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Oxidative metabolism genes in ovarian neoplasms

Elena V. Proskurnina[1], Mariya V. Fedorova[2], Ekaterina A. Savinova[1], Vladimir I. Voznesenskii[3], Svetlana V. Kostyuk[1], Elena A. Sosnova[4]

[1] Research Centre for Medical Genetics, Moscow, Russian Federation;
[2] Central Research Institute for Epidemiology, Moscow, Russian Federation;
[3] D.D. Pletnev City Clinical Hospital, Moscow, Russian Federation;
[4] I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation

ABSTRACT

BACKGROUND: Reactive oxygen species play important and ambiguous role in carcinogenesis, and local oxidative metabolism may differ significantly from systemic metabolism and determine the processes occurring in tumor tissues.

AIM: This study aimed to examine the expressions of key oxidative metabolism genes, particularly *CYB5R, POR, NOX4, SOD1, NF-κB,* and *NRF2*, in ovarian neoplasm tissues, and determine cytochrome *b5* reductase and cytochrome P450 reductase activity, blood neutrophil activity, and antioxidant indices in the blood plasma and peritoneal fluid.

MATERIALS AND METHODS: The study included two groups of patients: a study group (*n*=10) with ovarian adenocarcinoma and a comparison group (*n*=6) with benign ovarian neoplasms. The expressions of *CYB5R1, CYB5R2/R4, CYB5R3, POR, BIRC3, NOX4, NRF2, NF-κB, SOD1, HMOX1,* and *BCL2* genes, cytochrome *b5* reductase, and cytochrome P450 reductase activity, oxidative activity of blood neutrophils, and antioxidant potential of plasma and peritoneal fluid were evaluated in these two groups of women.

RESULTS: The expression levels of *CYB5R3* and *BCL2* were significantly lower in adenocarcinoma tissues. The activities of cytochrome *b5* reductase and cytochrome P450 reductase increased in the group with adenocarcinoma. On average, the activity of blood neutrophils corresponded to the reference values. For blood plasma, the antioxidant capacity were not different, whereas the antioxidant capacity in the peritoneal fluid increased approximately twofold in ovarian cancer.

CONCLUSIONS: Significantly increased cytochrome *b5* reductase activity in adenocarcinoma tissues may be a response to intracellular oxidative stress, whereas *CYB5R3* gene expression may be reduced by a negative feedback mechanism. The activities of cytochrome P450 reductase and its gene change to a lesser extent in the presence of ovarian adenocarcinoma. The oxidative balance in the blood and peritoneal fluid correlated with the tissue expressions of *NF-κB* and *NRF2*.

Keywords: cytochrome *b5* reductase; cytochrome P450 reductase; *NRF2; NF-κB*; blood plasma; antioxidant capacity; neutrophil activity; ovarian cancer.

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Гены оксидативного метаболизма при новообразованиях яичников

Е.В. Проскурнина[1], М.В. Фёдорова[2], Е.А. Савинова[1], В.И. Вознесенский[3], С.В. Костюк[1], Е.А. Соснова[4]

[1] Медико-генетический научный центр им. академика Н.П. Бочкова, Москва, Российская Федерация;
[2] Центральный научно-исследовательский институт эпидемиологии, Москва, Российская Федерация;
[3] Городская клиническая больница им. Д.Д. Плетнёва, Москва, Российская Федерация;
[4] Первый Московский государственный медицинский университет им. И.М. Сеченова, Москва, Российская Федерация

АННОТАЦИЯ

Введение. Активные формы кислорода играют важную и неоднозначную роль в канцерогенезе, при этом локальный оксидативный метаболизм может сильно отличаться от системного метаболизма и определять процессы, происходящие в ткани опухоли.

Цель исследования — изучить экспрессию ключевых генов оксидативного метаболизма, в частности генов *CYB5R, POR, NOX4, SOD1, NF-κB, NRF2*, в тканях новообразований яичника параллельно с определением активности цитохром *b5*-редуктазы, цитохром P450-редуктазы, активности нейтрофилов крови и антиоксидантных показателей плазмы крови и перитонеальной жидкости.

Материалы и методы. В исследование включили две группы пациенток: основную группу (*n*=10) с аденокарциномой яичников и группу сравнения (*n*=6) с доброкачественными новообразованиями яичников. У этих двух групп женщин проведено изучение экспрессии генов *CYB5R1, CYB5R2/R4, CYB5R3, POR, BIRC3, NOX4, NRF2, NF*-κB, *SOD1, HMOX1, BCL2*, изучение активности цитохром *b5*-редуктазы и цитохром P450-редуктазы, а также определение оксидативной активности нейтрофилов крови и антиоксидантного потенциала плазмы и перитонеальной жидкости.

Результаты. Установлено, что экспрессия генов *CYB5R3* и *BCL2* была значимо ниже в тканях аденокарциномы. Активность цитохром *b5*-редуктазы и цитохром P450-редуктазы оказалась повышена в группе пациенток с аденокарциномой. Активность нейтрофилов крови в среднем соответствовала референтным значениям. Для плазмы крови значения антиоксидантной ёмкости не имели различий, а антиоксидантная ёмкость перитонеальной жидкости в случае рака яичников была увеличена примерно в два раза.

Заключение. Существенно увеличенная активность цитохром *b5*-редуктазы в тканях аденокарциномы может являться ответом на внутриклеточный оксидативный стресс, при этом экспрессия гена *CYB5R3* может быть снижена по механизму отрицательной обратной связи. Активность цитохром P450-редуктазы и её гена в меньшей степени изменяется при аденокарциноме яичников. Оксидативный баланс крови и перитонеальной жидкости взаимосвязан с тканевой экспрессией *NF-κB* и *NRF2*.

Ключевые слова: цитохром *b5*-редуктаза; цитохром P450-редуктаза; *NRF2*; *NF*-κB; плазма крови; антиоксидантная ёмкость; активность нейтрофилов; рак яичников.

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BACKGROUND

Ovarian cancer is one of the major causes of death in women from cancer diseases [1]. One of the main mechanisms of its pathogenesis is oxidative stress, which is involved in the occurrence, development, and progression of ovarian cancer and chemoresistance, since it causes phenotypic modifications of tumor cells through cross-interaction between tumor cells and the surrounding stroma. Oxidative stress leads to an adaptive response of cancer cells through metabolic reprograming in the short term, and genetic reprograming provides long-term adaptation, whereas reactive oxygen species (ROS) can contribute to molecular genetic changes causing cancer progression, and in contrast, long-term increased ROS levels have a cytotoxic effect and can induce activation of apoptotic pathways [2].

Oxidative stress, inflammation, and apoptosis are interrelated in carcinogenesis [3]. Inflammation, especially chronic inflammation, is characterized by sustained tissue damage, injury-induced cell proliferation and repair [4]. In ovarian cancer, oxidative stress regulates the expression of inflammatory genes and activates activator protein 1, hypoxia-inducible factor 1α, heat shock factor 1, universal transcription factor *NF-κB*, transcription factor *NRF2*, and tumor suppressor p53 [2]. NF-κB promotes the initiation of carcinogenesis and plays a crucial role in tumor cell proliferation and survival, but may also perform a protective function in ovarian cancer by regulating antioxidant gene expression [2]. Increased *NF-κB* activation in invasive malignant ovarian lesions compared with benign or borderline neoplasms confirms the relationship between carcinogenesis and systemic inflammation [5].

Elevated ROS levels activate *NRF2* signaling, inducing the expression of antioxidant enzymes such as heme oxygenase (HMOX), catalase, superoxide dismutase (SOD), and glutathione transferase. *NRF2* plays a critical anti-inflammatory role; however, although *NRF2* helps maintain the stability of the normal environment of ovarian cells and genome under conditions of oxidative stress, it protects cancer cells from oxidative damage and from the effects of cytotoxic drugs, thereby increasing resistance to chemotherapy [2].

One of the main sites for the synthesis of intracellular ROS is microsomal respiratory chains, represented by reductases integrated into the membrane of the endoplasmic reticulum, which transport electrons from nicotinamide adenine dinucleotide (NADH; reduced form) or nicotinamide adenine dinucleotide phosphate (NADPH; reduced form) to cytochromes. NADH-dependent cytochrome *b5* reductase (*CYB5R*) participates in the synthesis of cholesterol, elongation of fatty acids, and microsomal hydroxylation of xenobiotics and steroid hormones and is part of the transmembrane redox system, which maintains the antioxidants ascorbate and coenzyme Q10 in a reduced state and protects the cell from apoptosis [6].

The role of cytochrome *b5* reductase in carcinogenesis has not been sufficiently studied; however, its increased expression is known to correlate with a poor prognosis in patients with estrogen receptor-negative breast cancer, and a decrease in the expression of the gene for this enzyme reduces significantly metastatic spreading to the lungs in a mouse model [7]. NADPH-dependent cytochrome P450 reductase (*POR*) reduces cytochrome P450 and can transfer an electron to cytochrome *b5*, heme oxygenase, squalene monooxygenase, and 7-dehydrocholesterol reductase. The most crucial task of this chain is to catalyze the metabolism of drugs, especially antitumor drugs [8]. Studies available in the literature are mainly focused on the participation of this enzyme in the metabolism of anticancer drugs.

This study aimed to analyze the expression of key genes involved in oxidative metabolism, inflammation, and apoptosis (*CYB5R, POR, NOX4, SOD1, HMOX1, NFKB1, NRF2, BCL2, BIRC3*) in ovarian adenocarcinoma tissues and determine the activity of cytochrome *b5* reductase, cytochrome P450 reductase, and some indicators of oxidative metabolism (activity of blood neutrophils and antioxidant indicators of blood plasma and peritoneal fluid).

MATERIALS AND METHODS

Overall, 16 female patients aged 47–57 years were included. The main group consisted of 10 patients with histologically confirmed ovarian cancer (moderate and poorly differentiated serous adenocarcinoma), and the comparison group comprised 6 patients with benign ovarian tumors (serous-mucinous cystadenoma). The exclusion criteria were age >75 years and presence of multiple primary tumors of other locations. All patients signed voluntary informed consent for inclusion in the study and use of medical data obtained.

Surgical intervention and follow-up of patients were performed in the D.D. Pletnev City Clinical Hospital of the Moscow Department of Health, as well as the morphological verification of the diagnosis in the Anatomic Pathology Department. The study materials were samples of malignant tissue, peritoneal fluid, blood plasma, and whole blood obtained on the day of surgery. Blood and peritoneal fluid samples were transported in a vacutainer with Li-heparin at a temperature of +4°C and analyzed no later than 2 hours after the material collection. Tissue samples were transported in physiological solution (0.9% NaCl solution), and then divided into two parts: one part was frozen at –80°C and gene expression was studied a month later, and in the other part, the activity of microsomal reductases was determined no later than 2 hours after taking the material.

Evaluation of gene expression by polymerase chain reaction

The level of gene expression was assessed by real-time polymerase chain reaction (PCR). RNA was isolated from tissue using YellowSolve kits (Klonogen, Russia) according to standard methods, followed by phenol–chloroform extraction and precipitation with chloroform and isoamyl

alcohol (49:1). The RNA concentration was determined using the Quant-iT RiboGreen RNA reagent dye (MoBiTec, Germany) on a plate reader (EnSpire equipment, Finland) λ_{ex} = 487 nm, λ_{fl} = 524 nm. Reverse transcription was performed using reagents from Silex (Russia) according to standard methods.

PCR was performed using the appropriate primers (Synthol) and intercalating dye SYBR Green on a StepOnePlus device (Applied Biosystems, USA). The following primers (Syntol, Moscow, Russia) were used:

NRF2 (*NFE2L2*) (F: TCCAGTCAGAAACCAGTGGAT, R: GAATGTCTGGCGCCAAA AGCTG);
NOX4 (F: TTGGGGCTAGGATTGTGTCTA, R: GAGTGTTCGGCACATGGGTA);
BIRC3 (F: AAGCTACCTCTCAGCCTACTTT, R: CCACTGTTTTCTGTACCCGGA);
BCL2 (F: GCCTTCTTTGAGTTCGGTGG; R: ATCTCCCGGTTGACGCTCT);
NFKB1 (F: CAGATGGCCCATACCTTCAAAT, R: CGGAAACGAAATCCTCTCTGTT);
HMOX1 (F: TCCTGGCTCAGCCTCAAATG; R: CGTTAAACACCTCCCTCCCC);
SOD1 (F: AGGGCATCATCAATTTCGAGC; R: GCCCACCGTGTTTTTCTGGA);
POR (F: GGGATGCGAGGCATGTCAG; R: CAGGGCGTTGTCGATCTCT);
CYB5R1 (F: TCAGGCCATACACTCCTGTCA; R: CACACCCCTTCAGGTAGACCTT);
CYB5R2 (F: CAAGGGGACGCTTGTTTTACC; R: AGGTGATCGGCCAGTGTTTTT);
CYB5R3 (F: TCTACCTCTCGGCTCGAATTG; R: CCTTGTCATCATCGCTGGAGAT);
and *TBP* (reference gene) (F: GCCCGAAACGCCGAATAT, R: CCGTGGTTCGTGGCTCTCT).

Determination of microsomal reductase activity

For recording the activity of cytochrome *b5* reductase and cytochrome P450 reductase, a protocol based on recording tissue chemiluminescence in the presence of lucigenin and NADH or NADPH, respectively, was used. Registration was performed on a Lum-1200 device (DISoft, Russia). The reagents Krebs–Ringer solution (pH 7.4), lucigenin (10,10-dimethyl-9,9-biacridinium dinitrate, Sigma-Aldrich, USA), and NADH and NADPH (Sigma-Aldrich, USA) were used. Before analysis, samples were washed three times with Krebs–Ringer solution, and three portions weighing 15.5±0.5 mg were taken with a 20-G biopsy needle (GTA, Italy). Samples were placed in cuvettes with Krebs–Ringer solution and lucigenin (final concentration, 60 μM), chemiluminescence was recorded at 37°C for 5 min, 10 μl of 10 mM NADH or NADPH was added, and the signal was recorded for 20 min. The average intensity of the stimulated luminescence of I_{NADH} and I_{NADPH} was calculated for three parallel measurements.

Determination of the oxidative activity of neutrophils

Determination of the oxidative activity of blood neutrophils was performed according to the following method. First, 25 μl of whole blood collected in vacutainers with heparin was placed into a cuvette containing Hanks solution stabilized with HEPES and luminol (45 μM) (all reagents from Sigma-Aldrich, USA), and spontaneous chemiluminescence was recorded for 10 min. Then, a priming stimulus, phorbol 12-myristate 13-acetate (50 ng/ml), was added. After 30 min of incubation, a second stimulus, N-formyl-methionyl-leucyl-phenylalanine (10 μM), was added, and the response was recorded for at least 60 min. The amplitude of the neutrophil response after the two-stage stimulation was calculated. The reference interval for apparently healthy donors (*n*=110) was determined earlier and was 3.5–9.0 relative units.

Determination of the antioxidant capacity of blood plasma and peritoneal fluid

Chemiluminescence was recorded at 37°C in a system containing the free radical generator 2,2'-azobis(2-amidinopropane) dihydrochloride (ABAP) and a fluorescence activator luminol in a phosphate buffer solution (100 mM, pH 7.4) (all reagents from Sigma-Aldrich, USA). The initial fluorescence was recorded until a plateau was reached; 10 μl of plasma or peritoneal fluid, previously diluted 10 times with phosphate buffer solution (100 mM, pH 7.4), was added; and recording was performed until a new steady-state level was reached. Using PowerGraph 3.0 software (DISoft, Russia), the fluorescence suppression area *S* was determined, reflecting the antioxidant capacity of water-soluble antioxidants in blood plasma. The reference interval was previously determined for blood plasma (*n*=98) and is 195–405 relative units. A decrease in *S* corresponds to a state of oxidative stress.

Statistical processing

The Statistica software package, version 10.0 (StatSoft Inc., USA), was used for statistical data processing. The normality of distribution was tested using the Shapiro–Wilk test. A comparative analysis of two independent groups on a quantitative basis was performed using the Mann–Whitney *U* test. The differences were considered statistically significant at a value of $p \leqslant 0.05$. To assess correlations, the Spearman rank correlation coefficient was calculated.

RESULTS

Gene expression

In patients with moderately and poorly differentiated adenocarcinomas of high malignancy (*n*=10) and in women with benign neoplasms (*n*=6), gene expression was determined in the tumor tissue, namely, cytochrome *b5* reductase (*CYB5R1, CYB5R2/R4, CYB5R3*), cytochrome P450- reductase (*POR*), prooxidant enzyme NADPH oxidase 4 (*NOX4*), antioxidant

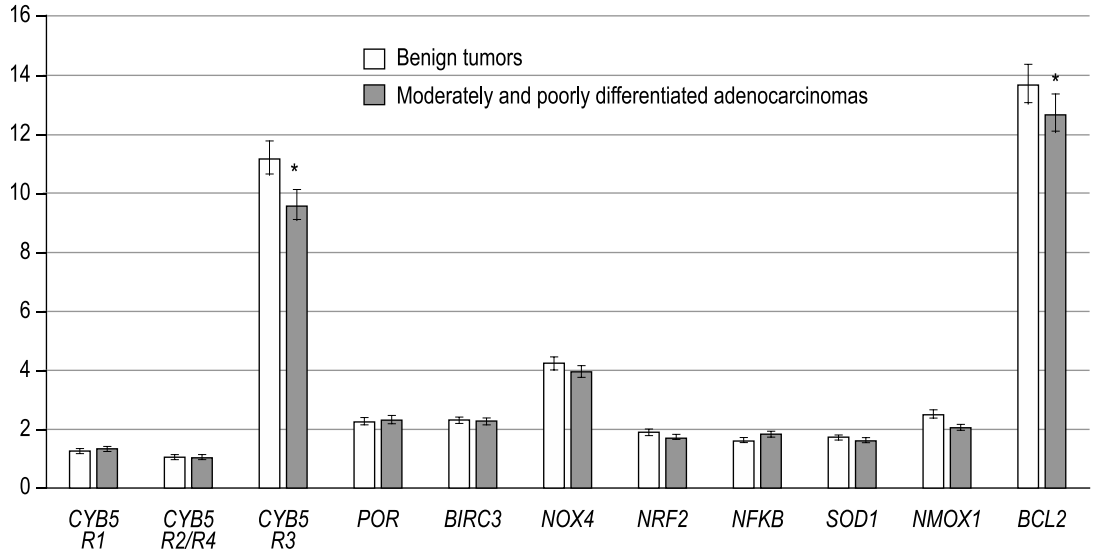

Fig. 1. Expression of key genes regulating oxidative metabolism in the tissue of ovarian neoplasms in two groups of patients (the average value of the MRNA level of the studied gene in three parallel experiments in relation to the RNA level of the gene of the internal *TBP* standard is given).

*Significant differences between groups (p <0.05, nonparametric U-test).

enzymes superoxide dismutase 1 (*SOD1*) and heme oxygenase 1 (*HMOX1*), proinflammatory pathway transcription factor *NFKB1*, anti-inflammatory pathway transcription factor *NRF2*, antiapoptotic oncogene protein *BCL2*, and apoptosis inhibitor *BIRC3* (Fig. 1).

Significant differences were obtained for the expression of cytochrome *b5* reductase (isoform 3) and the antiapoptotic protein *BCL2* (p=0.05). No significant differences were found in the expression of other isoforms of cytochrome *b5* reductase (1, 2, 4, and 5), and no significant differences were revealed in the expression of cytochrome P450 reductase.

Microsomal reductase activity

Table 1 presents the results of determining the activity of microsomal reductases in the tissues of ovarian tumors.

The activity of cytochrome *b5* reductase and cytochrome P450 reductase was significantly higher in the group of female patients with adenocarcinoma than in those with benign neoplasms, whereas the activity of cytochrome *b5* reductase increased by almost an order of magnitude, and the activity of cytochrome P450 reductase increased by four times. Thus, cytochrome *b5* reductase is a more sensitive metabolic link in ovarian cancer.

Oxidative activity of blood neutrophils and antioxidant capacity of blood plasma and peritoneal fluid

For each patient, the oxidative activity of neutrophils and the antioxidant capacity of blood plasma and peritoneal fluid were calculated (Table 2).

The activity of blood neutrophils corresponded to the reference values. For blood plasma, the antioxidant capacity values corresponded to the reference interval determined for apparently healthy donors and did not differ between groups. The antioxidant capacity of the peritoneal fluid for the comparison group corresponded to the blood plasma indicators, and in the case of malignant tumors, it approximately doubled.

Correlation between gene expression and indicators of oxidative metabolism

Based on the results of gene expression and previously obtained indicators of oxidative metabolism, correlations were calculated between the expression of the *CYB5R* and *POR* genes and activity of the corresponding microsomal reductases; between the expression of the *NFKB1* gene and oxidative activity of neutrophils; and between *NRF2* gene expression and antioxidant capacity of blood and peritoneal fluid (Table 3).

A weak negative correlation was observed between the expression of *CYB5R3* genes and activity of cytochrome *b5* reductase. A positive correlation of moderate strength was noted between *POR* and cytochrome P450 reductase activity. Furthermore, a positive correlation of moderate strength was obtained for the level of expression of the *NFKB1* gene with the activity of blood neutrophils, as well as for the *NRF2*

Table 1. The intensity of NADH- and NADPH-dependent chemiluminescence in the tissues of ovarian neoplasms (data are given in the form of mean and standard deviation)

Indicator	Benign neoplasms (n=6)	Ovarian adenocarcinoma (n=10)
I_{NADH}*, rel.units	0.88 (0.55)	7.70 (3.55)
I_{NADPH}**, rel.units	1.02 (0.77)	4.40 (2.56)

*$I_{НАДН}$ is proportional to the activity of cytochrome *b5* reductase;
**$I_{НАДФН}$ is proportional to the activity of cytochrome P450 reductase.

Table 2. Neutrophil activity and antioxidant capacity of blood plasma and peritoneal fluid (data are given in the form of mean and standard deviation), conl. units

Group of patients	Antioxidant capacity *S*		Activity of the blood neutrophils
	Blood plasma	Peritoneal fluid	
With benign neoplasms (*n* = 6)	370 (88)	333 (110)	5.1 (3.0)
With adenocarcinoma (*n* = 10)	328 (132)	618 (250)	4.3 (2.1)

Table 3. Spearman correlation coefficients between gene expression levels and indicators of oxidative metabolism

Parameter	Gene expressio				
	CYB53R	*POR*	*NFKB1*	*NRF2*	*NRF2*
Indicator of oxidative metabolism	Activity of cytochrome *b5* reductase	Activity of cytochrome P450 reductase	Activity of neutrophils	Antioxidant capacity of plasma	Antioxidant capacity of the peritoneal fluid
Correlation coefficient r_s*	–0.19	0.45	0.67	0.36	0.63

*Correlation of average strength is marked in bold in the bottom line: $0,3 \leqslant r_S < 0,7$.

gene expression level with the antioxidant capacity of blood plasma and peritoneal fluid, and the correlation with the antioxidant capacity of peritoneal fluid was significantly stronger.

DISCUSSION

The main results of the study include decreased expression of the *CYB5R3* gene in high-grade adenocarcinoma tissue with increased cytochrome *b5* reductase activity by an order of magnitude; absence of significant changes in the expression of the *POR* gene with several times increased activity of cytochrome P450 reductase; decreased expression of the antiapoptotic protein gene *BCL2*; direct correlation between neutrophil activity and *NFKB1* gene expression; direct correlation between the antioxidant capacity of peritoneal fluid and plasma and *NRF2* gene expression; and absence of significant changes in the expression of genes for the oxidative balance enzymes *NOX4, SOD1,* and *HMOX1* and inflammation *NFKB1* and *NRF2*.

No studies have analyzed the expression or activity of microsomal reductases in ovarian cancer. One of the few studies on the function of cytochrome *b5* reductase in estrogen-negative breast cancer showed a significant correlation between high expression of *CYB5R3* and low relapse-free and overall survival of patients [7]. Our own studies have shown an ambiguous change in the activity of cytochrome *b5* reductase and P450 reductase in papillary thyroid cancer, whereas for the most malignant cases, a sharp increase in the activity of these enzymes was registered [9]. Regarding cytochrome P450 reductase, research is mainly being conducted on its role in the metabolism of anticancer drugs because this enzyme can directly reduce substances [10]. The combination of the influence of cytochrome P450 reductase and the use of chemotherapeutic drugs may be a new strategy for treating tumors.

Our studies have shown an increase in the activity of cytochrome P450 reductase in high-grade adenocarcinoma tissues (about four times compared to benign tumors), whereas gene expression has changed insignificantly; however, the positive correlation of these indicators most probably indicates the regulation of the activity of this enzyme at the genetic level. The situation with cytochrome *b5* reductase is different, as with a significant decrease in expression, the activity of this enzyme in adenocarcinoma tissue increased by almost an order of magnitude. It can be assumed that cytochrome *b5* reductase is more actively involved in carcinogenesis, and this is explained by its multivalued role and localization in the endoplasmic reticulum and on the outer membrane of the mitochondria. In addition to reducing cytochrome *b5*, cytochrome *b5* reductase maintains coenzyme Q10 in a reduced state, thus regulating the intracellular antioxidant balance. It is possible that increased cytochrome *b5* reductase activity is a response to intracellular oxidative stress, and decreased gene expression is the result of negative regulatory feedback.

The antiapoptotic protein *BCL2*, along with BAX and p53, is the main regulator of drug-induced apoptosis, and *BCL2* is often overexpressed in adenocarcinoma tissues [11], and the level of this protein in the urine is also increased. The presence of *BCL2* expression in ovarian cancer is a favorable prognostic sign, especially in BAX-negative cases [12].

In contrast, Y. Mano et al. have reported that *BCL2* expression correlates with poor response to chemotherapy, especially in serous and endometrial adenocarcinomas [13]. Positive expression of *BCL2* and p53 in ovarian cancer is closely correlated with pathological stage, metastasis, and recurrence, i.e., with poor prognosis [14]. There is evidence that *BCL2* has no prognostic value in terms of response to chemotherapy and survival and is independent of the nature and malignancy of the tumor [15]. Thus, information about

the role of *BCL2* in the pathogenesis of ovarian cancer and its clinical significance is controversial.

In our study, *BCL2* gene expression was reduced in adenocarcinoma tissues, which is consistent with the results of a study [16] that discussed the feasibility of assessing *BCL2* expression in conjunction with *BAX*. Overall, the current standpoint is that proteins in this family may be promising therapeutic targets but must be considered in their entirety.

Moreover, the *NF-κB* signaling pathway is significant in the pathogenesis of ovarian cancer. The *p-STAT3/NF-κB*/IL-6 signaling pathway represents a cascade loop involved in angiogenesis in ovarian cancer [17]. Like many participants in oxidative metabolism, the role of this pathway is twofold, as inflammation promotes oncogenesis, proliferation, and survival of tumor cells; in addition, this pathway is a regulator of the expression of antioxidant genes [2]. Our study showed a trend toward increased gene expression, which is consistent with literature data; however, significant differences were not obtained, possibly because of the relatively small size of the groups.

NFKB1 gene expression was positively correlated with neutrophil activity. A recent meta-analysis has proven that an increase in the neutrophil/lymphocyte ratio is a poor prognostic sign in ovarian cancer [18]. Increased neutrophil activity indicates inflammation and may have a beneficial cytotoxic effect [19]; conversely, neutrophils are powerful inflammatory effector cells that promote tumor progression and metastasis, and extracellular neutrophil traps serve as activators of the *NF-κB* pathway [20]. Oxidative stress, which originated from neutrophils, is closely associated with inflammation and the activity of the *NF-κB* pathway [21], which is also confirmed by our data. In the present study, we used a new protocol for assessing neutrophil activity, using two-stage stimulation with a priming and main stimulus. This protocol allows the assessment of the full radical-producing potential of a neutrophil, reflecting its maximum activity. For the studied cohort, neutrophil activity on average corresponded to reference values, which confirms the absence of significant systemic inflammation and the absence of a significant increase in *NF-κB* expression.

The key role of *NRF2* in ovarian carcinogenesis has been supported by several studies, with aberrant activation of *NRF2* noted in most ovarian cancers, which is often associated with copy number loss in the *NRF2* inhibitory complex *KEAP1-CUL3-RBX1* [22]. In general, high *NRF2* expression is a favorable sign in ovarian cancer [23]. *NRF2* regulates the *HER1* signaling pathway and modulates the sensitivity of cancer cells to certain anticancer agents, which should be considered when developing treatment strategies. However, *NRF2* protects cells from oxidative stress and stimulates tumor growth and resistance to chemotherapy drugs by inactivating the oxidative stress caused by them.

Our studies showed a tendency toward a decrease in *NRF2* gene expression in the group of female patients with adenocarcinoma, although significant differences could not be detected. The values of the antioxidant capacity of blood plasma were not beyond the reference interval. A positive correlation between the expression of the *NRF2* gene and antioxidant system of the blood and peritoneal fluid confirms their relationship in a single antioxidant–anti-inflammatory system. The antioxidant capacity of plasma is provided primarily by uric acid, and uric acid, according to recent data, functions as an ROS interceptor and at the regulatory level, increasing the expression of mRNA, NRF2 proteins, and NRF2-sensitive genes, including the catalytic subunit of gamma-glutamate-cysteine ligase, heme oxygenase-1, and NQO1 [24]. Uric acid decreases *NRF2* ubiquitination and increases NRF2 protein nuclear translocation, thereby activating the *KEAP1-NRF2-ARE* pathway, whereas the effects of uric acid were significantly suppressed by the NRF2 inhibitor brusatol [25]. Thus, physiological concentrations of uric acid are a regulator of the anti-inflammatory NRF2 pathway; on the contrary, significantly elevated levels of uric acid significantly inhibit autophagy and protein levels of the *NRF2/SLC7A11/GPX4* signaling pathway, causing endothelial damage and atherosclerosis [26].

NADPH oxidase is the most crucial source of endogenous superoxide anion radicals in ovarian cancer, whereas epithelial ovarian cancer is characterized by a higher level of NADPH oxidase expression compared with normal ovarian tissues. *NOX4* expression is increased in malignant ovarian tumors than in benign ones [27]. Increased *NOX4* expression in ovarian cancer is induced by HIF-1 alpha and the insulin-like growth factor IGF-1 [1]. In our study, *NOX4* gene expression was slightly reduced in the adenocarcinoma group than in the group of patients with benign tumors; this requires further careful study because the regulation of *NOX* family genes is complex and determined by a specific cell type.

Gene expression in the antioxidant enzymes *SOD1* and *HNOX1* was slightly reduced in the group of patients with ovarian cancer. The decrease in *SOD1* gene expression is consistent with literature data demonstrating a decrease in the levels of superoxide dismutase, catalase, and low-molecular-weight antioxidants (vitamins C and E) in ovarian cancer [28]. Disorders of heme metabolism in ovarian cancer, primarily in endometriosis-associated cancer, are studied less. Experiments in ovarian cancer cell lines reveal that heme induces heme oxygenase-1 (HO-1) expression. Low levels of exogenous heme promoted the growth of ovarian cancer colonies, and higher doses of heme resulted in slower growth of cancer cell colonies in the induction of HO-1 [29]. Moreover, suppression of the *NRF2/HO-1/xCT/GPX4* cytoprotective pathway is the basis of the action of the ferroptosis inducer in ovarian cancer [30]. All this confirms the duality of the effects of participants in oxidative metabolism and the need for a thorough study of its role in carcinogenesis.

CONCLUSION

In high-grade adenocarcinoma tissues, the activity of cytochrome *b5* reductase is significantly increased, which can be due to a response to intracellular oxidative stress, whereas expression of the *CYB5R3* gene, but not *CYB5R1* and *CYB5R2\4*, is reduced. The decrease in *CYB5R3* gene expression may result from negative feedback. Additionally, the activity of cytochrome P450 reductase is increased, but to a lesser extent, and positively correlates with the *POR* gene expression. Thus, cytochrome *b5* reductase is involved in carcinogenesis in ovarian cancer, to a greater extent than cytochrome P450 reductase. The expression levels of the *NFKB1* gene did not differ between the groups, but correlated with the activity of blood neutrophils, the levels of which were generally normal. Furthermore, the expression levels of the *NRF2* gene did not differ between the groups and correlated with indicators of plasma antioxidant capacity. The correlation with peritoneal fluid antioxidant capacity was significantly stronger, indicating closer metabolic connections at the local level in the peritoneal cavity than at the systemic level.

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AUTHORS' INFO

***Elena V. Proskurnina,** MD, Dr. Sci. (Med.), assistant professor, Chief Researcher;
address: 115522, Moscow, Moskvorechye str., 1;
ORCID: 0000-0002-8243-6339;
e-mail: proskurnina@gmail.com

Mariya V. Fedorova, MD, obstetrician-gynecologist;
ORCID: 0000-0002-7859-6698;
e-mail: theklazontag@yandex.ru

Ekaterina A. Savinova, MD, research associate;
ORCID: 0000-0001-5286-516X;
e-mail: savinova.ekaterina96@yandex.ru

Vladimir I. Voznesenskii, MD, Cand. Sci. (Med.), oncologist, obstetrician-gynecologist;
ORCID: 0000-0002-5135-0997;
e-mail: vlad525@gmail.com

Svetlana V. Kostyuk, MD, Dr. Sci. (Med.), assistant professor, Head of the Laboratory;
ORCID: 0000-0002-6336-9900;
e-mail: svet-vk@yandex.ru

Elena A. Sosnova, MD, Dr. Sci. (Med.), Professor;
ORCID: 0000-0002-1732-6870;
eLibrary SPIN: 6313-9959;
e-mail: sosnova-elena@inbox.ru

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

***Проскурнина Елена Васильевна,** д-р мед. наук, доцент, главный научный сотрудник;
адрес: 115522, Москва, ул. Москворечье, д. 1;
ORCID: 0000-0002-8243-6339;
e-mail: proskurnina@gmail.com

Федорова Мария Витальевна, врач акушер-гинеколог;
ORCID: 0000-0002-7859-6698;
e-mail: theklazontag@yandex.ru

Савинова Екатерина Алексеевна, научный сотрудник;
ORCID: 0000-0001-5286-516X;
e-mail: savinova.ekaterina96@yandex.ru

Вознесенский Владимир Игоревич, канд. мед. наук, врач-онколог, акушер-гинеколог;
ORCID: 0000-0002-5135-0997;
e-mail: vlad525@gmail.com

Костюк Светлана Викторовна, д-р мед. наук, доцент, заведующая лабораторией;
ORCID: 0000-0002-6336-9900;
e-mail: svet-vk@yandex.ru

Соснова Елена Алексеевна, д–р мед. наук, профессор;
ORCID: 0000-0002-1732-6870;
eLibrary SPIN: 6313-9959;
e-mail: sosnova-elena@inbox.ru

*Автор, ответственный за переписку / Corresponding author