biology and medicine. Saarbrucken:LAP LAMBERT Acad. Publ. (Russian). 496 p.**)**

Олейник А. С., *Куприна Т. С.*, *Певнева Н. Ю.*, *Марков А. Ф.*, *Кандалинцева Н. В.*, *Просенко А. Е.*, *Григорьев И. А. 2007*. Синтез и антиоксидантные свойства *S*-[3-(гидроксиарил)пропил]тиосульфатов и [3-(гидроксиарил)пропан]-1-сульфонатов натрия. Изв. АН. Сер. хим. 6 : 1094—1101. **(***Oleinik A. S.*, *Kuprina T. S.*, *Pevneva N. Yu.*, *Markov A. F.*, *Kandalintseva N. V., Prosenko A. E., Grigoriev I. A. 2007*. Synthesis and antioxidant properties of sodium S-[3-(hydroxyaryl)propyl] thiosulphates and [3-(hydroxyaryl)propane]-1-sulfonates. Izvestiya RAS. Ser. khim. (Russian). 6 : 1094—1101.**)**

Турпаев К. Т. 2013. Сигнальная система Keap1-Nrf2. Механизм регуляции и значение для защиты клеток от токсического действия ксенобиотиков и электрофильных соединений. Биохимия. 78 (2) : 147—166. **(***Turpaev K. T. 2013*. Keap1-Nrf2 signaling pathway: mechanisms of regulation and role in protection of cells against toxicity caused by xenobiotics and electrophiles. Biochemistry (Moscow). 78 (2) : 111—126**.)**

Chikara S., *Nagaprashantha L. D.*, *Singhal J.*, *Horne D.*, *Awasthi S.*, *Singhal S. S. 2018*. Oxidative stress and dietary phytochemicals: role in cancer chemoprevention and treatment. Cancer Lett. 413 : 122—134.

Chu X. Y., *Liu Y. M.*, *Zhang H. Y. 2017*. Activating or inhibiting Nrf2? Trends Pharmacol. Sci. 38 : 953—955.

Dinkova-Kostova A. T., *Fahey J. W.*, *Kostov R. V.*, *Kensler T. W. 2017*. KEAP1 and done? Targeting the NRF2 pathway with sulforaphane. Trends Food Sci. Technol. 69 : 257—269.

Fedorova M., *Bollineni R. C.*, *Hoffmann R. 2014*. Protein carbonylation as a major hallmark of oxidative damage: update of analytical strategies. Mass Spectrom. Rev. 33 : 79—97.

Gazaryan I. G., *Thomas B. 2016*. The status of Nrf2-based therapeutics: current perspectives and future prospects. Neural Regenerat. Res. 11 : 1708—1711.

Giordano S., *Darley-Usmar V.*, *Zhang J. 2014*. Autophagy as an essential cellular antioxidant pathway in neurodegenerative disease. Redox Biol. 2 : 82—90.

Kapuy O., *Papp D.*, *Vellai T.*, *Banhegyi G.*, *Korcsmaros T. 2018*. Systems-level feedbacks of NRF2 controlling autophagy upon oxidative stress response. Antioxidants (Basel). 7 (3) : E39.

Kitamura H., *Motohashi H. 2018*. NRF2 addiction in cancer cells. Cancer Sci. 109 : 900—911.

Klimaszewska-Wisniewska A., *Halas-Wisniewska M.*, *Tadrowski T.*, *Gagat M.*, *Grzanka D.*, *Grzanka A. 2016*. Paclitaxel and the dietary flavonoid fisetin: a synergistic combination that induces mitotic catastrophe and autophagic cell death in A549 non-small cell lung cancer cells. Cancer Cell Int. 16 : 1—23.

Klionsky D. J., *Abdelmohsen K.*, *Abe A.*, *Abedin M. J. et al. 2016*. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Autophagy. 12 : 1—222.

Lee Y. J., *Lee G. J.*, *Yi S. S.*, *Heo S. H.*, *Park C. R.*, *Nam H. S.*, *Cho M. K.*, *Lee S. H. 2016*. Cisplatin and resveratrol induce apoptosis and autophagy following oxidative stress in malignant mesothelioma cells. Food Chem. Toxicol. 97 : 96—107.

Nabavi S. F., *Sureda A.*, *Dehpour A. R.*, *Shirooie S.*, *Silva A. S.*, *Devi K. P.*, *Ahmed T.*, *Ishaq N.*, *Hashim R.*, *Sobarzo-Sanchez E.*, *Daglia M.*, *Braidy N.*, *Volpicella M.*, *Vacca R. A.*, *Nabavi S. M. 2017*. Regulation of autophagy by polyphenols: paving the road for treatment of neurodegeneration. Biotechnol. Adv. 2017. Doi: 10.1016/j.biotechadv.2017.12.001.

Niki E. 2016. Oxidative stress and antioxidants: distress or eustress? Arch. Biochem. Biophys. 595 : 19—24.

Pajares M., *Cuadrado A.*, *Rojo A. I. 2017*. Modulation of proteostasis by transcription factor NRF2 and impact in neurodegenerative diseases. Redox Biol. 11 : 543—553.

Rajagopal C., *Lankadasari M. B.*, *Aranjani J. M.*, *Harikumar K. B. 2018*. Targeting oncogenic transcription factors by polyphenols: a novel approach for cancer therapy. Pharmacol. Res. 130 : 273—291.

Shabalala S., *Muller C. J. F.*, *Louw J.*, *Johnson R. 2017*. Polyphenols, autophagy and doxorubicin-induced cardiotoxicity. Life Sci. 180 : 160—170.

Sies H., *Berndt C.*, *Jones D. P. 2017*. Oxidative stress. Annu. Rev. Biochem. 86 : 715—748.

Wang W., *Chen D.*, *Zhu K. 2018*. SOX2OT variant 7 contributes to the synergistic interaction between EGCG and Doxorubicin to kill osteosarcoma via autophagy and stemness inhibition. J. Exp. Clin. Cancer Res. 37 : 37.

Zhao Y., *Song W.*, *Wang Z.*, *Jin X.*, *Xu J.*, *Bai L.*, *Li Y.*, *Cui J.*, *Cai L. 2018*. Resveratrol attenuates testicular apoptosis in type 1 diabetic mice: role of Akt-mediated Nrf2 activation and p62-dependent Keap1 degradation. Redox Biol. 14 : 609—617.

Поступила 26 VI 2018

ACTIVATION OF AUTOPHAGY AND OF Nrf2-DEPENDENT SIGNALING PATHWAY IN HUMAN BREAST ADENOCARCINOMA CELL LINE MCF-7 BY NOVEL MONOPHENOLIC ANTIOXIDANTS

E. B. Menshchikova,[1,*] *A. V. Chechushkov*,[1] *P. M. Kozhin*,[1] *S. V. Kholshin*,[2] *N. V. Kandalintseva*,[2] *G. G. Martinovich*,[3] *N. K. Zenkov*[1]

[1] Federal Research Center for Fundamental and Translational Medicine, Novosibirsk, 630117,
[2] Novosibirsk State Pedagogical University, Novosibirsk, 630126, and
[3] Belarusian State University, Minsk, 220030;
* e-mail lemen@centercem.ru

In order to find new drugs for neoplastic prevention and adjunct to anti-cancer treatment, we have studied the effect of novel water-soluble structurally related monophenolic compounds on the activity of two most important mechanisms of maintaining intracellular homeostasis, such as autophagy and the redox-sensitive signal system Keap1/Nrf2/ARE, in human breast adenocarcinoma cell line MCF-7 has. The investigation was performed using confocal microscopy. When studying the effect of synthesized compounds on autophagy, a change in the content of intracellular LC3B-positive vesicles (autophagosomes) was analyzed and the ability of the compounds to activate the Keap1/Nrf2/ARE system was determined by their effect on the translocation factor Nrf2 into the nucleus. The influence of tested substances on the rate of autophagosome biogenesis varied depending on their structure and concentration. When inhibitor of autophagosome-lysosomal fusion, chloroquine had been added in culture medium, asymmetrically hindered by *tert*-butyl-group phenols with thiosulfonate (TS-13) and sulfonate group in the *para*-propyl substituent (20 μM) increased the rate of autophagosome elimination in MCF-7 cells, and the shortening of the *para*-alkyl substituent by one methylene unit abolished the effect. But the addition of the second ortho-*tert*-butyl substituent restored it. Of the two tested compounds, both enhanced

the translocation of the transcription factor Nrf2 into the nucleus of MCF-7 cells (the key point to activation of the Keap1/Nrf2/ARE system): phenol asymmetrically hindered by *tert*-butyl-group and having selensulfonate group in *para*-propyl substituent after 4 hours of incubation (5—100 μM), TS-13 — after 24 hours of incubation (5—100 μM). Based on our data earlier provided on the toxicity features of this group of compounds in relation to MCF-7 cells, we can conclude that they are related to the difference in the effect of substances on autophagy and the activation of the signal system of the antioxidant-responsive element Keap1/Nrf2/ARE.

Key words: MCF-7 cell line, Keap1/Nrf2/ARE system, nuclear/cytoplasmic ratio, autophagosome, LC3B, chloroquine, synthetic monophenols, hindering