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ORIGINAL ARTICLE

Free radical oxidation and antioxidant defense in uterine myoma and endometrioid adenocarcinoma depending on its degree of differentiation

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ABSTRACT

Purpose of the study. To evaluate the features of free radical oxidation (FRO) and the principal enzymatic and non-enzymatic links of antioxidant defense in proliferating tissues of benign myoma and malignant endometrioid adenocarcinoma (EA) with varying degrees of differentiation.

Patients and methods. Patients who received surgical treatment for EA (n = 42) and uterine myoma (n = 14) were examined. Patients with stage Ia (n = 26) and stage Ib (n = 16) of disease were selected. 16 patients had highly differentiated (G1) EA, 12 had moderately differentiated (G2) EA, and 14 had low-differentiated (G3) EA. The activity of superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), glutathione transferase (GST), reduced glutathione (GSH), vitamins A and E, lipid peroxidation products diene conjugates (DC) and malondialdehyde (MDA) were determined colorimetrically in the tissues of EA, myoma and intact uterus.

Results. Compared with the level in intact tissue, SOD decreased by 3.2 times and GST increased by 2.7 times in myoma ($p < 0.01$). Similar changes were noted for EA G1 – on average by 5.3 times ($p < 0.01$) and also DC increased by 2.2 times ($p < 0.05$). In EA G2 tissue, SOD and GPx activities were lower than in the intact tissue, by 5.7 and 4.5 times, respectively ($p < 0.05$), and lower GST, GPx and GSH than in the EA G1, by 4.9, 8.9 and 1.6 times, respectively ($p < 0.05 – p < 0.01$). In EA G3 tissue, there was an increase in GSH, GPx and GST from 1.5 to 7.1 times ($p < 0.05 – p < 0.01$) and lipid peroxidation products by an average of 2.5 times ($p < 0.05$), as well as a decrease in vitamins A and E by 2.9 and 4.6 times, respectively ($p < 0.05$) compared with the intact tissue. The tissue of the EA G2 had a minimal level of activity of the GSH-dependent system.

Conclusion. The results reflect the differences in the mechanisms of proliferation regulation by FRO in myomas and in the EA tissue with changes in its differentiation. Knowledge of the characteristics of individual links in the regulation of FRO can play a certain role in the use of antioxidant therapy for benign or malignant tumors of the uterus.

Keywords: endometrial cancer, uterine myoma, endometrioid adenocarcinoma, degree of differentiation, free radical oxidation, antioxidant enzymes, glutathione-dependent system, vitamins A and E

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3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Состояние процессов свободнорадикального окисления и антиоксидантной защиты в миоме матки и в эндометриоидной аденокарциноме в зависимости от ее степени дифференцировки

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РЕЗЮМЕ

Цель исследования. Оценить особенности свободнорадикального окисления (СРО) и основных ферментативных и неферментативных звеньев антиоксидантной защиты в пролиферирующих тканях доброкачественной миомы и злокачественной эндометриоидной аденокарциномы (ЭА) с различной степенью ее дифференцировки.
Пациенты и методы. Обследованы больные, получившие хирургическое лечение по поводу ЭА (n = 42) и миомы матки (n = 14). Больные с ЭА Ia (n = 26) и Ib (n = 16) стадией. У 16 больных была высокодифференцированная (G1) ЭА, у 12 умереннодифференцированная (G2) ЭА, у 14 низкодифференцированная (G3) ЭА. В тканях ЭА, миомы, интактной матки колориметрически определяли активность ферментов супероксиддисмутазы (СОД), каталазы, глутатионпероксидазы (ГПО), глутатионтрансферазы (ГТ), содержание восстановленного глутатиона (GSH), витаминов А/Е, продуктов перекисного окисления липидов (ПОЛ) диеновых конъюгатов (ДК) и малонового диальдегида (МДА).
Результаты. По сравнению с уровнем в интактной ткани в миоме снижалась СОД в 3,2 раза и увеличивалась ГТ в 2,7 раза (p < 0,01). Аналогичные изменения отмечены для ЭА G1 – в среднем в 5,3 раза (p < 0,01) и увеличение ДК в 2,2 раза (p < 0,05). В ткани ЭА G2 активность СОД и ГПО была ниже, чем в интактной ткани, соответственно в 5,7 и 4,5 раза (p < 0,05) и более низкие ГТ, ГПО и GSH, чем при ЭА G1, соответственно в 4,9, 8,9 и 1,6 раз (p < 0,05 – p < 0,01). В ткани ЭА G3 отмечен рост GSH, ГПО и ГТ от 1,5 до 7,1 раза (p < 0,05 – p < 0,01) и продуктов ПОЛ в среднем в 2,5 раза (p < 0,05), а также снижение витаминов А и Е в 2,9 и 4,6 раза соответственно (p < 0,05) по сравнению с интактной тканью. Ткань ЭА G2 отличалась минимальным уровнем активности GSH-зависимой системы.
Заключение. Результаты отражают различия механизмов регуляции пролиферации посредством СРО в миомах и в ткани ЭА при изменении ее дифференцировки. Знание особенностей отдельных звеньев регуляции СРО может играть определенную роль в назначении антиоксидантной терапии доброкачественных или злокачественных опухолей матки.

Ключевые слова: рак эндометрия, миома матки, эндометриоидная аденокарцинома, степень дифференцировки, свободнорадикальное окисление, антиоксидантные ферменты, глутатионзависимая система, витамины А и Е

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Советом по этике при ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (протокол № 22 от 05.09.2023 г.). Информированное согласие получено от всех участников исследования

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INTRODUCTION

Endometrial cancer (EC) is one of the most common malignancies of the female reproductive system, ranking second in frequency after cervical cancer in the world. EC is formed from the mucous membrane of the uterine body, and the most common histological type is endometrioid adenocarcinoma (EA), the detection rate of which can reach up to 80–90 % of all cases of EC [1]. There is no tendency to decrease the incidence of EC, which is explained, on the contrary, by an increase in the prevalence of risk factors that create conditions for the occurrence of disorders in the body that contribute to endometrial malignancy (aging of women, a decrease in the number of births, an increase in the number of abortions, inflammatory diseases of the uterus), and directly affect endometrial malignancy (hyperestrogenism, metabolic disorders associated with obesity, diabetes mellitus).

The results of many years of research have helped to understand the important role of free radical oxidation (FRO) and reactive oxygen species (ROS) processes both in the normal physiology of the female reproductive system and in the development of its pathology – the involvement of ROS in the regulation of the ovarian cycle, the initiation of endometrial rejection, the development of infertility, endometriosis. The balance of pro- and antioxidants in uterine tissue is regulated by interrelated signaling cascades of inflammation, hypoxia, and angiogenesis [2, 3]. The uterus is particularly sensitive to the effects of hormonal factors, as well as various external lifestyle-related factors, which activate free radical processes that are inhibited by the body's antioxidant system. In particular, it was found that obesity, by inducing a pro–inflammatory environment and oxidative stress, promotes the transformation of myometrial stem cells into leiomyoma and endometrial into adenocarcinoma, activating proliferation and angiogenesis [4, 5]. It was found that the transcriptional activity of the genes responsible for estrogen reception and metabolism changes depending on the degree of tumor differentiation and the age of the affected women [6]. The occurrence of an imbalance in the processes of FRO, turning into oxidative stress, through complex mechanisms contributes to the formation of fibroids or leads to neoplastic transformation of the endometrium, the development of hyperplasia and the active growth of malignant tumors [3, 7, 8]. All these pathologies of the uterus have a common basis – increased activity of proliferative processes. However, as a result of such activation, tumors that are fundamentally different in nature are formed – benign fibroids or malignant carcinoma. Since FRO and the antioxidant system are important links in the pathogenesis of proliferation-related processes, it would be interesting to evaluate the features of FRO and the main enzymatic and non-enzymatic components of the antioxidant defense system in proliferating tissues of benign fibroids and malignant endometrioid adenocarcinoma with varying degrees of its differentiation, which was **the purpose of this study**.

PATIENTS AND METHODS

The present study included 42 patients with endometrioid adenocarcinoma (average age 60.8 ± 2.9years) and 14 patients with uterine fibroids (average age 49.4 ± 2.5 years) who underwent special treatment at the National Medical Research Centre for Oncology of the Ministry of Health of the Russian Federation, Rostov-on-Don. All patients signed a voluntary informed consent for medical intervention and the use of biological material for scientific purposes. The study was approved by the Ethics Council of the National Medical Research Centre for Oncology, Rostov-on-Don (Protocol No. 22 dated 09/05/2023).

The average body mass index of women with EC was 39.8 (from 24.3 to 49.7), the Quetelet index formula was used to calculate it, 12 women had type 2 diabetes mellitus, 10 had impaired glucose tolerance. The average body mass index in patients with uterine fibroids was 31.4 (from 21.9 to 38.4). Type 2 diabetes occurred in 2 patients with uterine fibroids, and in 2 patients with impaired glucose tolerance. In 9 patients, uterine fibroids were combined with genital endometriosis.

In patients with EC, the prevalence of the tumor process was within the Ia and Ib stages. In the group with G1 EA (n = 16), there were 14 patients with stage Ia and 2 with stage Ib. With G2 EA (n = 12) – 7 patients with Ia and 5 with stage Ib. In the group with G3 EA (n = 14), there were 5 with Ia and 9 with Ib.

Biomaterial (fibroids and intact uterus, EA tumor) was obtained during surgical treatment of these women. They did not receive neoadjuvant treatment. The biomaterial of all patients with EC was divided into 3 groups according to the degree of tumor differentiation – G1, G2, G3. 10 % homogenates were prepared from tumor tissues (fibroids, EA) and intact uterine tissue obtained during the removal of fibroids (uterine body tissue unaffected by the tumor process, containing endometrium and myometrium) obtained during the surgical stage, in which a number of indicators characterizing the intensity of FRO and the functioning of the antioxidant system by colorimetric methods were studied: superoxide dismutase (SOD) activity (EC 1.15.1.1) [9], the amount of enzyme that caused 50 % inhibition of the reaction was taken as the unit of activity and expressed in units/ml of homogenate; catalase activity (EC 1.11.1.6.) [10], expressed in μ mol H_2O_2/ min•mg of protein; glutathione peroxidase (GPx) activity (EC 1.11.1.9.) [11] and glutathione transferase (GST) activity (EC 2.1.5.18) [12], the activity of these enzymes was expressed in IU/ mg of protein. The state of the non-enzymatic link of the antioxidant system was assessed by the content of reduced glutathione (GSH) [12], expressed in μ mol/ mg of protein, and vitamins A and E [13], expressed in units/ml of homogenate. The intensity of lipid peroxidation (LPO) was assessed by the content of primary products in tumor tissues, diene conjugates (DC) [14] and the most stable secondary product, malondialdehyde (MDA) [12]. Protein concentration was determined by biuretic method, expressing it in mg/ml of homogenate. The results of colorimetric studies were evaluated using a U-2900 bi-beam spectrophotometer with UV Solutions software (Hitachi, Japan) and an INFINITE M NANO microplate automatic analyzer (Tecan Austria GmbH, Austria).

Statistical analysis

Statistical analysis of the results was carried out using Statistica 6.0. The Shapiro-Wilk test was used for testing the data sample normality, and using the Levene's test was checked the equality of variances. The data in the tables are presented as median and quartiles (Me; Q1; Q3). The statistical significance of the differences was assessed using the Mann-Whitney test, and the Holm-Bonferroni method was used for multiple comparisons to correct the achieved significance level of p. The critical level of significance of the differences is $p \leq 0.05$.

STUDY RESULTS AND DISCUSSION

During the study of the characteristics of FRO and the activity of individual links of the antioxidant system in benign and malignant proliferative processes, it was found that only the activity of SOD in fibroids significantly changed – a decrease of 3.2 times, and the activity of GST – an increase of 2.7 times compared with the level in intact tissue (Table 1). There were no significant changes in other links of the antioxidant system and the content of LPO products. (Tables 1, 2). A similar pattern was observed in the tissue of highly differentiated EA G1: lower SOD activity and higher GST activity, on average 5.2 times, than in intact tissue (Table. 1), however, in contrast to fibroids, there was a 2.2-fold increase in the level of DC compared with the level in intact tissue (Table. 2), which may indicate the appearance of an imbalance and an increase in FRO processes.

In the tissue of moderately differentiated EA G2, in addition to the lower activity of SOD – 5.7 times lower than the level in intact tissue, there was also a lower activity of GPx – 4.5 times lower than in intact tissue, at the same time, the activity of GST, GPx and the content of GSH were significantly lower than in EA G1 – b tissue. 4.9, 8.9, and 1.6 times, respectively (Table 1). There were no statistically significant changes in the content of vitamins and LPO products in EA G2 tissue (Table 2).

In the tissue of low–grade EA G3, a generally different picture of the state of the antioxidant system was observed than in fibroids and with EA of a higher degree of differentiation: the activity of SOD and catalase did not significantly differ from the level in intact tissue, but activation of all components of the glutathione-dependent system was noted – an increase in the content of GSH and the activity of GPx and GST, respectively, by 2.1, 1.5 and 7.1 times (Table 1). The content of vitamins A and E was 2.9 and 4.6 times lower, respectively, and the level of LPO products was 2.5 times higher on average than in intact tissue (Table. 2), which may reflect an increasing imbalance between FRO and antioxidant protection despite an increase in the activity of the glutathione-dependent system.

Analyzing the results, we can note the similarity of the state of the antioxidant system in fibroids and EA G1 tissue. With a decrease in the degree of tumor differentiation and intensification of proliferation, the balance in the system of enzymatic and non-enzymatic antioxidants and in the processes of FRO changes, which is manifested by an increase in the level of LPO products. It is noteworthy that in EA G2 tissue, the activity of the glutathione system is significantly lower than in EA G1 tissue – the GSH content is 1.6 times lower, the activity of GPx and GST is 8.9 and 4.9 times lower, respectively (Table 1). At the same time, in EA G3 tissue, compared with the level in EA G2 tissue, the activity of SOD and catalase was higher, respectively, by 6.2 and 2.5 (p = 0.0516) times, as was the activity of the glutathione-dependent system – the activity of GPx and GST was on average 6.8 times higher, and the level of GSH was 2.7 times above (Table. 1), while the content of vitamins A and E, on the contrary, was lower – 3.6 and 2.5 (p = 0.0501) times, respectively (Table. 2), and the level of LPO products is 6.3 (DC) and 2.1 (MDA) times higher (Table 2).

As a result of long-term studies, the great importance of the processes of free radical oxidation and redox of tissues in the physiological regulation of the female reproductive system and their imbalance in the process of pathological changes, in particular in the development of hyperplastic processes and oncogynecological pathology, has been established [2, 3, 15]. It was found that fibroids, hyperplasia, and endometrial adenocarcinoma are characterized by a decrease in mRNA levels, expression, and/or activity of the antioxidant enzymes SOD and catalase, which contributes to the creation of pro-oxidant conditions in the tissue that stimulate proliferation and tumor formation [16, 17]. Our results were somewhat similar – we observed a decrease in SOD activity in both benign fibroids and malignant high- and moderate-grade EA tissue, but not in low-grade EA, however, we did not find a significant decrease in catalase activity in any group. The change in SOD activity is adaptive in nature and its decrease may reflect both a decrease in the generation of superoxide anion radical and inhibition by the reaction product, H_2O_2, which suppresses proliferation, unlike

Table 1. Indicators of the antioxidant system and the content of lipid peroxidation products in tumor tissue in patients with uterine fibroids and patients with EC of varying degrees of differentiation

	SOD activity, units/ml	Catalase activity, μ mol H_2O_2/ min•mg protein	GSH content, μ mol/mg of protein	GPx activity, IU/ mg of protein	GST activity, IU/mg of protein
Intact uterine tissue n = 12	15.5; (12.5; 20.7)	2.2; (1.7; 2.7)	33.6; (32.4; 40.5)	181.6; (144.9; 224.6)	39.8; (29.4; 58.7)
Myomatous node n = 14	4.8; (2.1; 6.5) p = 0.0082	1.9; (1.8; 3.1)	30.6; (30.2; 61.8)	179.8; (120.2; 390.6)	107.6; (72.8; 157.9) p = 0.0065
EA G1 n = 16	2.9; (1.4; 4.5) p = 0.0105	3.6; (1.6; 6.7)	40.2; (31.4; 68.9)	360.0; (200.0; 415.4)	200.4; (175.0; 284.7) p = 0.0027
EA G2 n = 12	2.7; (2.4; 3.3) p = 0.0209	1.7; (1.3; 2.1)	25.8; (17.6; 26.8) p^1 = 0.0118	40.2; (28.8; 52.4) p = 0.0209 p^1 = 0.0105	41.1; (28.5; 43.8) p^1 = 0.0045
EA G3 n = 14	16.9; (13.1; 17.9) p^2 = 0.0143	4.3; (2.5; 5.6) p^2 = 0.0516	70.4; (64.9; 78.4) p = 0.0143 p^2 = 0.0139	272.2; (252.2; 286.1) p = 0.0500 p^2 = 0.0147	281.2; (137.1; 297.8) p = 0.0062 p^2 = 0.0090

Note: the achieved level of statistical significance of the differences: p – compared with the level of the indicator in the intact uterine tissue, p^1 – compared with the level of the indicator in EA G1, p^2 – compared with the level of the indicator in EA G2

superoxide anion radical, and activates apoptosis. Thus, a decrease in the production of H_2O_2 with low SOD activity and while maintaining catalase and GPx activity can contribute to a decrease in the content of H_2O_2 and an increase in the superoxide content in the tissue. Studies of the role of hypoxia in the pathogenesis of fibromyoma have shown, for example, a violation of the innate antioxidant mechanism occurs, aggravated by hypoxia, which manifests itself in the constant suppression of SOD and catalase mRNA expression in fibromyoma cells compared with cells of the normal myometrium after exposure to hypoxia [16, 18]. As suggested by the authors, hypoxia can stimulate the proliferation of fibroids cells, and possibly transformed endometrial cells, through the activation of the HIF-1α/TGF-β3/Smad3 signaling pathway and the expression of NADPH oxidase-4 (NOX4) enzymes, generating superoxide ions, as well as through the expression of double oxidase (DUOX1), generating H_2O_2, the activity of which contributes to the creation of pro-oxidant conditions [16].

As our results showed, higher SOD and catalase activity was observed in EA G3 tissue than in the tissues of moderately differentiated endometrial tumors, as well as significantly higher activity of glutathione-dependent antioxidant enzymes GPx and GST and a higher content of GSH itself, even compared with the tissue of the intact uterus. Obviously, this adaptive increase in the activity of protective antioxidant systems is associated with increased generation of ROS (especially superoxide) and FRO processes while reducing tumor differentiation to a low-grade state to ensure rapid proliferation and protect tumor cells from apoptosis. This assumption is supported by the accumulation of LPO – DC and significantly more stable MDA products in the tissue of low-grade EA. This was not observed in fibroids, which suggests that there may be different mechanisms of proliferation activation during the development of fibroids and EA. As is known, GSH and its associated enzymatic system are of key importance in maintaining the intracellular redox state, which regulates signaling pathways, gene expression, and cell death, and the functioning of its redox cycle is a cytoprotective mechanism for limiting FRO in various cells, especially tumor cells [19]. In this regard, the content of glutathione and related enzymes is often increased in a number of tumors – GSH exhibits antioxidant activity, restoring H_2O_2, lipid hydroperoxides and peroxynitrite, and GPx, metabolizing H_2O_2 and lipid hydroperoxides, increases cell resistance to oxidative damage [19].

Table 2. Indicators of the glutathione-dependent system in tumor tissue in patients with uterine fibroids and patients with EC of varying degrees of differentiation

	Vitamin A content, unit/ml	Vitamin E content, unit/ml	DC content, μ mol/ml	The content of MDA, nmol/mg of tissue
Intact uterine tissue *n* = 12	2.21; (2.06; 2.96)	5.61; (2.92; 5.81)	0.80; (0.18; 1.38)	2.31; (1.60; 3.14)
Myomatous node *n* = 14	3.58; (1.56; 3.97)	2.22; (1.04; 4.33)	0.74; (0.16; 2.65)	2.05; (1.92; 3.08)
EA G1 *n* = 16	2.54; (1.68; 4.65)	4.35; (2.94; 5.94)	1.78; (1.57; 2.57) *p* = 0.0233	2.30; (1.54; 3.59)
EA G2 *n* = 12	2.74; (2.66; 3.91)	3.05; (2.06; 6.61)	0.35; (0.25; 0.79)	2.18; (1.54; 2.56)
EA G3 *n* = 14	0.75; (0.59; 1.02) *p* = 0.0119 p^2 = 0.0163	1.21; (0.88; 1.94) *p* = 0.0275 p^2 = 0.0501	2.20; (1.29; 2.98) *p* = 0.0373 p^2 = 0.0233	4.87; (4.10; 6.41) *p* = 0.0179 p^2 = 0.0339

Note: the achieved level of statistical significance of the differences: *p* – compared with the level of the indicator in intact uterine tissue, p^2 – compared with the level of the indicator in EA G2

An interesting result was higher GST activity in both low-grade (maximum) and high-grade EA tissue, as well as in fibroid tissue (minimum). Glutathione transferase is a superfamily of enzymes representing the main cellular defense system that detoxify various hydrophobic and electrophilic endogenous compounds formed during metabolism [20]. In addition, GST, participating in a wide range of signaling mechanisms of mitogen-activated protein kinases (MAPK), such as c-Jun N-terminal kinase (JNK), apoptosis signaling kinase 1 (ASK1), and the 4-hydroxy-2-transnonenal pathway, ensure cell survival, thus playing a significant role in both in tumor formation and in established tumors [19, 21]. This role of GST in activating cellular maintenance, proliferation, and avoidance of apoptosis leads to an increase in GST expression in many malignant tumors, which is associated with a decrease in patient survival, in particular, in the work of Singh R. R. and Reindl K. M. (2021) provide information on a negative correlation between increased GSTA1 expression and survival in patients with endometrial cancer [20], and in the study Checa-Rojas A. et al. (2018) knockdown of GSTM3 and GSTP1 proteins showed increased apoptosis of cervical cancer cells of different lines and suppression of cell survival through various signaling pathways [22]. Thus, by regulating the activation of cellular stress signaling pathways, GST contributes to the adaptation of tumor cells to stressful conditions in the tumor microenvironment and their survival, and may be a common mechanism for avoiding apoptosis in fibroids.

In the study of Obukhova L. and co-authors. (2022) [23] showed consistent changes in free radical activity and glutathione metabolism in glioma tissue as their malignancy increased from Low Grade (I, II) to High Grade (III, IV), although these changes were not similar to those we found, which may be due to the peculiarities of local regulatory mechanisms.

Analyzing the results obtained, attention is drawn to the significantly lower content of vitamins A and E in the tissue of low-grade EA and the absence of significant changes in it in the tissues of higher-grade EA and fibroids, which is obviously related to the role of these vitamins in the processes of development and cellular differentiation, as well as participation in antioxidant protection. Vitamin A is classified as morphogens, metabolites that are of key importance in the processes of embryogenesis and tissue differentiation [24], which is consistent with our results, which showed no differences in its levels in the tissues of the intact uterus, fibroids and highly differentiated EA G1 and significantly lower levels in the tissue of low-differentiated EA G3. To date, it has been established that retinol metabolites, acting through genomic and non-canonical mechanisms, can have the opposite effect on tumor development: they participate in the induction of genes that activate cell differentiation, and their low levels in cells can stimulate proliferation through the MAPK signaling mechanism; they provoke an increase in the expression of the estrogen receptor α, which stimulates the progression of hormone-dependent tumors [24]. Under the influence of retinol metabolites, a change in the activity of aldehyde dehydrogenase 1, a key marker of malignant stem cells, weakens the signaling of the ALDH1/FoxM1/Notch1 pathway, thereby suppressing tumor growth in ovarian cancer; in the endometrium, vitamin A metabolites control the expression of the enzyme 17β-hydroxysteroid dehydrogenase type 2, involved in the cyclic change of estrogen-dependent proliferative and progesterone- dependent secretory phases [25]. Cellular components such as retinoic acid binding protein 1 (CRABP1) and fatty acid binding protein 5 (FABP5) mediate the ability of retinoic acid to cause differentiation, cell cycle arrest, and apoptosis: this metabolite has an enhanced apoptotic effect in cells with a high CRABP1/FABP5 ratio [26].

The importance of vitamin E in tumors is primarily associated with antioxidant properties and its antitumor effect: a number of studies have confirmed a link between high intake of vitamin E and a reduced risk of cervical cancer and endometrial cancer, and the established mechanisms of action of vitamin E include inhibition of the pro-tumor pathway NF-kB, suppression of the activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and neutralization of reactive oxygen species and nitrogen. However, a number of studies have shown opposite results [25, 27].

CONCLUSION

The presented very little information about the currently known molecular mechanisms of the involvement of FRO, the glutathione-dependent system, vitamins A and E in the processes regulating the

development and progression of malignant tumors, in particular, endometrial cancer, and benign fibroids leads to an understanding of the results obtained in this study as a reflection of differences in the mechanisms of regulation of proliferation by FRO in fibroids. and in the EA tissue with a consistent decrease in its differentiation. At the same time, knowledge of the features of individual links in the regulation of FRO can play a role in prescribing antioxidant therapy for benign or malignant uterine tumors, when not only the type of antioxidant, but also the stage of tumor development at which its use is expected may be important. The results obtained in the study of moderately differentiated EA, which was characterized by significantly lower activity of the glutathione-dependent system in comparison with the tissue of highly and low differentiated EA, look particularly interesting. In our opinion, this group of tumors is interesting because they change the ratio of biochemical processes that still regulate tissue-specific functions and already provide the main signs of malignancy (active proliferation, attenuation of apoptosis, activation of neoangio- and neurogenesis), which entails morphological changes.

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