INDICATORS OF THE ANTIOXIDANT SYSTEM OF THE RED BLOOD CELLS IN PATIENTS WITH LUNG CANCER

V.M.Nikolaev[1;2], F.G.Ivanova[1;4], A.G.Egorova[1], L.V.Grigorieva[1], N.K.Chirikova[3], S.S.Nahodkin[2;3],T.I.Ksenofontova[3], N.A.Barashkov[1;2], T.S.Markova[3], S.D.Efremova[1], F.V.Vinokurova[1], S.A.Fedorova[1;2], P.M.Ivanov[1;4]

[1]- Department of adaptation mechanisms Laboratory of immunological mechanisms of adaptation, FSBI « Yakut scientific center of integrated medical problems» Siberian branch of Russian Academy of Medical Sciences

[2]- Scientific Research Laboratory of Molecular Biology, M.K. Ammosov North-Eastern Federal University Biology and Geography Faculty

[3]- M.K. Ammosov North-Eastern Federal University Biology and Geography Faculty Biochemistry and Biotechnology Department

[4]- SBI Sakha Republic «Yakut republic oncologic dispensary» Department of chemotherapy

Summary

This paper presents the results of glutathione study in the patients with lung cancer. 40 patients with lung cancer admitted to the Yakut Republican Oncology dispensary with lung cancer diagnosis were examined. The control group of 60 patients was matched for age, sex and ethnicity. The main criterion for the selection of control group was absence of oncologic diseases. Research material was venous blood taken from the ulnar veins.

The intensity of free radical oxidation of lipids was determined by the spectrophotometric methods on accumulation TBA – active products (TBA-AP). The antioxidant defense quotients were determined by the activity of glutathione peroxidase, glutathione reductase, glutathione transferase, concentration of reduced glutathione.

The results show the intensification of free radical oxidation of lipids and depletion of glutathione system in the organism.

Keywords: glutathione, glutathione peroxidase, glutathione reductase, glutathione transferase, reduced glutathione.

Introduction

Special attention in the pathogenesis of cancer has been given to the role of oxidative stress in the body. Nowadays it is regarded as the universal unspecific mechanism of initiation of tumoral stature [1,13,7]. Active oxygens' molecules and reactions of peroxide lipoid oxidation can be

regarded as universal mechanism of tumoral transformation denotating spontaneous or induced carcinogenesis [6,11,4,5].

As long as free-radical reactions generate numerous pathologic changes there must be a system deterring excessive formation of radicals. Antioxidant system controls intensity of free-radical reactions in intracellular and extracellular space of organism [1,2,3]. System of glutathione can give the significant information about condition of antioxidant system in organism of patients with lung cancer [6].

The objective of research is the studying of level of reduced glutathione, glutathione transferase, glutathione peroxidase, glutathione reductase in patients with lung cancer.

Research material and methods

40 patients with lung cancer admitted to the Yakut Republican Oncology dispensary with lung cancer diagnosis were examined. The control group of 60 patients was matched for age, sex and ethnicity. The main criterion for the selection of control group was absence of oncologic diseases. Research material was venous blood which was taken from the ulnar veins.

The intensity of free radical oxidation of lipids was determined by the spectrophotometric methods on accumulation TBA – active products (TBA-AP) [8]. The antioxidant defense quotients were determined by the activity of glutathione peroxidase [8], glutathione reductase [8], glutathione transferase [10], concentration of reduced glutathione [9].

Statistical analysis of the data was performed using statistical software application package SPSS for Windows 10.0 .There were used standart methods of variation statistic: calculation of average values, standart errors , 95% confidential interval. The reliability of differences between means were evaluated using the criterion Student's t-distribution for independent samples.

Results and discussion

We observed an increase in the intensity of free radical oxidation in examined group of lung cancer patients. So in the body of patients the average content of TBA-AP in the blood was 1.5 higher than reference value (1.61 ±0.10 mmol/l) and equal to 2.39±0.32 mmol/l.

System status was evaluated by the concentration of reduced glutathione and enzyme activity: glutathione transferase, glutathione peroxidase, glutathione reductase.

It is known that in conditions of oxidative stress the erythrocytes are strengthened, hydrogen peroxide and other lipoperoxidase are compounded. Glutathione peroxidase provides the destruction of peroxidase in erythrocytes. The value of the activity of glutathione peroxidase in blood erythrocyte of patients was 3.2 times (0.19±0.001 mmol/min*gHb) lower than the same period in control group (0.61±0.005 mmol/min*gHb) (p=0.025).

Except of glutathione peroxidase, a family of glutathione transferase present in the cells, the

main function is – to protect cells against xenobiotics and lipid peroxidation products through their recovery, compounding to substrate of molecule glutathione or nucleophilic substitution of hydrophobic groups [3,14]. Unlike glutathione for which the best substrates are hydrophilic hydroperoxide , glutathione transferase do not react with hydrogen peroxide, but effectively reduced hydroperoxide polyunsaturated fatty acids (linoleic and arachidonic) phospholipid hydroperoxide and mononucleotide and DNA, participating in their repair. In addition glutathione transferase conjugate with reduced glutathione toxic products of lipid peroxidation (nonene, dotsenali) facilitating their removal from the body. The significance of a multigene family of glutathione transferase in cell protection in the development of different types of cancer is confirmed in many studies [16,15,12].

In our study, the average activity of glutathione transferase in cancer patients actually did not differ from controls. So in the body of patients with a tumor activity of glutathione transferase was 2.42±0.01 mol/min*gHb, in control group – 2.44±0.07 mol/min*gHb.

In studying of reduced glutathione's content we have found its concentration in tumor patients significally (p=0.042) decreased by 1.4 times compared with the control group (2.32±0.09 mmol/gHb) and equal to 1.65±0.01mmol/gHb. Decrease in the erythrocytes of reduced glutathione in patients with lung cancer can probably be caused by the high consumption rate and its low rate of recovery. The maintenance of high level of reduced glutathione due to the recovery of his disulfide form is provided by the glutathione reductase. In the studied group of patients the activity of glutathione reductase was (p=0.038) lower than the control significance (6.8±0.30 mol/min*gHb) 1.6 times and amounted to 4.30±0.05 mol/min*gHb. There is no regeneration of glutathione in blood erythrocytes in patients with oncopathology. The reason of this phenomenon is unsufficient regeneration of NADPH in the pentose phosphate pathway

Thus, the results of our study showed patients with lung cancer have depletion og glutathione , as evidenced by reduction in the concentration of reduced glutathione, glutathione peroxidase enzymes activity and glutathione reductase. But the level of activity of glutathione transferase did not differ from the average significance of this indicator in the control group.

Conclusions

1. It was found an increase in the concentration of TBA-AP in the blood of patients with lung cancer by 1.5 times as compared with those without cancer pathology that tells about intensification of free radical oxidation.

2. The depletion of glutathione as evidenced by decreased activity of enzymes of glutathione reductase and decrease in the concentration of reduced glutathione were observed in the body of patients with lung cancer.

3. The activity of glutathione do not differ from the significance of this indicator in the control group while depletion of glutathione in patients oncopathology.

References

1. Vinokourov E.A. Frank N. Boyarskikh N.V. et al. Antioksidantnaya aktivnost i perekisnoye okisleniye lipidov u bolnykh rakom endometriya [The antioxidant activity and lipid peroxidation in patients with endometrial cancer] Zh. Sibirskiy onkologicheskiy zhurnal [J. Siberian Journal of Oncology]. 2007, №1, pp. 125 - 126.

2. Dubinina E.E. Rol aktivnykh form kisloroda v kachestve signalnykh molekul v metabolizme tkaney pri sostoyanii okislitelnogo stressa [The role of reactive oxygen species as signal molecules in the metabolism of tissues in a state of oxidative stress] Zh. Voprosy meditsinskoy khimii [Questions of medicinal chemistry]. 2001, № 6, pp. 558 - 561.

3. Zenkov N.K. Menshchikova E.B. Okislitelnyy stress: Biokhimicheskiy i patofiziologicheskiy aspekty [Oxidative stress: Biochemical and pathophysiological aspects]. Moscow, 2001,343 p.

4. Kaynova E.A. Sravnitelnyy analiz vyzhivayemosti i limfoidno-epitelialnyye otnosheniya pri variantakh ploskokletochnogo raka legkogo [A comparative analysis of survival and lymphoid epithelial relationship with variants of squamous cell lung cancer] Sbornik nauchnykh rabot studentov i molodykh uchenykh YaGMA [Collection of scientific works of students and young scientists YAGMA].Yaroslavl, 2007, pp. 19 - 20.

5. Panchenko K.I. Vyzhivayemost bolnykh pri ploskokletochnom rake legkogo razlichnogo gistologicheskogo stroyeniya [Survival of patients with squamous cell carcinoma of lung different histological structure] 30 let klinicheskoy bolnitse №9 g. Yaroslavlya: Materialy nauchno-prakticheskoy konferentsii [30 years of clinical hospital № 9 of Yaroslavl: Proceedings of the conference]. Yaroslavl, 1998, pp.121- 123.

6. Bernstein L.M. Vakulenko A.V. Wisniewski A.S. Tsyrlina E.V. Perekisnoye okisleniye lipidov v tkani raka endometriya: svyaz s gormonochuvstvitelnostyu opukholi i gormonalnym kantserogenezom [Lipid peroxidation in the tissue of endometrial cancer: association with hormone-sensitive tumors and hormonal carcinogenesis] Zh. Voprosy onkologii [Problems of Oncology]. 1996, № 3. pp. 37 - 39.

7. Ivanov P.M. Tomskiy M.I. Kipriyanova N.S. et al. Sovremennoye sostoyaniye i problemy spetsializirovannoy onkologicheskoy pomoshchi naseleniyu Yakutii [The current state and problems of specialized cancer care to the population of Yakutia] Yakutskiy meditsinskiy zhurnal [Yakut Medical Journal]. Yakutsk, 2011, № 1, pp. 5 - 9.

8. Danilova L.A. Spravochnik po laboratornym metodam issledovaniya [Reference Laboratory Methods]. Saint Petersburg, 2003, pp. 398 - 399.

9. Griffith O.W. Determination of Glutathione and Glutathione Disulfide Using Glutathione Reductase and 2-Vinylpyridine / O.W. Griffith // Anal. Biochem. 1980. – V.106. P. 207 - 212.

10. Habig, W. H. Glutathione-S-transferases: The first enzymatic step in mercapturic acid formation / W. H. Habig, M. J. Pabst, W. B. Jakoby // J. Biol. Chem. - 1974. V.249. P. 7130–7139.

11. Lack of PTEN expression in endometrial intraepithelial neoplasia is correlated with cancer progression / J.P. Baak, B. Van Diermen, A. Steinbakk et al. //Hum. Pathol. – 2005. – V. 36, №5. P. 555 - 561.

12. A population-based study of glutathione S-transferase M1, T1 and P1 genotypes and risk for lung cancer / V. Nazar-Stewart, T.L. Vaughan, P. Stapleton et. al., // Lung Cancer. – 2003. - V.40. P.247 - 258.

13. Obeidat B. The diagnosis of endometrial hyperplasia on curettage: how reliable is it? /B. Obeidat, A. Mohtaseb, I. Matalka //Arch. Gynecol. Obstet. – 2009. – V.279, N4. P. 489 - 492.

14. Pennant, S. Endometrial atypical hyperplasia and subsequent diagnosis of endometrial cancer: a retrospective audit and literature review / S. Pennant, S. Manek, S. Kehoe // J. Obstet. Gynecol. – 2008. – V.28, N6. P. 632 - 633.

15. Combined effect of polymorphic GST genes on individual susceptibility to lung cancer / Saarikoski S.T., Voho A., Reinikainen M., et al., // Int J Cancer. - 1998. - V.77. P.516 – 521.

16. Isoenzyme(s) of glutathione transferase (class A) as a marker for the susceptibility to lung cancer: a follow up study / Seidegard J., Pero R.W., Markowitz M.M. et al. // Carcinogenesis. – 1990. – V.11. P.33 – 36.

Information about the authors:

1. Nikolaev Vyacheslav Mikhailovich, PhD, Senior Scientist, Laboratory of immunological mechanisms of adaptation, YSC CMP SB RAMS, Yakutsk, Russia, e -mail: Nikolaev1126@mail.ru.
2. Egorova Aytalina Grigor'evna, Ph.D, Senior Scientist of the laboratory of medical and social research and study of the functional reserve of human, YSC CMP SB RAMS, Yakutsk, Russia. E-mail: aitalina@mail.ru.
3. Grigorieva Lena Valer'evna, PhD, Head of the Laboratory of immunological mechanisms of adaptation, YSC CMP SB RAMS, Yakutsk, Russia. e -mail: lenagrigor@rambler.ru.
4. Markova Tuyana Sergeevna, Ph.D, Senior Scientist, Laboratory of immunological mechanisms of adaptation, YSC CMP SB RAMS, Yakutsk , Russia.
5. Barashkov Nikolai Alexeevich, PhD, Researcher, Laboratory of Molecular Biology, YSC CMP SB RAMS, Yakutsk, Russia. e -mail: barashkov2004@mail.ru
6. Efremova Svetlana Dmitr'evna, research assistant, laboratory of immunological mechanisms of adaptation, YSC CMP SB RAMS, Yakutsk, Russia.
7. Vinokurova Fekla Vasil'evna, junior Scientist, laboratory of immunological mechanisms of adaptation, YSC CMP SB RAMS, Yakutsk, Russia.
8. Fedorova Sardana Arkadyevna, D. of Biology, head of the Laboratory of Molecular Genetics, YSC CMP SB RAMS, Yakutsk, Russia, e -mail: sardaanafedorova@mail.ru
9. Ivanov Pyotr Mikhailovich, MD, prof., MI NEFU, Head of the Laboratory of precancerogenesis and malignant tumors, YSC CMP SB RAMS, Yakutsk, Russia.
10. Ivanova Feodosiia Gavril'evna, PhD, Head of the Department of chemotherapy, Yakut Republican Cancer Center, Yakutsk, Russia. E-mail: feodossiaiv@inbox.ru.
11. Chirikova Nadezhda Konstantinovna, PhD (pharmacy), Associate Professor of Department of Biochemistry and Biotechnology, BGF, MK Ammosov NEFU, Yakutsk, Russia, e -mail: hofnung@mail.ru
12. Nakhodkin Sergey Sergeevich, a graduate student, Department of Biochemistry and Biotechnology, BGF, MK Ammosov NEFU, Yakutsk, Russia, e -mail: sergnahod@mail.ru
13. Ksenofontova Tuyara Ivanovna, a graduate student, Department of Biochemistry and Biotechnology, BGF, MK Ammosov NEFU, Yakutsk, Russia.