The metabolomic profile features of some biological fluids in serous ovarian adenocarcinoma patients

Vlastnosti metabolomického profilu některých biologických tekutin u pacientek se serózním adenokarcinomem vaječníků

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Summary

Background: The search for effective biomarkers for ovarian cancer (OC) early diagnosis is an urgent task of modern oncogynecology. Metabolic profiling by ultra-high performance liquid chromatography and mass spectrometry (UHPLC-MS) provides information on the totality of all low molecular weight metabolites of patient's biological fluids sample, reflecting the processes occurring in the body. The aim of the study was to research blood plasma and urine metabolomic profile of patients with serous ovarian adenocarcinoma by UHPLC-MS. ***Material and methods:*** To perform metabolomic analysis, 60 blood plasma samples and 60 urine samples of patients diagnosed with serous ovarian carcinoma and 20 samples of apparently healthy volunteers were taken. Chromatographic separation was performed on a Vanquish Flex UHPLC System chromatograph (Thermo Scientific, Germany). Mass spectrometric analysis was performed on an Orbitrap Exploris 480 (Thermo Scientific, Germany) equipped with an electrospray ionization source. Bioinformatic analysis was performed using Compound Discoverer Software (Thermo Fisher Scientific, USA), statistical data analysis was performed in the Python programming language using the SciPy library. ***Results:*** Using UHPLC-MS, 1,049 metabolites of various classes were identified in blood plasma. In patients with OC, 8 metabolites had a significantly lower concentration ($P < 0.01$) compared with conditionally healthy donors, while the content of 19 compounds, on the contrary, increased ($P < 0.01$). During the metabolomic profiling of urine samples, 417 metabolites were identified: 12 compounds had a significantly lower concentration compared to apparently healthy individuals, the content of 14 compounds increased ($P < 0.01$). In patients with ovary serous adenocarcinoma, a significant change in the metabolome of blood plasma and urine was found, expressed in abnormal concentrations of lipids and their derivatives, fatty acids and their derivatives, acylcarnitines, phospholipids, amino acids and their derivatives, derivatives of nitrogenous bases and steroids. At the same time, kynurenine, myristic acid, lysophosphatidylcholine and L-octanoylcarnitine are the most promising markers of this disease. ***Conclusion:*** The revealed changes in the metabolome can become the basis for improving approaches to the diagnosis of serous ovarian adenocarcinoma.

Key words

serous ovarian adenocarcinoma – metabolomic profile – blood plasma – urine – ultra-high performance liquid chromatography and mass spectrometry

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Souhrn

Východiska: Hledání účinných biomarkerů pro včasnou diagnostiku ovariálního karcinomu (ovarian cancer – OC) patří k naléhavým úkolům moderní onkogynekologie. Metabolické profilování pomocí ultra vysokoúčinné kapalinové chromatografie a hmotnostní spektrometrie (ultra-high performance liquid chromatography and mass spectrometry – UHPLC-MS) poskytuje informace o souhrnu všech nízkomolekulárních metabolitů vzorku biologických tekutin pacienta, které odrážejí procesy probíhající v těle. Cílem studie bylo prozkoumat metabolomický profil krevní plazmy a moči pacientek se serózním ovariálním adenokarcinomem pomocí UHPLC-MS. ***Materiál a metody:*** K provedení metabolomické analýzy bylo odebráno 60 vzorků krevní plazmy a 60 vzorků moči pacientek s diagnózou serózního karcinomu vaječníků a 20 vzorků zdravých dobrovolníků. Chromatografická separace byla provedena na chromatografu Vanquish Flex UHPLC System (Thermo Scientific, Německo). Analýza hmotnostní spektrometrií byla provedena na Orbitrap Exploris 480 (Thermo Scientific, Německo) vybaveném elektrosprejovým ionizačním zdrojem. Bioinformatická analýza byla provedena pomocí Compound Discoverer Software (Thermo Fisher Scientific, USA), statistická analýza dat byla provedena v programovacím jazyce Python pomocí knihovny SciPy. ***Výsledky:*** Pomocí UHPLC-MS bylo v krevní plazmě identifikováno 1 049 metabolitů různých tříd. U pacientek s OC mělo 8 metabolitů významně nižší koncentraci ($p < 0,01$) ve srovnání se zdravými dárci, zatímco u 19 látek byly zjištěny vyšší hladiny ($p < 0,01$). Během metabolomického profilování vzorků moči bylo identifikováno 417 metabolitů: 12 látek mělo významně nižší koncentraci ve srovnání se zjevně zdravými jedinci a u 14 látek byly hladiny vyšší ($p < 0,01$). U pacientek se serózním adenokarcinomem vaječníků byla zjištěna významná změna v metabolomu krevní plazmy a moči, vyjádřená abnormálními koncentracemi lipidů a jejich derivátů, mastných kyselin a jejich derivátů, acylkarnitinů, fosfolipidů, aminokyselin a jejich derivátů, derivátů dusíkatých bází a steroidů. Mezi nejslibnější markery tohoto onemocnění přitom patří kynurenin, kyselina myristová, lysofosfatidylcholin a L-oktanoylkarnitin. ***Závěr:*** Odhalené změny v metabolomu se mohou stát základem pro zlepšení přístupů k diagnostice serózního ovariálního adenokarcinomu.

Klíčová slova

serózní ovariální adenokarcinom – metabolomický profil – krevní plazma – moč – ultra vysokoúčinná kapalinová chromatografie a hmotnostní spektrometrie

Introduction

Ovarian cancer (OC) is one of the most aggressive gynecological cancers: 7th in terms of incidence and 8th in terms of mortality among the female population in the world. Every year, more than 225,000 new cases and about 140,000 deaths from this disease are registered [1]. As a rule, OC has virtually no clinical manifestations until late stages, when women usually exhibit nonspecific symptoms [2]. Despite its high prevalence and high mortality, there are still no effective methods for early diagnosis of OC, which is why in most patients (70–90%) the diagnosis is made at stages III–IV, resulting in a 5-year survival rate of only 20–30%. Relapse rates in OC patients are very high. According to the literature, 85% of patients with this disease who achieved complete remission after the first line of therapy experience a relapse [3].

Modern OC diagnosis includes ultrasound examination of the abdominal organs, retroperitoneum, pelvis and cervico-supraclavicular region, chest X-ray, fibroesophagogastroduodenoscopy and fibrocolonoscopy. Typically, the level of tumor antigen CA-125 and human epididymal secretory protein 4 (HE-4) is tested. However, their sensitivity and specificity are often insufficient to detect the disease at an early stage [4]. Intravital pathological examination is a decisive method in establishing the diagnosis of ovarian cancer and choosing treatment tactics, as well as in diagnosing a possible relapse. However, this method of tumor analysis has certain limitations. Obtaining biological material for histological examination as the most accurate method of morphological verification of OC requires surgical intervention [5].

One of the tasks of modern gynecological oncology is the search for effective biomarkers, objectively measured compounds, changes in the level of which can be used for early diagnosis and predicting the success of planned treatment. A potential biomarker should be as sensitive and specific as possible, and its measurement should be minimally invasive [6].

For this reason, in recent years, liquid biopsy has received increasing attention in precision medicine because it is minimally invasive and can be repeated several times, facilitating real-time disease monitoring. Screening for a tumor marker or a combination of tumor markers with high sensitivity, specificity and prognostic significance for OC, determined in easily accessible biological material – plasma, blood serum or urine – is a promising area of research [7]. Most research has focused on identifying biomarkers in blood, but the ease of obtaining a biological sample such as urine suggests that this approach may also hold promise for screening patients for OC [7]. Compared to blood, urine is a completely non-invasive sample type and is available in large quantities, and is more stable compared to plasma/serum with respect to pre-analytical processing procedures [8].

Modern biomedical research is characterized by the use of high-performance technological platforms that describe the properties of a biological object at the genome, transcriptome, proteome and metabolome levels. Metabolomic research allows for high-throughput qualitative and quantitative analysis of metabolites of cells, tissues, organs and biological fluids in a given biological system. A metabolome is a collection of all low-molecular-weight biological sample metabolites, being a unique biochemical "fingerprint" reflecting ongoing processes in the body [9].

The metabolome study includes combined chromatographic and mass spectrometric systems used for analytes analyzed together with statistical and bioinformation processing of experimental data array. One of the leading analytical methods used in metabolomics is

high performance liquid chromatography and mass spectrometry (HPLC-MS), which allows for preliminary fractionation of chemical compounds of the analyzed sample, subsequent ionization, ions separation according to the mass-to-charge ratio (m/z) and their detection [10].

In recent decades, special attention has been paid to changes in the metabolome as one of the tumors hallmarks. For oncological diseases diagnosis, such compounds are oncometabolites – compounds whose concentration increases markedly in tumors or biological fluids. The key feature of this metabolites group is the existence of a clear mechanism linking the specific characteristics of the tumor with the accumulation of the metabolite and its participation in the development of malignant neoplasms [11].

In this regard, the aim of the research was to study blood plasma and urine metabolomic profile of serous ovarian adenocarcinoma patients using ultra-high performance liquid chromatography and mass spectrometry (UHPLC-MS).

Materials and methods

To perform metabolomic analysis, blood plasma and urine samples were taken from 100 patients with serous ovarian carcinoma and 30 apparently healthy volunteers. In each case, voluntary informed consent was obtained. Meta/synchronous cancer, mutation in *BRCA1/2,* comorbid pathology, pregnancy, age over 65 years were exclusion criteria from the study.

Blood plasma samples preparation

Blood was collected from patients on an empty stomach into tubes with K2EDTA as an anticoagulant (BD Vacutainer, USA). No later than 20 min after the collection procedure, the blood was centrifuged at 1,800 g (room temperature) for 10 min. To remove residual blood cells, an additional centrifugation step was performed at 16,000 g (4 °C) for 10 min. The resulting blood plasma was aliquoted into 1 mL cryotubes. The samples were stored at –75 °C until analysis. To carry out deproteinization, 300 µL of blood plasma was mixed with 900 µL of acetonitrile LC-MS (Merck, Germany) and methanol LC-MS (Merck, Germany) in a ratio of 3 : 1. Next, they were mixed using a vortex and incubated at –20 °C for 12 hours. Then centrifugation was carried out at 16,000 g (4 °C) for 15 min (5430R, Eppendorf, Germany). The supernatant liquid was transferred into 1.5 mL plastic Eppendorf tubes and their contents were evaporated using a SpeedVac vacuum evaporator (Eppendorf, Germany). The dry sediment was dissolved in a mixture of LC-MS acetonitrile (Merck, Germany) and water with 0.1% formic acid (Merck, Germany) in a ratio of 1 : 3.

Urine samples preparation

The first morning urine (middle portion) was collected for analysis. No later than 25 min after collection, the urine was centrifuged at 1,600 g (room temperature) for 10 min. Next, subsequent centrifugation was carried out at 16,000 g (4 °C) for 10 min. Then 6 mL of the resulting sample was divided into 3 aliquots of 2 mL each, placing them in plastic cryovials. Samples were stored at –80 °C until metabolomic analysis. To precipitate proteins, 300 µL of urine was mixed with 600 µL of acetonitrile LC-MS (Merck, Germany) and methanol LC-MS (Merck, Germany) solution (ratio 3 : 1). Next, they were mixed using a vortex and incubated at –20 °C for 12 hours. Then, proteins were precipitated at 16,000 g (4 °C) for 15 min (MiniSpin plus centrifuge, Eppendorf, Germany). The supernatant was transferred into clean plastic tubes. The sample was evaporated using a SpeedVac vacuum evaporator (Eppendorf). The resulting dry precipitate was dissolved in a mixture of acetonitrile LC-MS (Merck, Germany) and water (1 : 3) with 0.1% formic acid (Merck, Germany). Next, the samples were centrifuged at 16,000 g for 10 min and the resulting supernatant was used for gas chromatography-mass spectrometric analysis.

Sample separation and analysis

Chromatographic separation was carried out on a Vanquish Flex UHPLC System chromatograph (Thermo Scientific, Germany). Mass spectrometric analysis was performed on an Orbitrap Exploris 480 (Thermo Scientific, Germany) equipped with an electrospray ionization source.

Chromatographic separation was carried out on a Hypersil GOLD™ C18 column (1.9 µm, 150 × 2.1 mm) using the following eluents: A – 0.1% formic acid, B – acetonitrile containing 0.1% formic acid. The autosampler temperature was 4 °C. The following elution gradient was used: 0–1 min – 5% eluent A, 1–5 min – linear gradient of eluent B from 5 to 25%, 5–7 min – 25–55% eluent B, 7–13 min – 55–95% eluent B, 13–14 min – 95% eluent B, 0.5 min – change of eluent composition to 5% eluent B, 1 min – 5% eluent B. The column temperature was maintained at 40° C. The eluent flow was 200 µL/min. Mass spectra were obtained over a mass-to-charge ratio range of 80–900. Mass spectrometric peaks to be identified were matched to specific metabolites from the Human Metabolome Database [12]. For this purpose, an accurately measured mass of the chemical compound was used (additionally, the mass spectrum was calibrated using the internal standard EASY-IC fluoranthene).

Bioinformatic analysis was performed using Compound Discoverer Software (Thermo Fisher Scientific, USA), which provides easy interpretation of results using several powerful visualizations, including log2fold change and P-value distribution plots and biochemical pathway analysis using the KEGG PATHWAY Database. Statistical data analysis was carried out in the Python programming language using the SciPy library [13].

Research results

This study demonstrates the possibility of identifying differences in blood plasma metabolome from serous ovarian adenocarcinoma patients and apparently healthy volunteers using the UHPLC-MS method. To determine the optimal conditions for chromatographic separation and mass spectrometric detection of metabolites in the blood plasma and urine of patients, a review of the literature was carried out and different protocols for sample preparation, chromatographic separation, and mass spectrometry options were compared.

Analysis revealed the m/z of metabolites, the intensities of which change statistically significantly in the mass spectra. The P-values and Log2Fold-

Tab. 1. Changes in the plasma metabolome of serous ovarian carcinoma patients relative to conditionally healthy volunteers.

Compound	Log2FoldChange	P-value
phosphatidylcholine (18 : 2 / 0 : 0)	1.10973	5.70×10^{-4}
3-hydroxy-5-cholenic acid	−0.56711	4.11×10^{-3}
lysophosphatidylcholine (22 : 5 / 0 : 0)	0.63725	6.98×10^{-3}
lysophosphatidylcholine (18 : 2)	2.91042	5.11×10^{-6}
lysophosphatidylcholine (20 : 3)	1.71321	1.98×10^{-5}
lysophosphatidylcholine (20 : 4)	1.81851	6.64×10^{-7}
lisophosphatidylethanolamine (18 : 3)	0.61153	1.87×10^{-3}
myristic acid	1.41312	6.62×10^{-6}
3-oxododecanoic acid	−0.61212	2.60×10^{-4}
hippuric acid	−1.85080	1.91×10^{-4}
L-tryptophan	−0.50164	6.43×10^{-6}
L-phenylalanine	0.52041	2.86×10^{-4}
L-homocitrulline	−0.56390	5.01×10^{-4}
L-thyroxine	0.37025	9.86×10^{-3}
glutamyl-threonine	−1.37341	2.78×10^{-5}
capryloylglycine	−0.42213	2.10×10^{-4}
L-homocysteine	0.69047	1.10×10^{-4}
eicosadienoic acid	0.61892	2.15×10^{-4}
kynurenin	0.97640	1.32×10^{-5}
3-indole propionic acid	0.34142	1.87×10^{-2}
L-octanoylcarnitine	−4.06334	2.01×10^{-9}
3-hydroxybutyrylcarnitine	−0.48712	5.10×10^{-4}
2,6-dimethylheptanoylcarnitine	−1.86441	1.22×10^{-7}
hexanoylcarnitine	−2.01759	2.29×10^{-5}
malonylcarnitine	−0.47096	2.00×10^{-5}
b-aminoisobutyric acid	2.52378	1.47×10^{-4}
hypoxanthine	−0.70919	1.00×10^{-5}

Change were calculated for the intensities of mass spectrometric peaks of these metabolites.

A total of 1,156 metabolites of various classes were identified in blood plasma using UHPLC-MS. It was shown that in ovarian cancer patients 13 metabolites had a significantly lower ($P < 0.01$) concentration compared to conditionally healthy volunteers, the content of 14 compounds, on the contrary, increased ($P < 0.01$) (Tab. 1).

Blood plasma metabolites comparison with their biochemical pathways revealed changes in lipid metabolism (eicosadienoic acid, lysophosphatidylcholine (20 : 4), lysophosphatidylcholine (18 : 2), lysophosphatidylcholine (20 : 3), lysophosphatidylethanolamine (18 : 3), lysophosphatidylcholine (22 : 5 / 0 : 0), phosphatidylcholine (18 : 2 / 0 : 0), L-octanoylcarnitine, decanoyl-L-carnitine); bile acids (3-hydroxy-5-cholenic acid); amino acids and their derivatives (L-homocysteine, L-tryptophan (L-tryptophan, 3-indolepropionic acid, kynurenine), L-tyrosine (L-thyroxine, L-phenylalanine, hippuric acid), glutamyl-threonine, L-homocitrulline, b-aminoisobutyric acid); nucleotides (hypoxanthine).

During the metabolomic profiling of urine samples, 608 names of metabolites were identified. The m/z of metabolites were identified, the intensities of which in the mass spectra changed statistically significantly. The P-values and Log2FoldChange were determined for these metabolites (Tab. 2).

It was shown that in patients with OC, 14 metabolites (kynurenine, phenylalanyl-valine, lysophosphatidylcholine (18 : 3), lysophosphatidylcholine (18 : 2), alanyl-leucine, lysophosphatidylcholine (20 : 4), L-phenylalanine, phosphatidylinositol (34 : 1), 5-methoxytryptophan, 2-hydroxymyristic acid, 3-oxocholic acid, lysophosphatidylcholine (14 : 0), indoleacrylic acid, lysoosphatidylserine (20 : 4)) had significantly higher concentrations in urine compared to apparently healthy individuals. On the contrary, the concentration of 12 compounds (L-beta-aspartyl-L-phenylalanine, myristic acid, decanoylcarnitine, aspartyl-glycine, malonylcarnitine, 3-hydroxybutyrylcarnitine, 3-methylxanthine, 2,6 dimethylheptanoylcarnitine, 3-oxododecanoic acid, N-acetylproline, L-octanoylcarnitine, capryloylglycine) was decreased.

A comparison of the metabolome of blood plasma and urine of serous ovarian adenocarcinoma patients relative to conditionally healthy individuals showed that the content of 11 compounds was statistically significantly different simultaneously in blood plasma and urine from conditionally healthy volunteers ($P < 0.01$). At the same time, the ratios of the concentrations of kynurenine, myristic acid, lysophosphatidylcholine and L-phenylalanine were statistically significantly different in plasma and urine by 2.8 times, 5.0 times, 1.9 times and 2.7 times respectively ($P < 0.05$) (Tab. 3).

Discussion

Changes in metabolite levels contribute to tumor progression through various mechanisms, such as aerobic glycolysis, decreased oxidative phosphorylation and increased formation of biosynthetic intermediates. Discovering the metabolic transformation mechanism may make it possible to diagnose a tumor, or even stop its progression by blocking modified biochemical pathways [14].

One of the mechanisms that contribute to tumor evasion from the immune system is tryptophan metabolism modification. In the present study, the concentrations of several metabolites involved in the metabolism of L-tryptophan were significantly different in patients with ovarian cancer compared to the control group. Tryptophan and its metabolites play a key role in various physiological processes. The decrease in L-tryptophan in ovarian serous carcinoma is likely due to increased degradation of L--tryptophan ($P < 0.01$) catalyzed by indoleamine (2,3)-dioxygenase, as evidenced by an increase in kynurenine ($P < 0.01$). It is possible that altered L-tryptophan metabolism provides a metabolic microenvironment favorable for tumor growth [15,16].

Urinary concentrations of most fatty acid derivatives – 3-hydroxybutyrylcarnitine, 2,6-dimethylheptanoylcarnitine, myristic acid, L-octanoylcarnitine, malonylcarnitine, and decanoylcarnitine – were reduced in patients with ovarian tumors compared to the control group. It is now widely known that cancer cells exhibit significant changes in their lipid and fatty acid metabolism. There is compelling evidence that fatty acid utilization is increased in some types of cancer, while this pathway is suppressed in others. However, changes are not limited only to intrinsic cellular processes, such as membrane synthesis or the role of intracellular second messengers, but also extend to the remodeling of the entire tumor microenvironment through paracrine signaling mechanisms [17].

Tab. 2. Changes in the urine metabolome of serous ovarian carcinoma patients relative to apparently healthy individuals.

Compound	Log2FoldChange	P-value
kynurenin	2.45720	1.39×10^{-7}
indoleacrylic acid	0.44071	3.11×10^{-2}
phenylalanyl-valine	0.65042	2.00×10^{-4}
L-beta-aspartyl-L-phenylalanine	–1.57310	2.71×10^{-9}
L-phenylalanine	0.52714	2.18×10^{-5}
alanyl-leucine	0.41570	1.00×10^{-4}
aspartyl-glycine	–1.81871	1.61×10^{-4}
5-methoxytryptophan	0.51168	6.54×10^{-11}
N-acetylproline	–0.92310	8.15×10^{-4}
capryloylglycine	–0.47215	1.20×10^{-3}
lysophosphatidylcholine (20 : 4)	1.71890	6.61×10^{-12}
lysophosphatidylcholine (18 : 3)	1.60112	1.28×10^{-9}
lysophosphatidylcholine (18 : 2)	2.79230	5.01×10^{-12}
lysophosphatidylcholine (14 : 0)	0.68299	2.17×10^{-2}
lysophosphatidylserine (20 : 4)	3.98201	1.31×10^{-11}
phosphatidylinositol (34 : 1)	2.71689	1.25×10^{-10}
hexanoylcarnitine	–2.09750	2.29×10^{-9}
malonylcarnitine	–0.47912	3.00×10^{-4}
3-hydroxybutyrylcarnitine	–0.42701	1.02×10^{-2}
2,6-dimethylheptanoylcarnitine	–1.91404	1.82×10^{-8}
L-octanoylcarnitine	–4.16302	2.21×10^{-15}
myristic acid	–1.81812	6.68×10^{-9}
2-hydroxymyristic acid	0.31573	1.24×10^{-2}
3-oxododecanoic acid	–0.45029	2.60×10^{-3}
3-oxocholic acid	0.61741	1.20×10^{-3}
3-methylxanthine	–0.73597	1.00×10^{-4}

Myristic acid is involved in several antitumor mechanisms, such as the production of myristoleic acid, which induces apoptosis in tumors, and de novo ceramide synthesis. Plasma myristic acid levels are inversely associated with the risk of colon cancer. The mechanisms underlying this relationship are not fully understood [17].

In patients with ovarian tumors, compared with the control group, there was an increase in lysophosphatidylserine, which may further indicate a disorder of the immune system. In the tumor microenvironment, phosphatidylserine content varies significantly on the surface of tumor cells or tumor cell-derived microvesicles, which have immunosuppressive properties and promote tumor growth and metastasis [18].

Lysophospholipids are secreted by various types of cells, including cancer cells. These chemical compounds play an important role in the development, activation and regulation of the immune system [19]. The concentrations of most phospholipids in the present study increased in patients with ovarian tumors compared with controls. Changes in the composition and content of phospholipids and lysophospholipids have previously been shown in prostate cancer and are considered as potential biomarkers [20].

Indoleacrylic acid was elevated in patients with ovarian tumors compared to controls. Changes in the content of indoleacrylic acid may contribute to the development of anti-inflammatory reactions [21]. An increase in indoleacrylic acid is accompanied by an increase in kynurenine content. The kynurenine pathway of tryptophan metabolism is intensified in the body of cancer patients; its products have pro-oncogenic and immunosuppressive effects [22]. Changes in the metabolism of another aromatic amino acid, phenylalanine and its deri-

Tab. 3. Comparison of blood plasma and urine metabolome of serous ovarian adenocarcinoma patients relative to conditionally healthy volunteers.

Compound	Blood plasma, FoldChange (FC*)	Urine, FoldChange (FC*)
2,6-dimethylheptanoylcarnitine	0.29	0.27
kynurenin	1.97	5.49
myristic acid	1.41	0.28
3-oxododecanoic acid	0.87	0.65
lysophosphatidylcholine (20 : 4)	1.82	3.53
L-phenylalanine	0.53	1.44
3-hydroxybutyrylcarnitine	0.71	0.79
L-octanoylcarnitine	0.13	0.06
hexanoylcarnitine	0.28	0.23
capryloylglycine	0.76	0.74
malonylcarnitine	0.57	0.72

*FC values are presented – fold difference, FC – metabolite level in the urine or plasma of patients / metabolite level in the urine or plasma of conditionally healthy volunteers

vatives, are also associated with inflammation and immune activation. Neurauter et al. showed that the concentration of phenylalanine in the blood serum of patients with ovarian carcinoma correlates with the concentration of immune activation markers and oxidative stress development [23].

In this study, the xanthine derivatives concentration was reduced in biological samples from cancer patients. 3-methylxanthines (C6H6N4O2) – a class of organic compounds, methyl derivatives of xanthine (3,7-dihydropurine-2,6--dione) – have anticancer effects by inhibiting PI3K/Akt/mTOR and stimulating PTEN, thereby promoting apoptosis and autophagy [24,25].

Thus, based on the results of UHPLC--MS profiling of blood plasma and urine, changes were detected in key cascades and signaling pathways involved in the metabolomic reprogramming of the ovarian tissue.

Conclusion

Currently, there is no highly effective and minimally invasive diagnostic test for serous ovarian adenocarcinoma accepted in clinical practice, which hinders the detection of the disease at an early stage. Metabolomic studies are a source of information for bridging the gaps in understanding the mechanisms involved in the progression of ovarian serous carcinoma and valuable markers of this disease. Thus, in ovarian serous carcinoma patients, a significant change in the metabolome of blood plasma and urine was found, expressed in abnormal concentrations of lipids and their derivatives, fatty acids and their derivatives, acylcarnitines, phospholipids, amino acids and their derivatives, derivatives of nitrogenous bases and steroids. At the same time, kynurenine, myristic acid, lysophosphatidylcholine and L-octanoylcarnitine are the most promising markers of this disease. The identified changes in the metabolome can become the basis for improving approaches to the serous ovarian adenocarcinoma diagnosis.

Disclosure

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