UDC 616.24-002-092.4

S. S. Bondar'[1], I. V. Terekhov[1], V. K. Parfenyuk[2], N. V. Bondar'[3], V. S. Nikiforov*[4]

[1] Federal State Budgetary Educational Institution of Higher Education Tula State University, Tula, Russia

[2] Federal State Budgetary Educational Institution of Higher Education Saratov State Medical University named after V. I. Razumovsky of the Ministry of Health of the Russian Federation, Saratov, Russia

[3] Federal State Budgetary Educational Institution of Higher Education Oryol State University named after I. S. Turgenev, Oryol, Russia

[4] Federal State Budgetary Educational Institution of Higher Education North-Western State Medical University named after I. I. Mechnikov, Saint-Petersburg, Russia

THE RELATIONSHIP OF THIOL STATUS, AND COMPONENTS OF SIGNALING PATHWAYS THAT REGULATE INFLAMMATION IN CONVALESCENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

Abstract

The study discusses the relationship of thiol concentrations in intercellular fluid with the level of peripheral blood mononuclear cells (MNCs) components of mitogen-activated (MAPK) / stress-activated (SAPK) and JAK/STAT signaling pathways, and nuclear transcription factor NF-κB in community-acquired pneumonia (CAP) convalescents. The content and level of phosphorylation of JAK2 protein kinase, signal transducers and transcription activators STAT3, STAT5A, STAT6, NF-κB nuclear transcription factor inhibitor (IκBα), JNK, ERK stress-activated protein kinases, and the level of nuclear transcription factor NF-κB p50 subunit were determined by ELISA in MNCs. The results of the study indicate that the stage of CAP convalescence is characterized by a lack of antioxidant protection manifested by a decrease in the concentration of thiol-containing compounds in cell culture supernatants, on the background of which there is a decrease in the level of phosphorylation of JAK2 protein kinase, factors STAT3, STAT5, STAT6, JNK, which is also associated with an increase in the level of phosphorylation of ERK protein kinase. The analysis showed that the thiol status is characterized by a positive relationship with the activity of STAT5A, JNK, p50. The thiol level and ERK, as well as STAT3, was characterized by a negative relationship. Thus, the increase in the thiol level contributes to an increase in the activity of the transcription factor STAT5A and a decrease in the activity of the transcription factor STAT3 with a corresponding change in cell reactivity with respect to specific cytokines, as well as a specific effect on the differentiation of individual populations of immunocompetent cells.

Key words: *thiol status, STAT5A, pneumonia, NF-κB*

For citation: Bondar' S. S., Terekhov I. V., Parfenyuk V. K., Bondar' N. V., Nikiforov V. S. THE RELATIONSHIP OF THIOL STATUS, AND COMPONENTS OF SIGNALING PATHWAYS THAT REGULATE INFLAMMATION IN CONVALESCENTS WITH COMMUNITY-ACQUIRED PNEUMONIA. The Russian Archives of Internal Medicine. 2018; 8(6): 451-457. [In Russian]. DOI: 10.20514/2226-6704-2018-8-6-451-457

DOI: 10.20514/2226-6704-2018-8-6-451-457

* Contacts. E-mail: viktor.nikiforov@szgmu.ru

ERK — extracellular signal-regulated protein kinase, IκBα — nuclear transcription factor inhibitor κB, NF-κB — nuclear transcription factor κB, JAK — Janus kinases, JNK — c-jun-N-terminal protein kinase, MAPK — mitogen-activated protein kinase, p50 — nuclear κB transcription factor p50 subunit, SAPK — stress-activated protein kinases, STAT — signal transducers and transcription activators, AOP — antioxidant protection, CAP — community-acquired pneumonia, ICC — immunocompetent cells, MNC — mononuclear cells, LPO — lipid peroxidation, TC — thiol-containing compounds

As is well known, antioxidant protection (AOP) determines the activity of sanogenesis processes in various pathological conditions. Antioxidant deficiency or low AOP enzyme activity leads to an increase in lipid peroxidation (LPO), which is accompanied by membrane structure and function disruption, molecule enzymatic activity disorder, activation of apoptosis processes and pro-inflammatory activation preservation of immunocompetent cells [1]. At the same time, LPO plays an important physiological role by regulating prostaglandin, leukotriene and thromboxane biosynthesis, which determines the importance for the normal sanogenesis processes of maintaining LPO/AOP at the optimal level, avoiding a significant deficit of antioxidants [2, 3]. The balance of AOP/LPO is maintained due to the functioning of specific enzymes that catalyze the splitting of reactive oxygen species, including superoxide dismutase, catalase, thioredoxin reductase, etc. The deficiency of antioxidants, including thiol-containing compounds (TC), is associated with increased viral infections, including those caused by respiratory syncytial virus and metapneumovirus. In this case, AOP suppression is accompanied by an excessive pro-inflammatory activation of immunocompetent cells, a decrease in the efficiency of phagocytosis, increased cytokine production and prolonged resolution of the pathological process, which is associated with various complications in such patients [4]. It has also been shown that many intracellular molecular regulators, such as protein kinases that are part of the intracellular signaling pathways, are redox-sensitive molecules that respond to antioxidant deficiency by activating and stimulating metabolic processes leading to immunocompetent cell apoptosis or differentiation, in particular, macrophage polarization, T-helper differentiation, etc. [2]. In addition, intracellular signaling pathway activation, in particular MAPK/SAPK and JAK/STAT in response to cell stimulation with bacterial components and cytokines leads to antioxidant pool depletion due to their increased expenditure while forming a systemic inflammatory reaction occurring amid increasing production of reactive oxygen species [2, 3]. Convalescence of an acute infectious-inflammatory process, often accompanied by dysregulation of intracellular signaling mechanisms, also takes place with AOP deficiency, which is determined by decreased antioxidant production [4–6].

At the same time, antioxidant deficiency contributes to the progression of such chronic non-infectious diseases as coronary artery disease, atherosclerosis, diabetes mellitus, also contributing to premature body aging and suppression of reparative processes in tissues [1, 3]. Despite the importance of this issue, the relationship between intracellular molecular regulators that determine cellular reactivity with respect to external signals and the LPO/AOP state at the final stage of the inflammatory process has not been fully investigated. In this regard, the aim of this study was to investigate the relationship of MAPK/SAPK components and JAK/STAT signaling pathways with thiol-containing compound concentration in cell culture supernatants in community-acquired pneumonia (CAP) convalescents.

Materials and Methods

The material of this study was venous blood from the cubital vein taken in the morning (from 7:00 to 7:30 AM). Thirty male patients (mean age: (26 ± 5.2) years) with bacterial mild CAP (60–65 points of the PORT score) on 15–17 days of disease (just before discharging from the hospital) were included in the main (study) group. The control group consisted of 15 healthy male blood donors, aged 20–37 years (mean age: (27 ± 6) years).

The diagnosis of pneumonia was verified in accordance with national clinical guidelines (2013). Criteria for the inclusion of patients in

the study were: X-ray verification of infiltrative lung changes, unilateral segmental nature of infiltrative changes; bacteriological verification of gram-positive microorganisms that are typical pneumonia etiological agents (S. pneumoniae, S. aureus), as well as M. pneumoniae; uncomplicated disease course; positive therapy effect (reduction of infiltrative changes volume no less than 2/3 from the initial level by the time of discharge from the hospital). All patients received parenteral antibiotic therapy with third-generation cephalosporins (cefotaxime) at an average daily dose of 2 g, or clarithromycin at an average daily dose of 1 g, nonsteroidal anti-inflammatory drugs and physiotherapy.

The clinical study was approved by the Academic Council and the Local Ethics Committee of the Medical Institute of the Federal State Budgetary Educational Institution of Higher Education Tula State University (Protocol No. 2, September 1, 2014). All patients and donors signed an informed consent form.

In this work, we used kits for whole blood cell cultivation and mitogenic stimulation Cytokine-Stimul-Best (ZAO Vector-Best, Novosibirsk). In aseptic conditions, 1 ml of whole blood was introduced into a vial containing 4 ml of supporting medium DMEM, heparin (2.5 U/ml), gentamicin (100 μg/ml) and L-glutamine (0.6 mg/ml). All blood samples were placed in a thermostat (37 °C) and incubated for 24 hours. After incubation, 1 ml of the supernatant was taken from blood sample vials to determine the concentration of thiol-containing compounds by ELISA.

To obtain the MNC fraction, 4 ml of the cell suspension was layered on a ficoll-verografin solution (ρ = 1.077, MedBioSpectr, Russia), followed by centrifugation at 5,000 rpm for 30 minutes. The isolated MNCs were washed twice in phosphate-saline buffer and 1 ml of cell suspension containing 5×10^6 cells, lysed using a following composition solution (Sigma-Aldrich, USA): 10 mM Tris, pH 7.4; 100 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM NaF, 20 mM $Na_4P_2O_7$, 2 mM Na_3VO_4, 1% Triton X-100, 10% glycerol, 0.1% SDS, 0.5% deoxycholate, 1 mM PMSF (matrix 0.3 M solution in DMSO). A 1% protease inhibitor (Sigma-Aldrich, USA) was added to the lysing solution (ex tempore) and kept on ice (at t = +4–5 °C) for 15 minutes, aliquoted and frozen at –76 °C.

In the lysates, we evaluated the content (in relative units per ng of protein — U/ng) of twice tyrosine 1007/1008 phosphorylation of JAK2 receptor protein kinase, tyrosine 705 phosphorylation of the signal transducer form and transcription activator STAT3, 694 phosphorylation of STAT5A form, and 641 phosphorylation of STAT6 form, using the ELISA. We also determined the level of tyrosine 202/204 phosphorylation of ERK protein kinase (isoforms 1 and 2), as well as the tryptophan and tyrosine 183 phosphorylation level and tyrosine 185 phosphorylation level of JNK protein kinase (isoforms 1 and 2). In addition, the concentration of the nuclear transcription factor NF-κB p50 subunit was determined.

The studies were carried out using Cusabio Biotech (China), Panomix (USA), Cloud-Clone (USA), IBL (Germany), and Bender Medsystems (Austria) kits. The enzyme immunoassay was performed on a Personal LAB analyzer (Adaltis Italia S.p.A., Italy) in accordance with the protocol recommended by the reagent kit manufacturer.

Cell counting and their viability analysis were performed on the TC20 cell counter (Bio-Rad, USA). The viability of isolated MNCs exceeded 90%.

Statistic processing was carried out using Statistica 7.0 software. The study results are presented in the following form: mean value (x), sample median (Me); 25th and 75th percentiles (25%, 75%). The statistical significance (p) for intergroup differences was assessed using the Mann-Whitney U-test. The relationship between the studied factors was assessed by linear regression analysis with step-wise variable inclusion in the mathematical model.

Results and Discussion

The results of the study are presented in Table 1.

The conducted analysis showed that for CAP convalescents, against the background of thiol-containing compound deficiency, there is a decrease in the phosphorylation level of JAK2 and JNK protein kinases, as well as STAT factors. These changes were associated with increased activity in the MNC of ERK protein kinase.

The statistical significance of the identified differences is presented in Table 2.

Table 1. *The level of the studied parameters in groups*

Factors	Control group				Main group			
	x	25%	Me	75%	*x*	25%	Me	75%
JAK2, U/ng	0.82	0.71	0.82	0.94	0.6	0.42	0.59	0.73
STAT3, U/ng	0.99	0.82	0.99	1.17	0.91	0.67	1.0	1.11
STAT5A, U/ng	0.81	0.78	0.81	0.84	0.65	0.56	0.66	0.72
STAT6, U/ng	2.29	2.29	2.30	2.3	1.82	1.34	1.68	2.02
JNK, U/ng	1.03	1.03	1.03	1.03	0.9	0.67	0.83	1.13
ERK, U/ng	3.17	3.08	3.17	3.26	3.32	2.67	3.25	3.6
ρ50, ng/ml	1.38	1.36	1.39	1.41	1.35	1.11	1.34	1.56
TC, μmol/ml	2.46	2.17	2.46	2.75	2.12	1.65	2.21	2.66

Table 2. *Statistical significance of the identified differences*

Factors	Intergroup difference value	Level of difference significance (ρ)
JAK2	–26.8	0.007
STAT3	–8.1	0.007
STAT5	–19.8	0.007
STAT6	–20.5	0.00001
JNK1/2	–12.6	0.00001
ERK1/2	4.7	0.007
ρ50	–2.2	0.35
TC	–13.8	0.007

Table 3. *Results of linear regression analysis*

Factor	β	$m_β$	B	m_B	t	ρ
STAT3	–0.41	0.2	–0.95	0.45	–2.1	0.046
STAT5	0.7	0.23	2.26	0.73	3.09	0.005
JNK1/2	0.67	0.22	0.76	0.25	3.01	0.006
ERK1/2	–0.57	0.27	–0.88	0.41	–2.11	0.045
ρ50	0.64	0.22	1.03	0.36	2.9	0.008

Note: B — regression coefficient; β — standardized regression coefficient; m_B — standard error of regression coefficient estimation; $m_β$ — standard error of standardized regression coefficient estimation; t — T-test value for the factor included in the model; ρ — significance level of the T-test.

Table 4. *The results of the evaluation of partial correlations*

Factor	Partial correlation (r)	Semi-partial correlation (r)	Coefficient of determination (R^2)
STAT3	–0.31	–0.04	0.96
SATA5A	0.39	0.07	0.98
JNK1/2	0.37	0.09	0.95
ERK1/2	–0.09	–0.02	0.96
ρ50	0.38	0.06	0.96

The analysis of the statistical significance of the identified intergroup differences indicates that the convalescence phase is accompanied by the normalization of the level in the MNC of MAPK/SAPK signaling pathway, in particular ERK and JNK. However, against this background, there is an increase in the ERK protein kinase activity, as well as a decrease in JNK activity, which is seen in the corresponding change of their phosphorylation status.

The study of the relationship between the signaling pathway components and the concentration of thiol-containing compounds was carried out by linear regression analysis with inclusion of step-by-step variables in the regression model, the results of which are presented in Table 3.

The results of the regression analysis show that the correlation coefficient of the regression equation (R) reflecting the connection strength between thiol concentration and the combination of factors included in the model, was 0.98. The coefficient of determination was 0.96 (adjusted coefficient of determination was 0.94); it determines the variation proportion in the concentration of thiol-containing compounds explained by the resulting mathematical model (R^2), indicating a high influence of the studied parameters on the TC.

The model is characterized by statistical significance, as indicated by the F value (F = 266.5; $\rho < 0.0000$) and low residuals correlation (Durbin-Watson coefficient = 1.7; linear residuals correlation coefficient = 0.15). The standard absolute error in model estimating is 0.54 units, which is 25.5% of the mean estimated thiol concentration. In this model, the STAT5A factor state, the JNK protein kinase content and the nuclear transcription factor NF-κB p50 subunit have the most significant positive effect on the thiol status, while the ERK factor concentration and the STAT3 phosphorylation level have a negative effect on thiol-containing compound concentration.

The statistical analysis shows that the dependence of thiol concentration on the signaling pathway component level and activity that we identified may be shown as follows:

$$TS = 2.26 \times STAT5A + 0.76 \times JNK + \\ + 1.03 \times p50 - 0.88 \times ERK - 0.95 \times STAT3$$

Table 4 shows the partial and semi-partial component correlation values, which show the nature of the relationship between each specific signaling pathway component included in the model and the thiol-containing compound concentration, while excluding the influence of other factors.

Partial correlation analysis indicates that the studied factors, in general, are characterized by a moderate connection with thiol concentration, while the connection between thiol-containing compounds and ERK level is weak. At the same time, a high determination coefficient identifies the relevant significance level in the revealed correlations reflecting the existing indirect relationships.

Discussion

The postclinical CAP phase proceeds with a decrease in JAK/STAT signaling pathway components, as well as JNK protein kinase, with an increase in the ERK protein kinase activity accompanied by a decrease in the thiol-containing compound concentration. This circumstance indicates the dysregulatory changes and AOP deficiency in the examined patients [5, 6]. The statistical analysis allowed us to assess the nature of the relationship between the investigated regulatory components and the thiol status representing the AOP state in the whole blood cell intercellular medium. At the same time, a significant association of thiol concentration in the extracellular medium was revealed with STAT5A and p50 factors in the MNC, as well as JNK and ERK protein kinases. Taking into account the moderate nature of the relationship between thiol status and the signaling pathway components and their stochastic nature, it is obvious that the mechanism of the revealed relationship is the indirect influence of thiol on the redox-sensitive component status of the molecular mechanism regulators, including phosphatases such as PTP1B, PP2CA, MCP-1 directly governing the activity of MAPK/SAPK and JAK/STAT signaling pathways [2, 7].

The described mathematical model linking the thiol level and the signaling molecular cell reactivity mechanisms can also be considered as predictive. It can be assumed that an increase in the blood thiol level will be accompanied by an

increase in the STAT5A transcription factor activity, which, in turn, suggests an increase in cell sensitivity to cytokines such as IL-2, IL-3, as well as erythropoetin and thrombopoetin, stimulating hematopoiesis [8, 9]. At the same time, a decrease in STAT3 activity accompanied by a reduction in cell sensitivity to pro-inflammatory cytokines, including IL-6 and IL-5, as well as T-helper 17 differentiation inhibition, suggests the formation of pro-inflammatory effect from an increase in thiol concentration in the blood. In addition, the JNK protein kinase content stimulation in convalescents under thiol influence can stimulate the repair of the double-stranded DNA breaks due to sirtuin phosphorylation [10]. Moreover, an increase in the STAT5A level determines the activation of sanogenesis mechanism identifying the restoration of the normal AOP level [11, 12]. Taking into account the obtained results, it can be assumed that the dynamics of the thiol-containing compound level in the body can be considered as one of the goals for lower respiratory tract infection treatment, as well as immune rehabilitation of such patients, characterized by preserving the proinflammatory activation of immunocompetent cells (ICC) in the convalescence CAP phase reflecting incomplete pathological process by the time of clinical recovery [13]. Under these conditions, stimulation of restored thiol-containing compounds accumulation in the extracellular fluid, while increasing the antioxidant status, will accelerate the recovery from an infectious-inflammatory process, including the normalization of ICC reactivity [14].

The study results suggest that ICC stimulation by pathogen components, as well as by cytokines with intracellular molecular pathway activation for the receptor information transmission plays an important role in maintaining the LPO/AOP balance and it is necessary to maintain the antioxidant level in the intercellular medium. At the same time, excessive suppression of the key signaling pathway components studied during this research can negatively affect AOP, in particular, can result in the decrease of the TC level in patients coming through CAP. So, it is advisable to avoid over-suppressing immune response when providing medical care to such patients, including by limiting the adrenal gland hormone use without absolute indications and unreasonably long-term antibacterial drug therapy. Considering the revealed dependence of the effect of thiol-containing compounds on the activation of the terminal signaling pathway components, it is reasonable to prescribe water-soluble antioxidants, in particular taurine, cysteine or lipoic acid along with the main therapy to such patients in order to maintain optimal biochemical process activation in ICC [1, 3, 14].

Conclusions

1. Among CAP convalescents with thiol-containing compound deficiency, there is a statistically significant decrease in the JAK2 protein kinase phosphorylation level by 26.8%, STAT3 factors by 8.1%, STAT5 by 19.8%, STAT6 by 20.5%, JNK by 12.6%, while a slight increase was observed in the ERK protein kinase phosphorylation level by 4.7%. These changes indicate a close relationship between the activity of the studied signaling pathways and the LPO/AOP state.

2. Regression analysis showed that the thiol status is characterized by a positive relationship with the STAT5A factor activity in the MNC, the JNK protein kinase content in the cell, the nuclear transcription factor NF-κB p50 subunit, while the negative relationship is characterized by the ERK factor content and the STAT3 phosphorylation level. The mathematical model linking the thiol level and ICC reactivity molecular mechanisms allows to judge the potential antioxidant effect, as well as possible pathophysiological AOP manifestations in the CAP convalescence phase. It can facilitate the prediction of the effectiveness of immune rehabilitation in these patients.

3. Taking into account the nature of the identified relationships, it is possible to formulate a hypothesis that an increase in the thiol level contributes to an increase in the activity of the transcription factor STAT5A and a decrease in STAT3 activity with increased cell sensitivity to IL-2, IL-3, erythropoetin and thrombopoetin while reducing ICC sensitivity to pro-inflammatory cytokines, including IL-6 and IL-5, as well as T-helper 17 differentiation inhibition. So, water-soluble antioxidant

therapy in CAP convalescents may promote the correction of the state of intracellular signal transduction mechanisms and accelerate recovery after CAP.

Conflict of interests

The authors declare no conflict of interests.

References:

1. Shahristova E.V., Stepovaya E.A., Ivanov V.V., Nosareva O. L., Ryazanceva N.V., Novickij V.V. Oxidative modification of proteins and glutathione system in adipocytes with diabetes mellitus. Bulletin of Siberian medicine. 2014; 13(3): 84-90. [In Russian]
2. Stepovaya E.A., ZHavoronok T.V., Petina G.V., Ryazanceva N.V., Ivanov V.V., Tetenev F.F., Ageeva T.S., Novickij V.V. The participation of the thiol-disulfide system in the regulation of the oxidative modification of proteins in neutrophils under oxidative stress. Siberian Scientific Medical Journal. 2010; 30(5): 64-69. [In Russian]
3. Kalinina E.V., Chernov N.N., Saprin A.N. Participation of thio-, peroxy-and glutaredoxins in redox-dependent cellular processes. Advances in biological chemistry. 2008; (48): 319-358. [In Russian]
4. Komaravelli N., Tian B., Ivanciuc T., Mautemps N., Brasier A.R., Garofalo R.P., Casola A. Respiratory syncytial virus infection down-regulates antioxidant enzyme expression by triggering deacetylation-proteasomal degradation of Nrf2. Free Radic Biol Med. 2015; 88 (Pt B): 391-403. doi: 10.1016/j.freeradbiomed.2015.05.043.
5. Gromov M.S., Terekhov I.V. Characterization of the systemic inflammatory response in patients with community-acquired pneumonia over time using active microwave radiometry. Kazan Medical Journal. 2010; 91(5): 611-614. [In Russian]
6. Terekhov I.V., Bondar' S.S., Hadarcev A.A. Laboratory determination of intracellular factors of antiviral protection in community-acquired pneumonia in assessing the effects of low-intensity microwave radiation. Clinical laboratory diagnosis. 2016; 61 (6): 380-384. [In Russian]
7. Parsons Z.D., Gates K.S. Thiol-dependent recovery of catalytic activity from oxidized protein tyrosine phosphatases. Biochemistry. 2013; 52(37): 6412-23. doi: 10.1021/bi400451m.
8. Linher-Melville K., Singh G. The complex roles of STAT3 and STAT5 in maintaining redox balance: Lessons from STAT-mediated xCT expression in cancer cells. Molecular and Cellular Endocrinology. 2017; 451: 40-52. doi: 10.1016/j.mce.2017.02.014.
9. Bourgeais J., Gouilleux-Gruart V., Gouilleux F. Oxidative metabolism in cancer: A STAT affair? *JAK-STAT*. 2013; 2(4): e25764. doi:10.4161/jkst.25764.
10. Van Meter M., Simon M., Tombline G., May A., Morello T.D., Hubbard B.P., Bredbenner K., Park R., Sinclair D.A., Bohr V.A., Gorbunova V., Seluanov A. JNK Phosphorylates SIRT6 to Stimulate DNA Double-Strand Break Repair in Response to Oxidative Stress by Recruiting PARP1 to DNA Breaks. Cell Rep. 2016; 16(10): 2641-2650. doi: 10.1016/j.celrep.2016.08.006.
11. Soloduhin K.A., Nikiforov V.S., Gromov M.S., Parfenyuk V.K., Bondar' S.S., Terekhov I.V. The effect of low-intensity microwave irradiation on intracellular processes in mononuclear cells in pneumonia. Medical Immunology. 2012; 14(6): 541-544. [In Russian]
12. Cholez E., Debuysscher V., Bourgeais J., Boudot C., Leprince J., Tron F., Brassart B., Regnier A., Bissac E., Pecnard E., Gouilleux F., Lassoued K., Gouilleux-Gruart V. Evidence for a protective role of the STAT5 transcription factor against oxidative stress in human leukemic pre-B cells. Leukemia. 2012; 26(11): 2390-2397. doi: 10.1038/leu.2012.112.
13. Terekhov I.V., Nikiforov V.S., Bondar' S.S., Bondar' N.V., Voevodin A.A. The change in the content of the components of the IL/TOLL signaling pathway and NF-kB in mononuclear cells of whole blood under the influence of low-intensity electromagnetic radiation at a frequency of 1 GHz. Genes and cells. 2017; 12(2): 90-96. [In Russian]
14. Hosakote Y.M., Komaravelli N., Mautemps N., Liu T., Garofalo R.P., Casola A. Antioxidant mimetics modulate oxidative stress and cellular signaling in airway epithelial cells infected with respiratory syncytial virus. Am J Physiol Lung Cell Mol Physiol. 2012; 303(11): L991-1000. doi: 10.1152/ajplung.00192.2012.

Article received on 31.08.2018
Accepted for publication on 04.10.2018