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Molecular mechanisms of inflammation in the pathogenesis of respiratory disorders in patients with pulmonary tuberculosis

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ABSTRACT

Aim. To assess external respiration (ER) and its relationship with the activity of enzymes involved in purine metabolism in patients with acute and chronic forms of pulmonary tuberculosis (TB).

Materials and methods. In patients with acute and chronic TB, we assessed the activity of adenosine deaminase (ADA)-1, 2 in the blood serum (eADA), mononuclear cells, and neutrophils, the concentration of ecto-5'-nucleotidase (eNT5E) in the blood serum, the level of CD26 (dipeptidyl peptidase-4, DPPIV) in the blood serum and mononuclear cells, production of reactive oxygen intermediates (ROI) and reactive nitrogen intermediates (RNI) in mononuclear cells and neutrophils, as well as parameters of ER.

Results. Patients with TB were found to have an increase in the concentration of eNT5E and eADA-2 activity in the blood serum, stimulated production of ROI in neutrophils, a decrease in the concentration of DPPIV (CD26) in mononuclear cells, and a fall in the production of RNI in mononuclear cells and neutrophils. In patients with chronic TB, a decrease in the activity of ADA-1 in mononuclear cells and a fall in the concentration of DPPIV (CD26) in the blood serum were noted. In patients with acute TB, a decrease in the activity of eADA-1 in the blood serum and ADA-1 in neutrophils, reduced production of ROI in mononuclear cells, and an increase in spontaneous production of ROI in neutrophils were revealed. Correlations were found between the parameters of ER and the concentration of eNT5E in the blood serum, spontaneous production of ROI in mononuclear cells and production of RNI in neutrophils in chronic TB, as well as between eADA-2 in the blood serum, ADA-1 in neutrophils, DPPIV (CD26) activity in mononuclear cells, and ROI and RNI production in mononuclear cells and neutrophils.

Conclusion. The data obtained make it possible to associate regulation of external respiration with parameters of purine metabolism, in particular with the concentration and activity of enzymes responsible for generation and metabolism of adenosine, that determine its level outside cells and inside mononuclear cells and neutrophils, with expression of cofactor molecules, as well as with the duration of activation of cells in innate immunity, neutrophils, and monocytes/ macrophages, determined largely by the potential of adenosine regulation.

Keywords: purine metabolism, inflammation, pulmonary tuberculosis, respiratory function

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Молекулярные механизмы воспаления в патогенезе нарушений внешнего дыхания у больных туберкулезом легких

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РЕЗЮМЕ

Цель. Оценить функцию внешнего дыхания и ее связь с активностью воспаления и активностью ферментов пуринового метаболизма у больных острой и хронической формой туберкулеза легких (ТЛ).

Материалы и методы. У больных острой (ОФТЛ) и хронической формой ТЛ (ХФТЛ) оценивали активность аденозиндезаминазы (ADA-1, 2) в сыворотке крови (eADA), мононуклеарах и нейтрофилах, концентрацию экто-5'-нуклеотидазы (eNT5E) в сыворотке крови, CD26 (дипептидилпептидазы-4, DPPIV) в сыворотке крови и мононуклеарах, продукцию активных форм кислорода (АФК) и азота (АФА) в мононуклеарах и нейтрофилах, функцию внешнего дыхания (ФВД).

Результаты. У больных ТЛ выявлено: увеличение концентрации eNT5E и активности eADA-2 в сыворотке крови, стимулированной продукции АФК нейтрофилами; снижение концентрации DPPIV (CD26) в мононуклеарах, продукции АФА мононуклеарами и нейтрофилами; при ХФТЛ снижение активности ADA-1 в мононуклеарах и концентрации DPPIV (CD26) в сыворотке крови; при ОФТЛ снижение активности eADA-1 в сыворотке крови, ADA-1 в нейтрофилах, продукции АФК мононуклеарами и увеличение спонтанной продукции АФК нейтрофилами. Выявлены корреляции между параметрами ФВД и концентрацией eNT5E в сыворотке крови, спонтанной продукцией АФК мононуклеарами, АФА нейтрофилами при ХФТЛ; активностью eADA-2 в сыворотке крови, ADA-1 в нейтрофилах, DPPIV (CD26) в мононуклеарах, продукцией АФК и АФА мононуклеарами и нейтрофилами.

Заключение. Полученные данные позволяют связать регуляцию внешнего дыхания с показателями пуринергического обмена, в частности с концентрацией и активностью ферментов, ответственных за образование и метаболизм аденозина, определяющих его уровень вне клеток и внутри мононуклеаров и нейтрофилов, с экспрессией кофакторных молекул, а также с длительностью активации клеток врожденного иммунитета, нейтрофилов и моноцитов/макрофагов, определяемой в значительной степени возможностями аденозиновой регуляции.

Ключевые слова: пуриновый метаболизм, воспаление, туберкулез легких, функция внешнего дыхания

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено независимым этическим комитетом Санкт-Петербургского научно-исследовательского института фтизиопульмонологии (протокол № 57 от 11.09.2012).

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INTRODUCTION

One third of the world's population is infected with *Mycobacterium tuberculosis (Mtb)*, and 10 million new cases of tuberculosis are registered annually [1–3]. In pulmonary tuberculosis (TB), granulomatous inflammation emerges, supported by a complex cascade of inflammatory signaling molecules – cytokines and autacoids, such as the purine nucleoside adenosine. Adenosine (ADO) regulates the activity, volume, duration, and resolution of the inflammatory response by changing the metabolism of involved cells through the activation of specific receptors (ADORA A_1, A_{2A}, A_{2B}, A_3), which are widely present on body cells [4].

ADO has been shown to have anti-inflammatory and tissue protective effects in acute inflammation, in particular, lung injury [5–7]. However, in chronic lung injury, ADO enhances proinflammatory and profibrotic processes [8].

During inflammation, ischemia, and cell death, the concentration of extracellular ADO increases. Stressed cells release adenosine triphosphate (ATP), which is gradually dephosphorylated to ADO by coordinated activity of ecto-nucleotidase, mainly ectonucleoside triphosphate diphosphohydrolase 1 (CD39, E-NTPDase1) and ecto-5'-nucleotidase (CD73, eNT5E). Extra- and intracellular ADO is deaminated by adenosine deaminase (ADA) or is transformed into adenosine monophosphate by the enzyme adenosine kinase [9].

ADA isoenzymes (ADA-1 and ADA-2) are key enzymes in purine rescue pathways and are essential in the regulation of purine metabolism [10]. ADA-1 is localized not only in the cytosol and nucleus of cells, but is also present as an "ecto" form on the cell membrane, where it forms complexes with dipeptidyl peptidase IV (CD26) and / or adenosine receptors A_1 and A_{2B} [11].

ADA-2 is localized mainly in the extracellular space, predominating in the blood serum. The main source of ADA-2 is macrophages / monocytes, in which both isoforms, ADA-1 and ADA-2, coexist [12]. With physiological concentrations of ADO, the catalytic activity of ADA-2 is close to zero; however, this isoform is effective for deamination at elevated levels of adenosine in a slightly acidic environment, for example, during hypoxia [13].

Since the purinergic regulation by ATP and ADO affects the functional state of cells in the respiratory and immune systems, the study of the molecular mechanisms of inflammation in the lung tissue can help understanding the pathogenesis of lung damage in patients with pulmonary TB and indicate new targets for targeted therapy, which is necessary to improve the effectiveness of treatment for pulmonary TB patients.

The aim of this study was to assess external respiration (ER) and its relationship with the activity of inflammation and expression and activity of enzymes involved in purine metabolism in patients with acute and chronic forms of pulmonary TB.

MATERIALS AND METHODS

The study included 60 patients with a verified diagnosis of pulmonary TB who were treated in the clinic of the St. Petersburg State Research Institute of Phthisiopulmonology. The group of patients with acute pulmonary TB (APTB) consisted of 15 patients with newly diagnosed infiltrative pulmonary tuberculosis, 6 men and 9 women aged 25.0–31.0 years (average age 29.0 years). A group of patients with chronic pulmonary TB (CPTB) encompassed 45 patients with fibrous – cavernous pulmonary TB, 30 men and 15 women aged 28.0–42.0 years (average age 32.0 years). All patients with pulmonary TB underwent a comprehensive study of the function of external respiration (ER). The exclusion criterion was chronic obstructive pulmonary disease. The control group (CG) included 20 practically healthy donors with comparable characteristics by sex and age.

The groups of patients with pulmonary TB significantly differed in the smoking status (smokers / non-smokers – 33.3 / 66.7% and 71.4 / 28.6%; $p = 0.01$) and disease duration (disease duration up to a year – 100.0 and 17.1%; $p = 0.00001$). Patients

with CPTB smoked 2 times more often and were ill for much longer.

Purine metabolism was assessed by the activity of adenosine deaminase-1 and 2 (ADA-1 and ADA-2) in the blood serum (eADA-1 and eADA-2) and mononuclear and neutrophil lysates (by triple freezing and thawing), determined by the ADA assay described by G. Giusti (1974) on a spectrophotometer PV 1251C (Belarus) as well as by concentrations of ecto-5'-nucleotidase (eNT5E) and CD26 (dipeptidyl peptidase-4, DPPIV) proteins (soluble form, sCD26 (DPPIV)) in the serum and mononuclear lysate by the enzyme-linked immunosorbent assay (ELISA) (Ecto NT5E, USCN, China and Human sCD26 Platinum ElISA, eBioscience, Austria).

Production of reactive oxygen species by phagocytes was assessed by respiratory burst parameters in the nitroblue tetrazolium test (NBT test): spontaneous NBT test (NBTs.) and zymosan-induced NBT test (NBTi).

Mononuclear cells (MNs) were isolated from peripheral blood using Ficoll – verografin density gradient centrifugation (1.077 g / l). From the remaining sediment (after erythrocyte lysis and additional centrifugation), neutrophils (NPHs) were isolated. Nitric oxide generation was determined by the level of nitrites (NO_2^-) and nitrates (NO_3^-) in MNs and NPHs by ELISA (R&D Systems, Canada).

A comprehensive study of the ER function included spirometry, body plethysmography, and a study of the diffusing capacity of the lungs using the MasterScreen Body Diffusion unit (VIASYS Healthcare, Germany) according to international recommendations for standardization of pulmonary function tests and the national guidelines for functional diagnostics [14–18]. We analyzed total lung capacity (TLC), vital capacity (VC), residual volume (RV), the RV / TLC ratio, inspiratory capacity (IC), expiratory reserve volume (ERV), and airway patency parameters, such as forced expiratory volume in 1 second (FEV_1) and the FEV_1 / forced vital capacity (FVC) ratio (the Tiffeneau – Pinelli index). Pulmonary gas exchange was assessed by diffusing capacity of the lungs (DLCO) and the carbon monoxide transfer coefficient – the DLCO to alveolar volume (DLCO / VA) ratio. To eliminate the influence of anthropometric characteristics, the values of parameters with due values (D) were expressed as percentage of D for the corresponding sex, height, body weight, and age. The due values proposed by the European Coal and Steel Community (1993) [19] were used as reference values.

The analysis of ER parameters in patients with APTB and CPTB revealed that the values of most functional characteristics were within the reference range, except for significantly reduced DLCO% (71.4 and 78.6% in patients with APTB and CPTB, respectively). Patients with pulmonary TB differed significantly only in the value of the Tiffeneau – Pinelli index, which was higher in the APTB group compared with the CPTB group (83.6 (75.9–85.7) and 76.5 (70.2–81.1), respectively, $p = 0.025$).

Statistical processing of the results was carried out using the Statistica software for Windows, version 13.0. Quantitative variables were presented as the median and the interquartile range *Me (LQ–UQ)*. Tests for homogeneity were performed for two samples using the Mann – Whitney *U* test. The Spearman's rank correlation coefficient was used in the correlation analysis of quantitative variables. The differences were considered statistically significant at $p < 0.05$.

RESULTS

Studying the parameters of purine metabolism in the examined patients with pulmonary TB revealed a significant increase in the concentration of eNT5E in the blood serum, which affects the production of ADO, and a decrease in the concentration of DPPIV (CD26) in mononuclear cell lysates, compared with the control group. It indicates a decrease in the expression of this protein on the membrane of these cells, which results in a decrease in its ability to form complexes with eADA-1 and impairs the immunoregulatory ability of monocytes in relation to T lymphocytes (Table 1). In patients with CPTB, the concentration of sCD26 (DPPIV) in the blood serum was also significantly reduced compared with the control group.

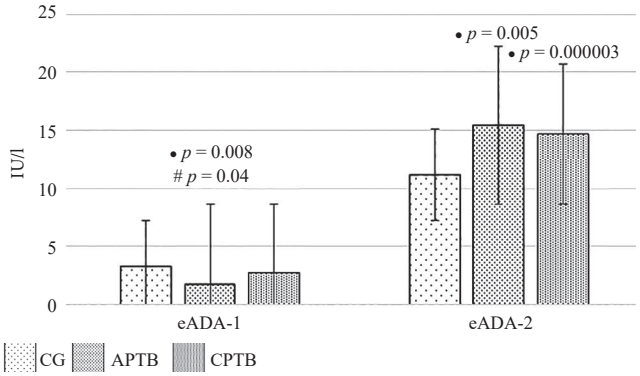
Table 1

Serum concentrations of enzymes involved in purine metabolism in patients with APTB and CPTB, *Me* (*LQ–UQ*)

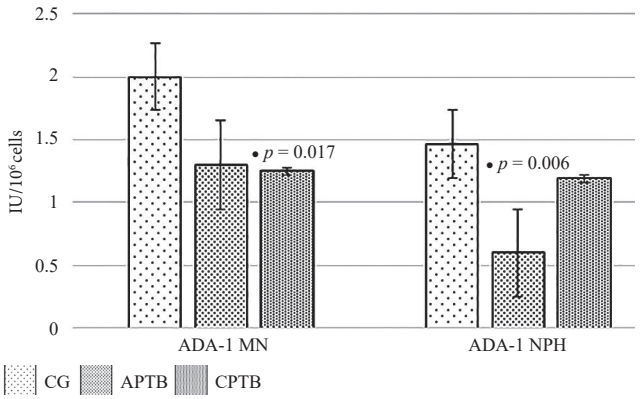
Parameters	Groups		
	CG	APTB	CPTB
eNT5E, ng / ml	0.06 (0.01–0.6)	0.7 ($p = 0.006$) (0.46–1.3)*	0.9 ($p = 0.01$) (0.45–1.4)*
sDPPIV-(CD26), ng / ml	692.5 (625.0–875.0)	560.0 (550.0–585.0)	473.5 ($p = 0.04$) (265.0–628.2)*
DPPIV-(CD26) MN, ng /10^6 cells	19.2 (12.8–25.0)	1.46 ($p = 0.0004$) (1.03–3.0)*	3.95 ($p = 0.0008$) (1.2–6.6)*

Note: CG – control group, APTB – acute pulmonary TB, CPTB – chronic pulmonary TB, eNT5E – ecto-5'-nucleotidase, DPPIV (CD26) – dipeptidyl peptidase-4, sDPPIV(CD26) – its soluble form.
* the level of statistical significance of differences compared with the control group.

The activity of eADA-1 and eADA-2 in the blood serum (Fig. 1, *a*) in the groups of patients with pulmonary TB mainly changed in the same direction compared with the CG. A significant decrease in the eADA-1 activity was revealed in patients with APTB. For eADA-2, which main function is degradation of extracellular ADO, an increase in activity was recorded in both groups of patients with pulmonary TB. ADA-1 activity in the mononuclear cell lysate was lower in CPTB patients than in the CG. ADA-1 activity in the neutrophil lysate was lower in APTB patients compared with the CG. However, there were no differences in ADA-1 activity in mononuclear and neutrophil lysates in patients with APTB and CPTB ($p = 0.91$ and $p = 0.28$, respectively, Fig. 1, *b*).



a



b

Fig. 1. Parameters of extracellular (*a*) and intracellular (*b*) activity of adenosine deaminase in groups of patients with APTB and CPTB and in the CG. Here and in Figures 2 and 3: CG – control group, APTB – acute pulmonary TB, CPTB – chronic pulmonary TB. eADA-1 and eADA-2 – activity of adenosine deaminase-1 and -2 in the blood serum, ADA-1 MN and NPH – activity of adenosine deaminase in mononuclear cells and neutrophils.

* level of statistical significance of differences compared with the control group, # level of statistical significance of differences between the groups; the level of significance is given in brackets.

Therefore, in both APTB and CPTB groups, the distribution of the activity of enzymes involved in purine metabolism and associated molecules indicates an increase in the concentration of extracellular ADO and a decrease in the immunoregulatory properties of cells of the immune system. At the same time, in patients with APTB, a significant decrease in eADA-1 activity provides conditions for a more pronounced increase in the ADO level and suppression of the function of monocytes and T lymphocytes.

Innate immune cells, such as monocytes, macrophages, and neutrophils, are known to play a key role in regulating the spread of *Mycobacterium tuberculosis (Mtb)* and the activity of tissue inflammation. The functional state of these cells can be assessed by their production of reactive oxygen species (ROS) and reactive nitrogen species (RNS).

The data presented in Figure 2 indicate that in both examined groups of patients with pulmonary TB, the production of ROS by neutrophils stimulated by bacteria was increased. It indicates a high degree of their activation. In the group of patients with APTB, spontaneous and stimulated production of ROS by mononuclear cells was significantly reduced compared with the CG. In patients with CPTB, stimulated production of ROS was reduced. It indicates significant impairment of the functional capabilities of these cells. At the same time, both spontaneous and stimulated ROS production by neutrophils in this group of patients was significantly higher than in the CG.

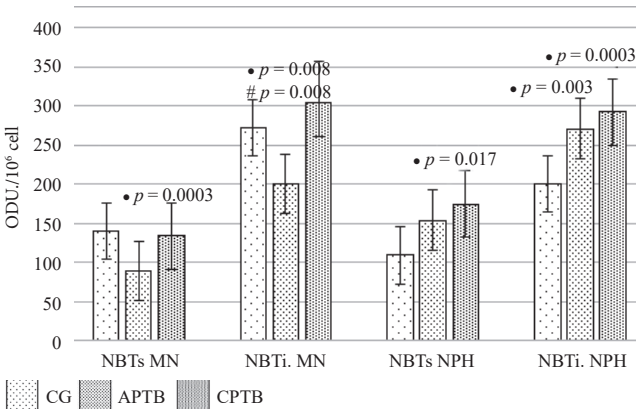


Fig. 2. Parameters of respiratory burst in groups of patients with APTB and CPTB and in the CG. Here and in Table 2: NBTs. MN, NPH and NBTi. MN, NPH – nitroblue tetrazolium test: spontaneous NBT test (NBTs.) and zymosan-induced NBT test (NBTi.) in mononuclear cells and neutrophils.

* level of statistical significance of differences compared with the control group, # level of statistical significance of differences between the groups; the level of significance is given in brackets.

An essential component for elimination of *Mtb* is RNS, which have a microbicidal effect against intracellular pathogens. The number of nitrite (NO_2^-) and nitrate (NO_3^-) radicals produced by mononuclear cells and neutrophils of TB patients was significantly reduced compared with the CG. At the same time, production of nitrite (NO_2^-) and nitrate (NO_3^-) radicals by neutrophils of the APTB patients was even more reduced than in the CPTB patients (Fig. 3). Neutrophils are actively involved in inflammation in pulmonary TB. Unlike activated macrophages, they do not produce a significant number of NO metabolites [20].

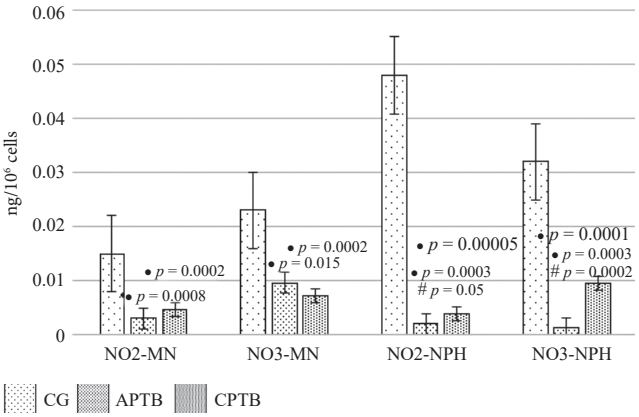


Fig. 3. Generation of RNS in groups of patients with APTB and CPTB and in the CG. Here and in Table 2: NO_2^- MN, NPH and NO_3^- MN and NPH are the levels of nitrites and nitrates in mononuclear cells and neutrophils.

* significant differences compared with the control group, # significant differences between the analyzed groups; the level of significance is given in brackets.

In general, the reduced production of NO metabolites by MNs and NPHs in patients with pulmonary TB impairs the immune response to *Mycobacterium tuberculosis*, and a more pronounced decrease in the production of NO metabolites by neutrophils, observed in patients with APTB, can be regarded as a more serious impairment of microbicidal functions, compared with patients with CPTB.

A revealed positive correlation ($r = 0.7$; $p = 0.037$) between the level of stimulated ROS production by neutrophils and the activity of intracellular ADA-1 in neutrophils indicates involvement of enzymes of purine metabolism in the regulation of phagocyte activity in patients with CPTB. Interestingly, for patients with APTB, a correlation of stimulated ROS production by neutrophils with the activity of intracellular ADA-1 in neutrophils was negative ($r = –0.4$; $p = 0.03$). Therefore, in patients with APTB, when neutrophils are activated, the level of intracellular ADO increases, which contributes to strong suppression of their functions.

The analysis of the relationship of abnormal ER parameters with the ability of phagocytes to produce ROS and RNS showed that in patients with CPTB, the parameters of static lung volumes (VC and ERV) and the DLCO /VA ratio, characterizing the gas exchange function of the lungs, were associated with spontaneous production of ROS by mononuclear cells and generation of nitrite and nitrate radicals by neutrophils ($r = –0.4$; $p = 0.04$, $r = –0.6$; $p = 0.04$, $r = –0.7$; $p = 0.01$, respectively). In patients with APTB, more correlations between phagocyte activity and ER parameters were revealed, which indicates greater tension in ER regulation [21].

The parameters of static lung volumes (TLC, VC, ERV, RV, RV / TLC ratio, IC), dynamic lung volumes, which characterize the airway patency (FEV_1, the Tiffeneau – Pinelli index), and DLCO, which characterizes the gas exchange function of the lungs, had significant correlations with spontaneous ROS production by mononuclear cells, spontaneous and induced ROS production by neutrophils, and generation of nitrate radicals by mononuclear cells and nitrite radicals by neutrophils (Table 2). Therefore, the revealed correlations confirm that the activation and dysfunction of neutrophils and mononuclear cells are associated with changes in the ER parameters in patients with pulmonary TB.

Table 2

Correlations between the respiratory burst parameters, nitric oxide metabolites, and external respiration parameters (correlation coefficient and its significance) in patients with acute pulmonary tuberculosis

Pairs of parameters		APTB
NBTs. MN	RV / TLC	0.7 (0.02)
	FEV_1	–0.6 (0.05)
NBTs. NPH	IC	–0.6 (0.01)
	TLC	–0.6 (0.04)
	DLCO	–0.7 (0.02)
NBTi. NPH	RV / TLC	0.6 (0.03)
	RV	0.6 (0.04)
NO_3^- MN	ERV	0.7 (0.02)
	IC	–0.7 (0.04)
	DLCO	–0.7 (0.02)
NO_2^- NPH	FEV_1 / FVC	0.7 (0.04)
	VC	–0.7 (0.03)

Note: TLC – total lung capacity, RV – residual volume, RV / TLC – their ratio, FEV_1 – forced expiratory volume in 1 second, IC – inspiratory capacity, DLCO – diffusing capacity of the lungs, ERV – expiratory reserve volume, VC – vital capacity, FEV_1 / FVC – the Tiffeneau – Pinelli index.

ADO plays an important role in modulating the activity of phagocytes and releasing microbicidal oxygen and nitrogen radicals. Our study showed that in CPTB, there is a significant correlation between the Tiffeneau – Pinelli index, which characterizes airway patency, and the serum concentration of eNT5E, an enzyme that synthesizes ADO ($r = 0.5$; $p = 0.02$).

In patients with APTB, positive correlations were revealed between the ER parameters (ERV, RV) and the activity of enzymes (eADA-2 in the blood serum, ADA-1 in neutrophils), which destroy ADO to cytoprotective inosine ($r = 0.7$; $p = 0.004$, $p = 0.04$, respectively). A decrease in the concentration of DPPIV (CD26) in mononuclear cells was negatively correlated with FEV_1 ($r = –0.7$; $p = 0.04$).

DISCUSSION

Fibrous – cavernous tuberculosis (FCTB) is defined as a chronic form of TB and an unfavorable outcome of untreated or ineffectively treated infiltrative TB. It should be noted that even after microbiological cure for pulmonary TB, 50% of patients still have post-tuberculous lung disease (PTLD) [22]. PTLD is caused by damage to the parenchyma, respiratory tract, blood vessels, and mediastinum, which determines pathomorphological changes in the organs. The cause of PTLD and its severity are associated with the influx of neutrophils and their excessive activity [23, 24].

Our data confirmed that in both examined groups of TB patients, neutrophils, indeed, produced an excess amount of ROS capable of damaging their own cells and intercellular structures (when the antioxidant system is depleted, which is typical of chronic inflammation). At the same time, the ability to produce NO metabolites important for microbicidal activity against mycobacteria was reduced both for neutrophils (more pronounced in patients with APTB) and for mononuclear cells in patients with pulmonary TB.

The results of our study showed that, judging by the activity of eNT5E, the level of ADO was equally increased in patients with pulmonary TB, regardless of the clinical form of the disease. In TB infection, at high levels of extracellular ADO, activated macrophages released eADA-2, which is a marker of the inflammatory response and the severity of the TB infection [25].

The regulatory effect of ADO on ER parameters (indirectly through the regulation of phagocyte activity) was confirmed by the revealed positive correlation between the activity of eADA-2 in the blood serum and ERV (a parameter characterizing the static lung volumes in patients with APTB). Another significant correlation was revealed between ADA-1 activity in neutrophils of patients with APTB (2.2 times lower than in the CG) and RV.

In patients with APTB, a decrease in intracellular ADA-1 activity can lead to a rise in the intracellular concentration of ADO, which determines an increase in the expression of P1 receptors, in particular, the low-affinity A_{2B} receptor, which stimulation inhibits inflammation and promotes tissue repair [4, 26]. When immune cells are activated at high levels of ADO, the expression of A_{2A}, A_{2B}, and A_3 receptors on macrophages increases, and their production of nitric oxide is inhibited [27]. Apparently, the differences in the duration of innate immune cell activation and their expression of P1 receptors determine the revealed multidirectional correlations between the intracellular activity of ADA-1 and the level of induced respiratory burst in neutrophils in APTB and CPTB.

Extracellular ADO not only regulates the inflammatory response, but also modulates the interaction between cells of innate and adaptive immunity. T. Hashikawa et al. (2006) showed that necrotic cells could become a source of eADA-1 during inflammation, which can subsequently form a complex with DPPIV (CD26). Our study revealed a decrease in the expression of DPPIV (CD26) by mononuclear cells (most pronounced in APTB) [28]. Apparently, a disruption of the monocyte – T lymphocyte interaction during decreased expression of DPPIV (CD26) by mononuclear cells and reduced activity of eADA-1 in the blood serum in patients with APTB caused impaired regulation of inflammation and a negative correlation between the level of DPPIV expression by mononuclear cells and FEV. The level of the soluble form of DPPIV in chronic diseases has been shown to inversely correlate with the severity of the disease, the severity of inflammation, and the prevalence of pulmonary fibrosis [29, 30].

In our study, a significantly reduced serum level of the soluble form of DPPIV (CD26) was registered in patients with CPTB. It caused a decrease in compensatory capabilities in the chronic course of the infectious and inflammatory process and explained the decrease in ER parameters that was found in patients with CPTB. At the same time, in patients with APTB, whose serum level of the soluble form of DPPIV was maintained within the reference values, the ER function was not impaired (measured parameters were within the reference values).

CONCLUSION

The data obtained make it possible to link the regulation of ER with the parameters of purine metabolism, in particular, with (1) the concentration and activity of enzymes that are responsible for the production and metabolism of ADO and that determine its level outside cells and inside mononuclear cells and neutrophils; (2) the expression of cofactor molecules; and (3) the duration of activation of innate immune cells, neutrophils, and monocytes / macrophages, affected to a large extent by ADO regulation potential. The revealed regularities make it possible to outline new approaches to modern diagnosis, prevention, and, possibly, treatment of developing respiratory failure in patients with pulmonary TB.

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