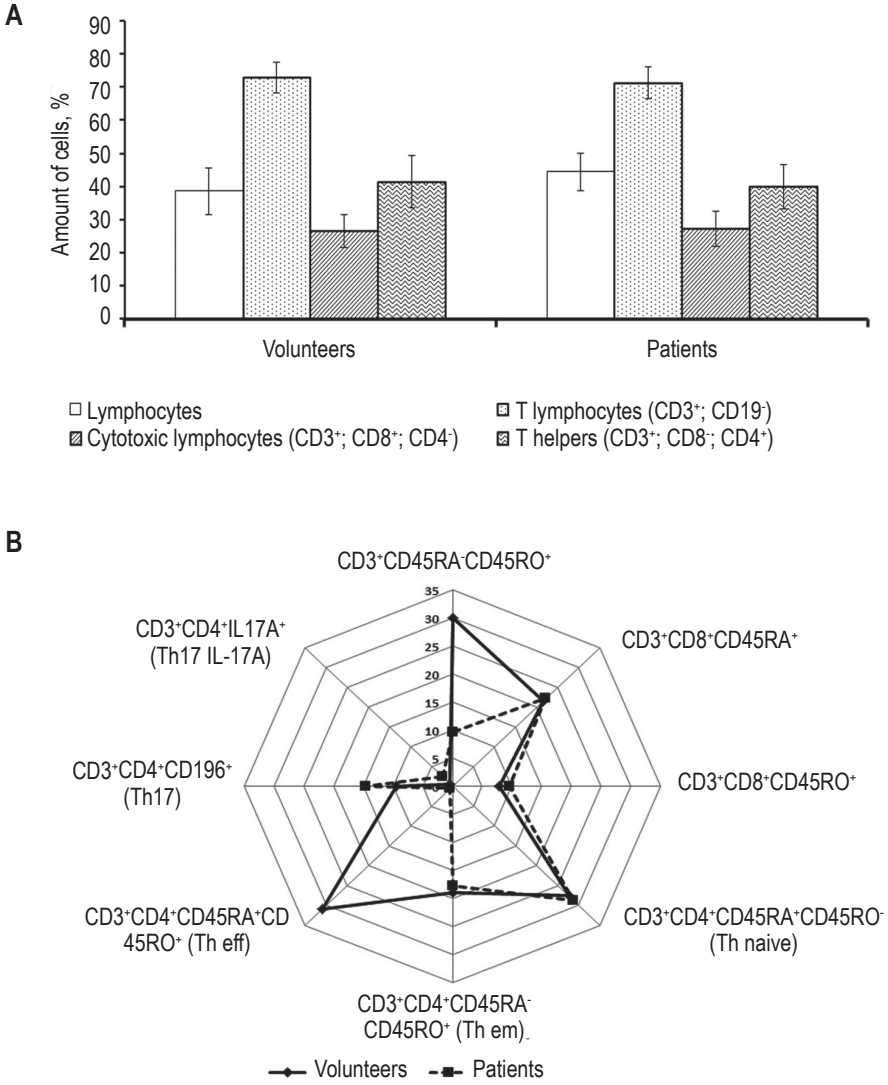

Figure 2. Structural-quantitative characterization of lymphocyte and T cell subpopulations in peripheral blood of children with allergic diseases of respiratory organs and healthy peers

of a receptor of CD45RO and CD45RA on the surface. In children in allergic bronchial asthma, in combination with allergic asthma, there was a tendency to increase the differentiated population of CD3CD4 positive T helpers ($p < 0.05$) and to increase the amount of Th effector type expressing both isoforms of the $CD4^+5RA$ and CD45RO receptor at one time ($p < 0.01$). The specific weight in children with allergic respiratory diseases CD4CD45RO positive memory cells was determined significantly lower ($p < 0.001$) and $CD3^+CD19^+$ higher ($p < 0.05$) than in healthy peers. The absolute number of these cells did not differ between groups. The number of $CD8^+CD45RO^+$T lymphocytes was significantly higher in children with allergic diseases ($p < 0.025$) (Figure 2B).

CD196 selectively binds chemokine MIP-3α/CCL20, which is secreted by many cells and tissues of the body. When interacting with chemokines, chemotactic activity of immature memory T cells and conversion to Th17 are induced [15]. The cytometric analysis showed that at healthy children Th17 population ($CD3^+CD4^+$CD196 lymphocytes) made 9.49±1.6% of $CD3^+CD4^+$ of cells (Figure 2B), the number of such lymphocytes was significantly increased to 14,5±0.77 in children with allergic diseases ($p < 0.001$). Absolute numbers of Th17 were 93,0±9.30 and 127, 0±72.0 kl/μl respectively ($p = 0.002$). Correlation analysis showed no significant dependence on age and period of disease ($r_2 = 0.12$, $p = 0.21$ control group and $r_2 = 0.06$, $p = 0.25$ children with allergic diseases). When the age adjustment was taken into account, the frequency of difference in Th17 between the two groups was 0.013. Similar data were obtained from the cell population of the production-positive IL-17A Th17. In group of control the percent of population of IL-17A of positive cells made 0.53±0.08% of $CD3^+CD4^+$ of lymphocytes, at children with bronchial asthma and allergic renitis made 2.38±0.70% ($p < 0.001$).

The peripheral blood of patients with bronchial asthma shows an imbalance in the quantitative ratio of T cells, more pronounced when the disease is exacerbated by allergen exposure. In this study, in children with allergic respiratory diseases compared to healthy peers, there were no differences in the percentage and quantity of CD3 and CD8 positive T cells, with an increase in specific gravity and absolute number of T helper population, which is consistent with the data of other authors [3].

At patients with allergic diseases showed a change in the subpopulations of memory T cells $CD4^+$ and $CD8^+$ positive T lymphocytes, the percentage of $CD4^+CD45RO^+$ cells was significantly lower than in healthy individuals, with no difference between absolute values. The decrease in specific gravity $CD4^+CD45RO^+$T cells is likely due to the withdrawal of this population from peripheral blood to the site of inflammation. This assumption is supported by evidence of decreased CD45RO receptor expression on sputum T cells in patients with bronchial asthma associated with oral glucocorticoid administration [8, 10]. In the real research the correlation between weight of a course of a disease and degree of an expression of a marker of cells of memory (CD45RO) on $CD4^+$T cells is not revealed, at higher percent of $CD4^+CD45RO^+$ of T cells of children with an allergopathology. The increase in the number of CD8CD45RO positive T cells found in allergic diseases illustrates the involvement of these cells in immune mechanisms of allergic inflammation. They are able to secrete profile Th2 cytokines, including IL-4, IL-5 and IL-13. Indicate the relationship of the number of $CD8^+$T cells in the bronchial biopsy in asthma to the decrease in lung function [14].

Maturing T cells are known to change the set of chemokine receptors and adhesion molecules depending on extracellular signals, which determines their movement to the zone of performance of specific effector functions. In allergic bronchial asthma, CCR6 expression plays an important role in regulating the recruitment of effector T cells in tissue [3]. In bronchial tubes at bronchial asthma of Th17 lymphocytes influence products of a mucin and a hyperplasia of goblet cell, by synthesis of cytokine of IL-17A. IL-17F together with IL-17A causes chemokine production, affects mRNA transcription and protein translation [1, 2]. In the conducted research at children with allergic diseases of respiratory organs the imbalance in subpopulation structure T helper due to prevalence of Th2 and Th17, activation of synthesis of IL-17A, IL-4, IL-8, IL-13, the low IFNγ level, changes of force and orientation of interrelations of a cytokine profile and range T subpopulations is revealed.

Conclusion

At allergic diseases of respiratory organs at children tension of T cellular immunity, decrease in maintenance of T cells of memory and increase in quantity of Th2 and Th17, reduction of long-living population of $CD3^+CD4^+CD45RA^+CD45RO^+$ (Th eff) is defined. This research illustrates that the quantitative ratio of populations of $CD3^+CD8^+CD45RA^+$ and $CD3^+CD8^+CD45RO^+$ of T cells and increase in level of cytokine, synthesizable Th2 and Th17, in peripheral blood informatively at realization of allergic diseases of respiratory organs and supplements knowledge of immune mechanisms of pathogenesis of allergic diseases for individualization of programs of therapy.

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Авторы:

Турянская А.И. *— ассистент кафедры клинической лабораторной диагностики, общей и клинической иммунологии, аспирант ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ, г. Владивосток, Россия*

Плехова Н.Г. *— д.б.н., заведующая центральной научно-исследовательской лабораторией, профессор кафедры клинической лабораторной диагностики, общей и клинической иммунологии ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ, г. Владивосток, Россия*

Authors:

Turyanskaya A.I., *Assistant Professor, Department of Clinical Laboratory Diagnostics and General and Clinical Immunology, Postgraduate Student, Pacific State Medical University, Vladivostok, Russian Federation*

Plekhova N.G., *PhD, MD (Biology), Head, Central Research Laboratory, Professor, Department of Clinical Laboratory Diagnostics and General and Clinical Immunology, Pacific State Medical University, Vladivostok, Russian Federation*

Сабыныч В.А. *– к.м.н., доцент кафедры клинической лабораторной диагностики, общей и клинической иммунологии ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ, г. Владивосток, Россия*

Sabynych V.A., *PhD (Medicine), Associate Professor, Department of Clinical Laboratory Diagnostics and General and Clinical Immunology, Pacific State Medical University, Vladivostok, Russian Federation*

Просекова Е.В. *– д.м.н., профессор, заведующая кафедрой клинической лабораторной диагностики, общей и клинической иммунологии ФГБОУ ВО «Тихоокеанский государственный медицинский университет» Министерства здравоохранения РФ, г. Владивосток, Россия*

Prosekova E.V., *PhD, MD (Medicine), Professor, Head, Department of Clinical Laboratory Diagnostics and General and Clinical Immunology, Pacific State Medical University, Vladivostok, Russian Federation*

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