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ASSESSMENT OF ENDOGENOUS INTOXICATION AND INDICATORS OF FREE RADICAL OXIDATION IN PATIENTS WITH BREAST CANCER AND PAGET'S CANCER

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Syndrome of endogenous intoxication is among the most common syndromes in the practice of clinical oncology. Manifestations of endotoxemia in patients with cancer are multicomponent and are in interrelation with the free radical oxidative processes.

The aim of the study was a comparative evaluation of endogenous intoxication and some indicators of free radical oxidation in patients with breast cancer and Paget's cancer. It has been established that in patients with breast cancer, along with a decrease in the total albumin concentration, there are significant changes in its functional characteristics, while in patients with Paget's cancer there is only a slight decrease in the functional activity of albumin. With breast cancer, there were more significant changes in the system of nitric oxide derivatives, manifested in a greater increase (than with Paget's cancer) in the level of peroxynitrite, a trend towards an increase in nitrosoglutathione as well as in a ratio of the level of peroxynitrite and the forms of nitrogen oxide deposition. In patients with breast cancer, an almost twofold decrease in the intensity of chemiluminescence and ceruloplasmin activity was observed, while in Paget's cancer there was an increase in the oxidase activity of ceruloplasmin in the absence of a statistically significant change in the intensity of chemiluminescence. The results are consistent with the clinically more favorable course of the process in patients with Paget's cancer compared with patients with breast cancer. The possible sequence of events with increasing prevalence of malignant lesions of the breast is discussed.

Keywords: *breast cancer, Paget's cancer, endogenous intoxication, albumin, middle-weight molecules, nitric oxide derivatives, chemiluminescence of blood, ceruloplasmin.*

References

1. Pedder V.V., Naboka M.V., Kosenok V.K., Gerunova L.K., Boiko T.V., Simonova I.A., Sizykh Yu.A., Durina D.S., Mironenko V.N., Popov S.P. O vozmozhnosti korrektsii sindroma endogennoi intoksikatsii u onkologicheskikh bol'nykh s primeneniem kompleksa fizicheskikh i fizikokhimicheskikh faktorov [On the possibility of correction of the syndrome of endogenous intoxication in cancer patients with the application of a complex of physical and physicochemical factors]. *Omskii nauch. vestn*. 2012, No. 1 (108), pp. 120-125.

2. Latipova D.Kh., Protsenko S.A., Novik A.V., Semenova A.I., Nevedomskaya N.N., Kotova Z.S., Komarov Yu.I., Abramovskii S.V., Akhaeva Z.Yu., Semiglazova T.Yu. Mesto efferentnoi terapii v lechenii solidnykh opukholei [Place of efferent therapy in the treatment of solid tumors]. *Voprosy onkologii*. 2015, No. 2, pp. 174-179.

3. Goroshinskaya I.A., Neskubina I.V., Nerodo G.A., Men'shenina A.P., Gus'kova E.A., Kachesova P.S., Nemashkalova L.A., Surikova E.I., Shalashnaya E.V. Uroven' endogennoi intoksikatsii u onkoginekologicheskikh bol'nykh [The level of endogenous intoxication in oncogynecological patients]. *Klin. lab. diagnostika.* 2016, vol. 61, No. 5, pp. 279-282.

4. Goroshinskaya I.A., Neskubina I.V., Vladimirova L.Yu., Tikhanovskaya N.M., Snezhko I.V., Matveev I.A., Nemashkalova L.A., Storozhakova A.E. Sostoyanie sistemy endotoksikoza pri limfoproliferativnykh zabolevaniyakh [The state of the endotoxicosis system in lymphoproliferative diseases]. *Mezhdunar. zhurn. prikl. i fundam. issledovanii*. 2016, No. 3, ch. 4, pp. 560-564.

5. Marzhokhova A.R. *Pokazateli sindroma intoksikatsii u bol'nykh rozhei : dis. ... kand. med. nauk* [Indicators of intoxication syndrome in patients with erysipelas]. Nalchik, 2015, 172 p.

6. Gorozhanskaya E.G. Svobodnoradikal'noe okislenie i mekhanizmy antioksidantnoi zashchity v normal'noi kletke i pri opukholevykh zabolevaniyakh (lektsiya) [Free radical oxidation and mechanisms of antioxidant protection in a normal cell and in tumor diseases (lecture)]. *Klin. lab. diagnostika.* 2010, No. 6, pp. 28-44.

7. Yudakova O.V., Grigor'ev E.V. Intensivnost' POL i AOA, uroven' molekul srednei massy kak pokazatelya endogennoi intoksikatsii pri rasprostranennom peritonite [The intensity of LPO and AOA, the level of medium-mass molecules as an index of endogenous intoxication with prevalent peritonitis]. *Klin. lab. diagnostika*. 2004, No. 10, pp. 20-22.

8. Yur'eva E.A., Sukhorukov V.S., Tsaregorodtsev A.D., Vozdvizhenskaya E.S., Kharabadze M.N., Novikova N.N., Koval'chuk M.V. Izmenenie belkovykh molekul pri endogennoi intoksikatsii organizma kak faktor riska khronicheskikh obmennykh boleznei [Changes in protein molecules in endogenous intoxication of the body as a risk factor for chronic metabolic diseases]. *Molekulyarnaya meditsina*. 2013, No. 3, pp. 45-52.

9. Ray G., Husain S.A. Oxidants, antioxidants and carcinogenesis. *Indian J. Exp. Biology*. 2002, vol. 40, No. 11, pp. 1213-1232.

10. Kolb I.P. Mechanisms involved in the pro- and antiapoptotic role of NO in human leukemia. *Leukemia*. 2000, vol. 14, No. 9, pp. 1685-1694.

11. Su-Ying Q., Zhao-Xiong X., Yan-Min C. Izmeneniya oksida azota, endotelinov i superoksiddismutazy
v krovi bol'nykh gemoblastozami [Changes in nitric oxide, endothelin and superoxide dismutase in the blood of patients with hemoblastosis]. *China J. Cancer Prev. and Treat.* 2002, vol. 9, No. 5, pp. 459-461.

12. Maeda Kh., Akaike T. Oksid azota i kislorodnye radikaly pri infektsii, vospalenii i rake [Nitric oxide and oxygen radicals in infection, inflammation and cancer]. *Biokhimiya*. 1998, vol. 63, iss. 7, pp. 1007-1019.

13. Vanin A.F. Dinitrosyl iron complexes with thiol-containing ligands as a «working form» of endogenous nitric oxide. *Nitric Oxide*. 2016, vol. 54, pp. 15-29.

14. Stepuro A.I., Piletskaya T.P., Stepuro I.I. Rol' tiol'noi formy tiamina v obmene oksida azota [The role of the thiamine form of thiamine in the exchange of nitric oxide]. *Biokhimiya*. 2005, vol. 70, Iss. 3, pp. 416-429.

15. Shumaev K.B., Gubkin A.A., Gubkina S.A., Gudkov L.L., Sviryaeva I.V., Timoshin A.A., Topunov A.F., Vanin A.F., Ruuge E.K. Vzaimodeistvie dinitrozil'nykh kompleksov zheleza s intermediatami okislitel'nogo stressa [Interaction of dinitrosyl complexes of iron with intermediates of oxidative stress]. *Biofizika*. 2006, vol. 51, Iss. 3, pp. 472-477.

16. Vladimirov Yu.A., Proskurnina E.V. Svobodnye radikaly i kletochnaya khemilyuminestsentsiya [Free radicals and cellular chemiluminescence]. *Uspekhi biol. khimii*. 2009, vol. 49, pp. 341-388.

17. Men'shchikova E.B., Lankin V.Z., Zenkov N.K., Bondar' I.A., Krugovykh N.F., Trufakin V.A. *Okislitel'nyi stress. Prooksidanty i antioksidanty* [Oxidative stress. Prooxidants and antioxidants]. Moscow: Slovo, 2006, 556 p.

18. Semiglazov V.F., Merabishvili V.M., Semiglazov V.V., Komyakhov A.V., Demin E.V., Atroshchenko A.V., Kharitonov M.V. Epidemiologiya i skrining raka molochnoi zhelezy [Epidemiology and screening of breast cancer]. *Voprosy onkologii*. 2017, vol. 63, No. 3, pp. 375-384.

19. Kit O.I., Shatova Yu.S., Todorov S.S., Gudtskova T.N. Chastota vstrechaemosti razlichnykh molekulyarno-biologicheskikh podtipov raka molochnoi zhelezy v zavisimosti ot reproduktivnogo statusa [Frequency of occurrence of different molecular and biological subtypes of breast cancer depending on reproductive status]. *Ros. onkol. zhurn*. 2014, vol. 19, No. 5, pp. 24-27.

20. Kit O.I., Shatova Yu.S., Todorov S.S., Lisutin A.E., Gudtskova T.N., Kechedzhieva E.E. Geterogennost' lyuminal'nogo raka molochnoi zhelezy u zhenshchin s razlichnym reproduktivnym statusom [Heterogeneity of luminal breast cancer in women with different reproductive status]. *Ros. onkol. zhurn*. 2014, vol. 19, No. 6, pp. 14-17.

21. Nikitina E.A., Nechushkin M.I., Trigolosov A.V., Vishnevskaya Ya.V. Rak Pedzheta molochnoi zhelezy (obzor literatury) [Cancer of the Paget of the breast (review of the literature)]. *Opukholi zhenskoi reproduktivnoi sistemy*. 2016, vol. 12, No. 4, pp. 37-46.

22. Matveev S.B., Spiridonova T.G., Klychnikova E.V., Nikolaeva N.Yu., Smirnova S.V., Golikov P.P. Kriterii otsenki endogennoi intoksikatsii pri ozhogovoi travme [Criteria for assessing endogenous intoxication with burn trauma]. *Klin. lab. diagnostika*. 2003, No. 10, pp. 52-53.

23. Shestakov V.A., Boichevskaya N.O., Sherstnev M.P. Khemilyuminestsentsiya plazmy krovi v prisutstvii perekisi vodoroda [Chemiluminescence of blood plasma in the presence of hydrogen peroxide]. *Vopr. med. khimii*. 1979, vol. 25, Iss. 2, pp. 132-137.

24. Kamyshnikov V.S. *Metody klinicheskikh laboratornykh issledovanii* [Methods of clinical laboratory research]. 6th ed. Moscow: MEDpress-inform, 2013, 736 p.

25. *Lobysheva I.I., Serezhenkov V.A., Vanin A.F.* Vzaimodeistvie dinitrozil'nykh tiolsoderzhashchikh kompleksov zheleza s peroksinitritom i perekis'yu vodoroda in vitro [Interaction of dinitrosyl thiol-containing iron complexes with peroxynitrite and hydrogen peroxide in vitro]. *Biokhimiya*. 1999, vol. 64, Iss. 2, pp. 194-200.

26. Goroshinskaya I.A., Vladimirova L.Yu., Shalashnaya E.V., Nemashkalova L. A. Issledovanie pokazatelei svobodnoradikal'nykh protsessov i sostoyaniya membran u bol'nykh rakom molochnoi zhelezy [Investigation of free radical processes and membrane states in patients with breast cancer]. *Voprosy boil., med. i farm. khimii*. 2004, No. 4, pp. 46-51.

27. Sidorenko Yu.S., Goroshinskaya I.A., Vladimirova L.Yu., Neskubina I.V., Nemashkalova L.A., Shalashnaya E.V. *Sposob opredeleniya rasprostranennosti patologicheskogo protsessa pri onkologicheskikh zabolevaniyakh* [A method for determining the prevalence of a pathological process in cancer diseases]. Certificate, No 2241987. 10.12.2004. Bull. No. 34.

28. Sidorenko Yu.S., Goroshinskaya I.A., Vladimirova L.Yu., Shalashnaya E.V., Nemashkalova L.A. *Sposob prognozirovaniya effektivnosti lecheniya bol'nykh rakom molochnoi zhelezy III – IV stadii* [A method for predicting the effectiveness of treatment of patients with breast cancer of III-IV stages]. Certificate, No 2254576. 20.06.2005. Bull. No. 17.

29. Berzin S.A. Biologicheskii smysl kantserogeneza [Biological meaning of carcinogenesis]. *Vestn. ural'skoi med. akad. nauki*. 2010, No. 1, pp. 84-88.

30. Kit O.I., Frantsiyants E.M., Vashchenko L.N., Shatova Yu.S., Vladimirova L.Yu., Novikova I.A., Bandovkina V.A., Khugaeva A.N., Tokmakov V.V., Vereskunova M.I. Lokal'nyi gormonal'nyi fon opukholi i perifokal'noi zony u bol'nykh v postmenopauze pri razlichnykh biotipakh raka molochnoi zhelezy [Local hormonal background of tumor and perifocal zone in patients in postmenopause under different biotypes of breast cancer]. *Sovremennye problemy nauki i obrazovaniya.* 2016, No. 3, p. 5. Available at: https://www.science-education.ru/ru/ article/view?id=24403 (accessed 02.06.2017).

31. Goroshinskaya I.A., Shevchenko A.N., Ushakova N.D., Filatova E.V., Nemashkalova L.A., Duritskii M.N. Otsenka endogennoi intoksikatsii i urovnya belkov ostroi fazy u onkourologicheskikh bol'nykh v zavisimosti ot techeniya zabolevaniya [Evaluation of endogenous intoxication and level of acute phase proteins in oncourologic patients depending on the course of the disease]. *Klin. lab. diagnostika*. 2017, vol. 62, No. 11, pp. 666-671.

32. Kopytova T.V., Kotkova E.V., Dobrotina N.A. Okislitel'naya modifikatsiya al'bumina syvorotki krovi cheloveka pri vospalitel'nykh zabolevaniyakh kozhi [Oxidative modification of human serum albumin in inflammatory skin diseases]. *Vestn. Nizhegorodskogo un-ta im. N.I. Lobachevskogo*. 2014, No. 3 (1), pp. 65-69.

33. Goroshinskaya I.A., Nerodo G.A., Surikova E.I., Kachesova P.S., Vnukov V.V., Shalashnaya E.V., Neskubina I.V., Nemashkalova L.A., Maksimova N.A., Sergeeva M.M. Intensivnost' khemilyuminestsentsii, sos-

toyanie antioksidantnoi sistemy i okislitel'naya modifikatsiya belkov plazmy krovi pri razvitii retsidiva raka yaichnikov [Intensity of chemiluminescence, the state of the antioxidant system and oxidative modification of plasma proteins in the development of recurrent ovarian cancer]. *Sib. onkol. zhurn.* 2013, vol. 26, No. 4 (58), pp. 45-49.

34. Goroshinskaya I.A., Shevchenko A.N., Filatova E.V., Kachesova P.S., Nemashkalova L.A., Chudilova A.V. Vliyanie vnutripuzyrnoi khimioterapii, modifitsirovannoi skaniruyushchim elektromagnitnym polem, na uroven' endotoksikoza i okislitel'nye protsessy v krovi bol'nykh rakom mochevogo puzyrya [Influence of intravesical chemotherapy modified by a scanning electromagnetic field on the level of endotoxicosis and oxidative processes in the blood of patients with bladder cancer]. *Ros. onkol. zhurn.* 2017, vol. 22, No. 3, pp. 142-148.

35. Goroshinskaya I.A., Golotina L.Yu., Vladimirova L.Yu., Snezhko I.V., Shalashnaya E.V., Nemashkalova L.A., Neskubina I.A., Kachesova P.S. Prognosticheskoe znachenie pokazatelei sostoyaniya membran i svobodnoradikal'nykh protsessov v krovi onkologicheskikh bol'nykh [Prognostic value of indicators of the state of membranes and free radical processes in the blood of cancer patients]. *Izv. vuzov. Sev.-Kavk. region. Estestv. nauki*. Special Issue. 2005, pp. 27-30.

36. Turpaev K.T. Aktivnye formy kisloroda i regulyatsiya ekspressii genov [Active forms of oxygen and regulation of gene expression]. *Biokhimiya*. 2002, vol. 67, iss. 3, pp. 339-352.

37. Korman D.B., Potapov S.L. Rak molochnoi zhelezy i nenasyshchennost' lipidov krovi [Breast cancer and unsaturation of blood lipids]. *Voprosy onkologii*. 1997, vol. 43, No. 2, pp. 164-170.

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LEVELS OF SOME VEGF FAMILY MEMBERS IN CLEAR CELL RENAL CELL CARCINOMA

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Aim. *Comparable analysis of levels of VEGF-D, VEGF-A and VEGF-R1 in kidney tissues (tumor, its perifocal zone and intact tissues) in local and advanced clear cell renal cell carcinoma.*

Material and methods. *10% cytosolic fractions of kidney tissues (tumor, its perifocal zone and intact tissues) were studied. Levels of VEGF-D, VEGF-A and VEGF-R1 were determined by ELISA using standard test systems.*

Results. *Comparable analysis of VEGF-D, VEGF-A, and VEGF-R1 levels in kidney tissues (tumor, its perifocal zone and intact tissues) in local and advanced clear cell renal cell carcinoma was performed. VEGF-A levels in tumors in local cancer were significantly lower than in intact tissues – by 31%, and VEGF-R1 levels were 45% lower. Tumor tissues in advanced cancer showed overexpression of the angiogenic growth factor VEGF-A and inhibition of the angiogenesis suppressor VEGF-R1. VEGF-D levels in all tissues in local and advanced renal cancer were similar.*

Conclusions*. The results showed that lymphogenous tumor spread and development was not predominant in renal carcinoma. Advanced renal cancer was accompanied by the VEGF-A overexpression and the VEGF-R1 inhibition.*

Keywords: *growth factor, receptor, clear cell renal cell carcinoma, local cancer, advanced cancer.*

References

1. Ljungberg B., Bensalah K., Bex A., Canfield S., Dabestani S., Hofmann F., Hora M., Kuczyk M.A., Lam T., Marconi L., Merseburger A.S., Mulders P.F.A., Powles T., Staehler M., Volpea A. Rekomendatsii Evropeiskoi assotsiatsii urologov. 2014 g. Pochechno-kletochnyi rak: metodicheskie rekomendatsii [Recommendations of the European Association of Urologists. 2014 Renal cell cancer: methodological recommendations]. *RMZh*. 2014, No. 17, pp. 1218-1233.

2. Kaprin A.D. *Zlokachestvennye novoobrazovaniya v Rossii v 2015 g. (zabolevaemost' i smertnost')* [Malignant neoplasms in Russia in 2015 (morbidity and mortality)]. Eds. A.D. Kaprin, V.V. Starinskii, G.V. Petrova. Moscow: Mosk. nauch.-issled. onkol. in-t im. P.A. Gertsena – filial Nats. med. issled. radiol. tsentra Minzdrava Rossii, 2017, 250 p.

3. Gershtein E.S., Kolpakov A.V., Bezhanova S.D., Morozov A.A., Alferov A.A., Ognerubov N.A., Kazantseva I.A., Kushlinskii N.E. Markery angiogeneza v syvorotke krovi bol'nykh rakom pochki [Markers of angiogenesis in the serum of patients with kidney cancer]. *Vestn. TGU*. 2017, vol. 22, iss. 2, pp. 289-296.

4. Kushlinskii N.E., Krasil'nikova M.A. *Biologicheskie markery opukholei: fundamental'nye i klinicheskie issledovaniya* [Biological markers of tumors: fundamental and clinical research]. Moscow: Izd-vo RAMN, 2017, 634 p.

5. Kiseleva E.P., Krylov A.V., Starikova E.A., Kuznetsova S.A. Faktor rosta sosudistogo endoteliya i immunnaya sistema [Vascular endothelium growth factor and immune system]. *Uspekhi sovrem. biologii.* 2009, vol. 129, No. 4, pp. 336-347.

6. Kit O.I., Frantsiyants E.M., Dimitriadi S.N., Shevchenko A.N., Kaplieva I.V., Tripitaki L.K. Ekspressiya markerov neoangiogeneza i fibrinoliticheskoi sistemy v dinamike eksperimental'noi ishemii pochki u krys [Expression of markers of neoangiogenesis and fibrinolytic system in the dynamics of experimental kidney ischemia in rats]. *Eksperim. i klin. urologiya.* 2015, No. 1, pp. 20-23.

7. Khochenkova Yu.A., Chkadua G.Z., Malivanova T.F., Stepanova E.V. VEGF i protivoopukholevyi immunitet [VEGF and antitumor immunity]. *Immunologiya*. 2013, No. 3, pp. 172-175.

8. Tyrsina E.G., Nikulitskii S.I. Rol' regulyatornoi VEGF/VEGF-R1-sistemy v opukholevom angiogeneze (obzor literatury) [Role of the regulatory VEGF / VEGF-R1 system in tumor angiogenesis (review of the literature)]. *Onkoginekologiya*. 2015, No. 4, pp. 4-12.

9. Poveshchenko A.F., Konenkov V.I. Mekhanizmy i faktory angiogeneza [Mechanisms and factors of angiogenesis]. *Uspekhi fiziol. nauk*. 2010, vol. 41, No. 2, pp. 68-89.

10. Nefedova N.A., Davydova S.Yu. Rol' sosudisto-go endotelial'nogo faktora rosta (VEGF) i gipoksiei indutsibel'nogo faktora (HIF) v opukholevom angiogeneze [The role of vascular endothelial growth factor (VEGF) and hypoxia of inducible factor (HIF) in tumor angiogenesis]. *Sovrem. problemy nauki i obrazovaniya.* 2015, No. 3. Available at: https://www.science-education.ru/ru/article/view?id=17924 (accessed 19.10.2017).

11. Spirina L.V., Kondakova I.V., Usynin E.A., Vintizenko S.I. Regulyatsiya angiogeneza pri zlokachestvennykh novoobrazovaniyakh pochki i mochevogo puzyrya [Regulation of angiogenesis in malignant neoplasms of the kidney and bladder]. *Sib. onkol. zhurn*. 2008, No. 4 (28), pp. 65-70.

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EFFECT OF EXPERIMENTAL CHRONIC PAIN ON LEVELS OF BIOGENIC AMINES IN SKIN OF MICE IN DYNAMICS OF B16/F10 MELANOMA GROWTH

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Chronic pain is a prominent stressor with many neurotransmitters involved in its mechanisms. The greatest number of nociceptors is located in the skin, muscles and walls of blood vessels. ***The aim*** *of the study was the determination of levels of biogenic amines in the skin of mice with chronic pain in the dynamics of experimental B16/F10 melanoma growth.* ***Material and methods.*** *The study included female C57BL/6 mice (n=64) with transplanted B16/F10 melanoma divided into the main and control groups (animals with and without chronic pain, respectively). Levels of biogenic amines (histamine, serotonin, norepinephrine, dopamine and epinephrine) were determined by ELISA in homogenates of the skin, tumors and perifocal zone. Statistical processing of the data was performed using STATISTICA 10.0.* ***Results.*** *The experimental study demonstrated that chronic pain promoted B16/F10 melanoma progression in mice and triggered metastasis. Chronic pain caused an imbalance between the adrenergic and serotonergic systems contributing to the skin barrier dysfunction. As a result, melanoma was highly aggressive and metastasized rapidly.*

Keywords: *chronic pain, B16/F10 melanoma, biogenic amines, serotonin, norepinephrine, dopamine, histamine.*

References

1. Davydov O.S. Khronizatsiya boli: faktory riska, mekhanizmy i vozmozhnosti preduprezhdeniya [Chronic pain: risk factors, mechanisms and possibilities of prevention]. *Lechashchii vrach*. 2017, No. 5. Available at: https://www.lvrach.ru /2017/05/15436717/ (accessed 09.09.2017).

2. Ovechkin A.M. Klinicheskaya patofiziologiya i anatomiya ostroi boli [Clinical pathophysiology and anatomy of acute pain]. *Regionarnaya anesteziya i lechenie ostroi boli*. 2012, vol. 1 (6), pp. 32-40.

3. Kukushkin M.A., Khitrov N.K. *Obshchaya patologiya boli* [General pathology of pain]. Moscow, 2004, 141 p.

4. Franciane B., Alarcón Ferreira T.A., Cordova M.M., Dombroski P.A., da Cunha C., Kanha do Espiritu Santo C., Poli A., Gomez R., Pires W., Martins-Silva C., Sluka K.A., Soares Santos A.R. The role of brain serotonin in the analgesia produced by low intensity on neuropathic pain after sciatic nerve injury in mice. *Pain*. 2015, vol. 156 (12), pp. 2595-2606. DOI 10.1097/j.pain.0000000000000372. PMCID: PMC4666012. NIHMSID: NIHMS736878.

5. Calvani M., Pelon F., Comito G., Taddei M.L., Moretti S., Innocenti S., Nassini R., Gerlini G., Borgognoni L., Bambi F., Giannoni E., Filippi L., Chiarugi P. Norepinephrine promotes tumor microenvironment reactivity through β3-adrenoreceptors during melanoma progression. *Oncotarget*. 2015, vol. 6 (7), pp. 4615-4632.

6. Yang E.V., Kim S.J., Donovan E.L., Chen M., Gross A.C., Webster Marketon J.I., Barsky S.H., Glaser R. Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression. *Brain Behav Immun*. 2009, vol. 23 (2), pp. 267-275. DOI 10.1016/j.bbi.2008.10.005. PMID: 18996182.

7. Sloan E.K., Priceman S.J., Cox B.F., Yu.S., Pimentel M.A., Tangkanangnukul V., Arevalo J.M., Morizono K., Karanikolas B.D., Wu L., Sood A.K., Cole S.W. The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Res*. 2010, vol. 70 (18), pp. 7042-7052. DOI 10.1158/0008-5472.CAN-10-0522. PMID: 20823155.

8. Tilan J., Kitlinska J. Sympathetic Neurotransmitters and Tumor Angiogenesis-Link between Stress and Cancer Progression. *J. Oncol.* 2010, vol. 2010. Article ID 539706. DOI 10.1155/2010/539706. PMID: 20508839.

9. Zmijewski M.A., Slominski A.T. Neuroendocrinology of the skin: An overview and selective analysis. *Dermatoendocrinol.* 2011, vol. 3 (1), pp. 3-10. DOI 10.4161/derm.3.1.14617.

10. Slominski A. Neuroendocrine activity of the melanocyte. *Exp. Dermatol*. 2009, vol. 18 (9), pp. 760-773. DOI 10.1111/j.1600-0625.2009.00892.x. PMID: 19558501.

11. Cichorek M., Wachulska M., Stasiewicz A., Tymińska A. Skin melanocytes: biology and development Postepy. *Dermatol. Alergol.* 2013, vol. 30 (1), pp. 30-41. DOI 10.5114/pdia.2013.33376. PMID: 24278043.

12. Plonka P.M., Passeron T., Brenner M., Tobin D.J., Shibahara S., Thomas A., Slominski A., Kadekaro A.L., Hershkovitz D., Peters E., Nordlund J.J., Abdel-Malek Z., Takeda K., Paus R., Ortonne J.P., Hearing V.J., Schallreuter K.U. What are melanocytes really doing all day long?... *Exp. Dermatol.* 2009, vol. 18 (9), pp. 799-819. DOI 10.1111/j.1600-0625.2009.00912.x. PMID: 19659579.

13. Nikolakis G., Stratakis C.A., Kanaki T., Slominski A., Zouboulis C.C. Skin steroidogenesis in health and disease. *Rev. Endocr. Metab. Disord.* 2016, vol. 17 (3), pp. 247-258. PMID: 27761789.

14. Slominski A.T., Zmijewski M.A., Skobo C., Zbytek B., Slominski R.M., Steketee J.D. Sensing the environment: Regulation of local and global homeostasis by the skin neuroendocrine system. *Adv. Anat. Embriol. Cell. Biol.* 2012, vol. 212, p. 115. PMCID: PMC3422784. NIHMSID: NIHMS366475.

15. Situm M., Buljan M., Bulić S.O., Simić D. The mechanisms of UV radiation in the development of malignant melanoma. *Coll. Antropol.* 2007, vol. 31, suppl. 1, pp. 13-16. PMID: 17469742.

16. Gillbro J.M., Marles L.K., Hibberts N.A., Schallreuter K.U. Autocrine catecholamine biosynthesis and the beta-adrenoceptor signal promote pigmentation in human epidermal melanocytes. *J. Invest. Dermatol.* 2004, vol. 123, pp. 346-353.

17. Nordlind K., Azmitia E.C., Slominski A. The skin as a mirror of the soul: exploring the possible roles of serotonin. *Exp. Dermatol.* 2008, vol. 17, pp. 301-311.

18. Connelly W.M., Shenton F.C., Lethbridge N., Leurs R., Waldvogel H.J., Faull R.L., Lees G., Chazot P.L. The histamine H4 receptor is functionally expressed on neurons in the mammalian CNS. *Br. J. Pharmacol.* 2009, vol. 157 (1), pp. 55-63. DOI 10.1111/j.1476-5381.2009.00227.x. PMID: 19413571.

19. Galeotti N., Sanna M.D., Ghelardini C. Pleiotropic effect of histamine H4 receptor modulation in the central nervous system. *Neuropharmacology*. 2013, vol. 71, pp. 141-147. DOI 10.1016/j.neuropharm.2013.03.026. PMID: 23583928

20. Takeshita K., Sakai K., Bacon K.B., Gantner F. Critical Role of Histamine H4 Receptor in Leukotriene B4 Production and Mast Cell-Dependent Neutrophil Recruitment Induced by Zymosan in Vivo. *J. Pharmacol. Exp. Ther*. 2003, vol. 307 (3), pp. 1072-1078.

21. Lazewska D., Kiec-Kononowicz K. Azines as histamine H4 receptor antagonists. *Front Biosci. (School Ed).* 2012, vol. 4, pp. 967-987. PMID: 22202103.

22. Goncharenko E.N., Akhalaya M.Ya., Kudryasho va N.Yu. Vliyanie prirodnogo radioprotektora karnozina na sistemu gistamin-diaminoksidaza miokarda krys posle deistviya razlichnykh ekstremal'nykh faktorov [Influence of the natural radioprotector of carnosine on the histamine-diaminoxidase system of rat myocardium after the action of various extreme factors]. *Radiatsionnaya biologiya*. 2001, iss. 1, pp. 56-58.

23. Qin Y.S., Zhang X., Li L., Yu H.L. Effect of histamine on metastasis of melanoma B16 cell xenograft in C57BL/6 mice. *Ai Zheng*. 2007, vol. 26 (8), pp. 833-836.

24. Massari N.A., Medina V.A., Cricco G.P., Martinel Lamas D.J., Sambuco L., Pagotto R., Ventura C., Ciraolo P.J., Pignataro O., Bergoc R.M., Rivera E.S. Antitumor activity of histamine and clozapine in a mouse experimental model of human melanoma. *J. Dermatol Sci.* 2013, vol. 72 (3), pp. 252-262. DOI 10.1016/j.jdermsci.2013.07.012. PMID: 23999004.

25. Massari N.A., Nicoud M.B., Sambuco L., Cricco G.P., Martinel Lamas D.J., Herrero Ducloux M.V., Blanco H., Rivera E.S., Medina V.A. Histamine therapeutic efficacy in metastatic melanoma: Role of histamine H4 receptor agonists and opportunity for combination with radiation. *Oncotarget*. 2017, vol. 8 (16), pp. 26471-26491. DOI 10.18632/oncotarget.15594. PMID: 28460440.

26. Li S., Sun Y., Gao D. Role of the nervous system in cancer metastasis (Review). *Oncol. Letters*. 2013, vol. 5 (4), pp. 1101-1111. DOI 10.3892/ol.2013.1168.

27. Wnorowski A., Sadowska M., Paul R.K., Singh N.S., Boguszewska-Czubara A., Jimenez L., Abdelmohsen K., Toll L., Jozwiak K., Bernier M., Wainer I.W. Activation of β2-adrenergic receptor by (R,R')-4'-methoxy-1-

naphthylfenoterol inhibits proliferation and motility of melanoma cells. *Cell Signal*. 2015, vol. 27 (5), pp. 997-1007. DOI 10.1016/j.cellsig.2015.02.012. PMID: 25703025.

28. Wirdefeldt K., Weibull C.E., Chen H., Kamel F., Lundholm C., Fang F., Ye W. Parkinson's disease and cancer: a register-based family study. *Am. J. Epidemiol.* 2014, vol. 179, pp. 85-94.

29. Lubbe S.J., Escott-Price V., Brice A., Gasser T., Pittman A.M., Bras J., Hardy J., Heutink P., Wood N.M., Singleton A.B., Grosset D.G., Carroll C.B., Law M.H., Demenais F., Iles M.M. International Parkinson's Disease Genomics Consortium. Rare variants analysis of cutaneous malignant melanoma genes in Parkinson's disease. *Neurobiol. Aging.* 2016, vol. 48, pp. 222.e1-222.e7. DOI 10.1016/j.neurobiolaging.2016.07.013. PMID: 27640074.

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