PECULIARITIES OF AMINO ACID PROFILE IN MONOCYTES IN BREAST CANCER

Novoselova AV[1] ✉, Yushina MN[1], Patysheva MR[2,3], Prostakishina EA[2,3], Bragina OD[2], Garbukov EY[2], Kzhyshkowska JG[3,4,5,6]

[1] Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology, Moscow, Russia

[2] Cancer Research Institute, Tomsk National Research Medical Center, Tomsk, Russia

[3] Tomsk National State University, Tomsk, Russia

[4] Siberian State Medical University, Tomsk, Russia

[5] Institute of Transfusion Medicine and Immunology, Faculty of Medicine Mannheim, University of Heidelberg, Heidelberg, Germany

[6] German Red Cross Blood Service Baden-Württemberg-Hesse, Mannheim, Germany

Monocytes are large circulating white blood cells that are the main precursors of tissue macrophages as well as tumor-associated macrophages in the adult body. Different types of monocytes have multidirectional effects on the growth and metastatic spread of cancer cells, both activating and inhibiting these processes. Tumor progression is associated with the triggering of a whole cascade of inflammatory and immune reactions. These pathological processes are associated with changes in the amino acid content of monocytes, which can lead to disruption of their function, in particular their migration, division and maturation. The aim of the work was to profile the amino acids of monocytes, followed by a study of the amino acid composition of monocytes from patients with breast cancer using liquid chromatography with mass spectrometric detection. Significant differences in metabolite levels in monocytes of breast cancer patients and monocytes of healthy donors were found for glycine (p-value = 0.0127), asparagine (p-value = 0.0197), proline (p-value = 0.0159), methionine (p-value = 0.0357), tryptophan (p-value = 0.0028), tyrosine (p-value = 0.0127). In the study, we identified biological networks that could potentially be involved in altering the phenotype of monocytes affected by breast cancer (BC), using bioinformatic analysis of metabolic pathways involving the discovered amino acids. Mathematical models based on amino acid combinations with 100% sensitivity and specificity have been developed. Features of immune system cell metabolism in BC have been identified and potential diagnostic biomarkers have been proposed.

Keywords: monocytes, breast cancer, metabolomics, amino acids, mass spectrometry

ОСОБЕННОСТИ ПРОФИЛЯ АМИНОКИСЛОТ В МОНОЦИТАХ ПРИ РАКЕ МОЛОЧНОЙ ЖЕЛЕЗЫ

А. В. Новоселова[1] ✉, М. Н. Юшина[1], М. Р. Патышева[2,3], Е. А. Простакишина[2,3], О. Д. Брагина[2], Е. Ю. Гарбуков[2], Ю. Г. Кжышковска[3,4,5,6]

[1] Национальный медицинский исследовательский центр акушерства, гинекологии и перинатологии имени В. И. Кулакова, Москва, Россия

[2] Научно-исследовательский институт онкологии, Томский национальный исследовательский медицинский центр, Томск, Россия

[3] Национальный исследовательский Томский государственный университет, Томск, Россия

[4] Сибирский государственный медицинский университет, Томск, Россия

[5] Институт трансфузионной медицины и иммунологии, Медицинский факультет Маннгейм, Университет Гейдельберга, Гейдельберг, Германия

[6] Германский Красный крест Служба крови Баден-Вюртемберг — Гессен, Мангейм, Германия

Моноциты — крупные циркулирующие в крови лейкоциты, которые во взрослом организме являются основными предшественниками тканевых макрофагов, а также опухоле-ассоциированных макрофагов. Различные типы моноцитов имеют разнонаправленное действие в отношении роста и метастатического распространения раковых клеток, как активируют, так и подавляют данные процессы. Опухолевая прогрессия связана с запуском целого каскада воспалительных и иммунных реакций. Данные патологические процессы ассоциированы с изменением содержания аминокислот в составе моноцитов, что может привести к нарушению их функции, в частности миграции, деления и созревания. Целью работы было профилировать аминокислоты моноцитов с последующим изучением особенностей аминокислотного состава моноцитов пациентов с раком молочной железы при помощи жидкостной хроматографии с масс-спектрометрической детекцией. Статистически значимые различия уровней метаболитов в моноцитах пациентов с раком молочной железы и моноцитов здоровых доноров обнаружены для глицина (p-value = 0,0127), аспарагина (p-value = 0,0197), пролина (p-value = 0,0159), метионина (p-value = 0,0357), триптофана (p-value = 0,0028), тирозина (p-value = 0,0127). В результате биоинформатического анализа метаболических путей с участием задействованных аминокислот были определены биологические сети, которые потенциально могут вовлекаться в изменение фенотипа моноцитов под воздействием РМЖ. Разработаны математические модели, построенные на комбинации аминокислот, обладающие 100% чувствительностью и специфичностью. Выявлены особенности метаболизма клеток иммунной системы при РМЖ и предложены потенциальные диагностические биомаркеры.

Ключевые слова: моноциты, рак молочной железы, метаболомика, аминокислоты, масс-спектрометрия

Monocytes in the adult body are a dynamic population of the main cells of innate immunity, which are permanently formed from precursors in the bone marrow and circulate in the bloodstream for 3 to 6 days. Monocytes in the adult organism serve as major precursors of tissue macrophages, major sensors of innate immunity for exogenous and endogenous pathological factors from the blood, and key precursors of tumor-associated macrophages [1–5]. Representing a pool of effector cells of innate immunity with pattern-recognizing receptors, they can act as regulators of tumor growth. Different types of monocytes have mixed effects on the growth and metastatic spread of cancer cells, they both activate and inhibit these processes. Tumor progression is associated with the triggering of a whole cascade of inflammatory and immune reactions. These pathological processes are associated with changes in the amino acid content of monocytes, which can lead to impaired monocyte function [6–8].

Monocytes are precursors of tumor-associated macrophages (TAMs) and dendritic cells, which form the tumor microenvironment [9]. At the site of inflammation, they perform the function of phagocytosis and the production of pro-inflammatory cytokines. In a pro-inflammatory microenvironment, they differentiate into inflammatory macrophages and inflammatory dendritic cells, which subsequently migrate to lymph nodes and activate CD4+ and CD8+ T-lymphocytes. Activated immune cells are subsequently involved in metabolic pathways associated with cancer cell progression [10–13]. This commonality of metabolic processes creates a fundamental competition for the nutrient substrates required by both cancer and immune cells in the tumor microenvironment.

The development of analytical techniques, primarily liquid chromatography with mass spectrometric detection (LC-MS), has led to the formation of metabolomics [14–16], which is actively used to identify the metabolic features of cancer processes, to clarify the mechanisms of pathogenesis and search for new drug targets [14, 17]. To date, the study of the amino acid profile deserves special attention. Changes in amino acid levels may be important for the formation of a proper immune response [13, 18–20] and may lead to disruption of immune cell migration, division and maturation. Amino acids are involved in the control of a number of pathways that regulate immune cell responses, including mTOR signaling and NO production [19, 21]. Competition for metabolites and signaling interaction between host immune cells and pathogens can affect the development of disease, including tumor genesis [18].

Breast cancer (BC) remains the leading malignant neoplasm in women by prevalence [22]. This is the first type of cancer, for which the role of immune cells in tumor growth maintenance was demonstrated in experiments on animals [23]. Further

studies allowed to accumulate information on mutual influence of cancer cells and immune system cells [7, 9, 17, 24–29].

The study of monocyte heterogeneity and its role at different stages of cancer process progression is crucial to investigate the ability of cancer cells to obstruct immunological surveillance and hide from the aggression of immunocompetent cells. Work in this direction will make it possible in the future to identify new biomarkers of the cancer process and develop personalized cancer immunotherapy pathways [30].

The aim of this work was to determine the amino acid profile of monocytes isolated from the blood of BC patients.

METHODS

The study group included 13 patients aged 36–69 years with stage IIA-IIIA T1-2N0-1M0 breast cancer. All patients had Her2+ molecular tumor subtype (Ki-67 score of at least 30%). The control group included 10 healthy volunteers aged 50–67 years. Inclusion criteria for the control group: no acute chronic diseases, no history of cancer, no history of allergies or autoimmune diseases, signed informed consent to participate in the study.

The object of the study was peripheral venous blood taken on an empty stomach in test tubes with K3EDTA. Researchers obtained mononuclear cell fraction from blood by enrichment on a Ficoll density gradient (1.077 g/cm³). CD14+ monocytes were isolated from the obtained mononuclear cell fraction according to the Myltenyi Biotec positive magnetic separation protocol using a MidiMACS magnetic separator (Myltenyi Biotec; Germany). The purity of the obtained fraction was determined by flow cytometry on a Cytoflex (Beckman Coulter; USA) and was more than 92% CD14+ cells. Cell counts were based on flow cytometry data. Researchers separated an aliquot containing 4–5 million monocytes and washed it 3 times by centrifugation at 311 g for 5 min with cold 0.3% ammonium acetate. The resulting cell precipitate was dried in a nitrogen atmosphere and stored at –80 °C until extraction for not more than 6 months.

Sample preparation for LC-MS analysis

The study used acetonitrile, methanol, butanol, and chloroform (purification grades for liquid chromatography) purchased from Merck (Darmstadt; Germany), and a 37% aqueous hydrochloric acid solution (Acros Organics; USA). Deionized water was prepared using the Milli-Q Reference Water Purification System (Molesem; France).

We prepared samples according to the following procedure: add 480 µL of chloroform/methanol (2:1 vol./vol.) solution

Table 1. Composition of mobile phase for LC-MS analysis of amino acids

Time, minutes	%A	%B
0	95	5
0.1	95	5
0.2	75	25
5	70	30
15	45	55
20	30	70
20.5	5	95
25	5	95
25.5	95	5
40	95	5

Table 2. Transition parameters for mass spectrometric detection of amino acids

Amino acid	Ion precursor, m/z	Ion product, m/z	Accelerating potential of the impact cell, V	Collision energy, V
Methylhistidine	226.2	42.2	122	72
Amino butyric acid	160.1	143.1	83	4
5-Hydroxylysine	219.2	128.0	83	12
Alanine	146.1	39.2	83	20
Arginine	231.18	172.1	83	12
Asparagine	189.1	144.1	83	8
Aspartic acid	246.2	144.1	83	8
Citrulline	232.2	215.1	83	4
Cystine	353.16	130.1	122	20
Glutamic_acid	260.19	186.1	83	8
Glutamine	203.1	186.1	83	4
Glycine	132.1	76.2	44	4
Histidine	212.14	110.1	83	12
Leucine	188.17	30.3	83	20
Lysine	203.2	186.2	83	4
Methionine	206.1	104.1	83	8
Ornithine	189.2	172.2	83	8
Phenylalanine	222.1	103.1	83	40
Proline	172.1	116.1	83	12
Sarcosine	146.1	44.3	83	12
Serine	162.12	106.1	83	8
Threonine	176.13	158.1	83	4
Trans-4-hydroxyproline	188.1	86.2	83	12
Tryptophan	261.16	244.1	83	4
Tyrosine	238.1	136.1	83	12
Valine	174.15	72.2	83	12

to the monocyte sample; sonicate the sample for 10 min at room temperature, add 150 µL of water, stir sample for 5 min; centrifuge the resulting solution at 13,000 g for 5 min at room temperature; sample 150 µL of the upper aqueous-methanol layer; dry it in a nitrogen flow for 30 min at 60 °C; add 200 µL of hydrochloric acid solution in butanol (0.1 mol/L); stir it for 3 minutes; centrifuge it at 13,000 g for 15 s at room temperature; then incubate at 60 °C for 15 min for the derivatization reaction; centrifuge at 13,000 g for 15 s at room temperature; dry it in a nitrogen flow for 30 min at 60 °C; stir for 5 min; centrifuge at 13,000 g for 15 s at room temperature; transfer 200 µL of the resulting sample to a vial with an insert for further analysis.

LC-MS analysis and data processing

We analyzed the samples by high-performance liquid chromatography using a 1260 Infinity II chromatograph (Agilent; USA) with detection by a 6460 Triple Quad mass spectrometer (Agilent; USA). Samples were separated by liquid chromatography using an Agilent Zorbax Eclipse XDB-C18 2.1 × 100 mm column with a sorbent diameter of 1.8 µm (Agilent; USA).

For the analysis of amino acids, we injected 3 µL of the sample and as the mobile phase, we used two eluents, fed at a flow rate of 150 µL/min and maintained a column temperature
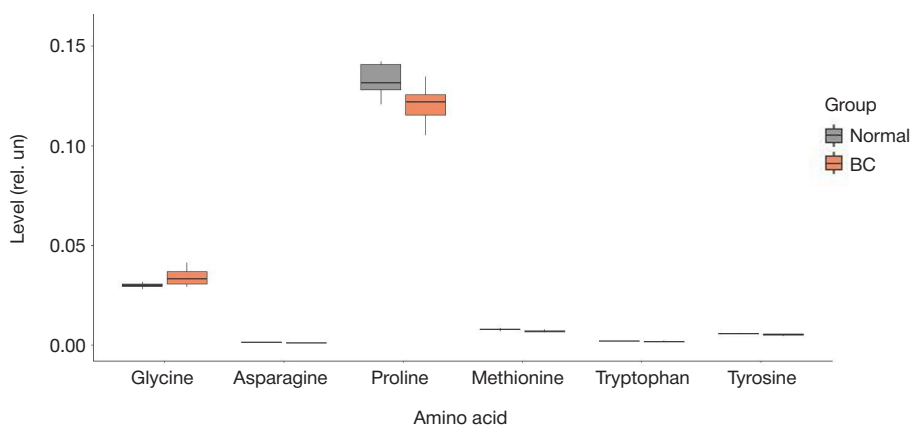

Fig. 1. Box plot of amino acids whose levels in monocytes differ significantly between the 'normal' and BC groups. The box boundaries are the first and third quartiles, the line in the middle of the box is the median; the error bars are the difference of the first quartile and the interquartile range, the sum of the third quartile and the interquartile range

Table 3. Metabolic pathways involving amino acids with significant differences in levels in monocytes from "normal" patients and breast cancer using the KEGG database

Metabolic pathway	Total number of metabolites involved	Number of metabolites that matched the experimental data	P	$-\text{Log}(P)$	Impact on the pathway
Biosynthesis of phenylalanine, tyrosine and tryptophan	4	1	0.015	1.812	0.5
Glycine, serine and threonine metabolism	33	1	0.121	0.916	0.246
Tryptophan metabolism	41	1	0.149	0.827	0.143
Tyrosine metabolism	42	1	0.152	0.818	0.14
Glyoxylate and dicarboxylate metabolism	32	1	0.118	0.929	0.106
Cysteine and methionine metabolism	33	1	0.121	0.916	0.104
Glutathione metabolism	28	1	0.104	0.984	0.089
Arginine and Proline Metabolism	38	1	0.139	0.858	0.078
Primary bile acid biosynthesis	46	1	0.166	0.781	0.008

at 20 °C. Eluent A was 10 mM ammonium acetate solution in water, eluent B was acetonitrile. We changed the composition of the mobile phase during the analysis according to Table 1.

Transitions between precursor ions and product ions for the analyzed amino acids are shown in Table 2. Parameters of the ion source were as follows: drying gas temperature — 150 °C, drying gas flow rate — 10 L/min, spray gas pressure — 2.76 bar, curtain gas temperature — 400 °C, curtain gas flow rate — 10 L/min, capillary voltage — 2000 V.

We determined metabolite levels using QuantAnalysis software (Agilent; USA).

Statistical analysis of the data

All data were analyzed in the R software environment (http://www.r-project.org/, versions R 4.1.1, 4.1.2). For initial processing of data tables we used the packages tidyverse (version 1.3.1) and readxl (1.3.1). The results were visualized using ggplot2 (version 3.3.5) and ggforestplot (version 0.1.0).

Amino acid levels were compared using the nonparametric Wilcoxon-Mann-Whitney test. Medians (Me) and quartiles Q_1 and Q_3 were used to describe quantitative data. The value of the threshold level of significance p was taken to be 0.05.

The team of researchers developed logistic regression models to assess the possibility of classifying patients into groups on the basis of the parameters under study. Levels of individual amino acids were considered as independent variables in the models. The dependent variable was whether the sample belonged to the 'normal' or BC group. Of all the models developed, we selected the four with the highest area under the ROC curve (AUC). The quality of the models developed was assessed by plotting the ROC curve, determining the area under the ROC curve, and calculating sensitivity and specificity.

If amino acid levels differed in monocytes from those in BC patients, we analyzed the involvement in metabolic pathways using the MetaboAnalyst 5.0 resource (https://www.metaboanalyst.ca/home.xhtml)

RESULTS

Semi-quantitative data on the content of 26 amino acids in monocytes of healthy donors and in monocytes of BC patients were obtained in the analysis. The list of amino acids included methyl-histidine, aminobutyric acid, 5-hydroxylysine, alanine, arginine, asparagine, aspartic acid, citrulline, cystine, glutamic acid, glutamine, glycine, histidine, leucine, lysine, methionine, ornithine, phenylalanine, proline, sarcosine, serine, threonine, trans-4-hydroxy-proline, tryptophan, tyrosine, valine. We obtained amino acid profile by dividing the chromatographic peak area of each amino acid by the total peak area of all amino acids in the corresponding sample. To search for differences in amino acid profiles in monocytes obtained from "normal" and BC patients, we compared the data obtained by LC-MS using the Wilcoxon-Mann-Whitney method. Significant differences in metabolite levels were found for glycine (p-value = 0.0127), asparagine (p-value = 0.0197), proline (p-value = 0.0159), methionine (p-value = 0.0357), tryptophan (p-value = 0.0028), tyrosine (p-value = 0.0127) (Fig. 1).

Where the levels of amino acids differed significantly between monocytes of the "normal" and BC groups, we carried out a bioinformatic analysis of metabolic pathways involving these acids. The analysis was performed using the MetaboAnalyst resource. As a result, biological networks have been identified that could potentially be involved in altering the phenotype of monocytes under the influence of BC. As we analyzed the data presented in the KEGG database and SMPDB (Tables 3, 4), we

Table 4. Metabolic pathways involving amino acids with significant differences in levels in monocytes from "normal" patients and breast cancer using the SMPDB database

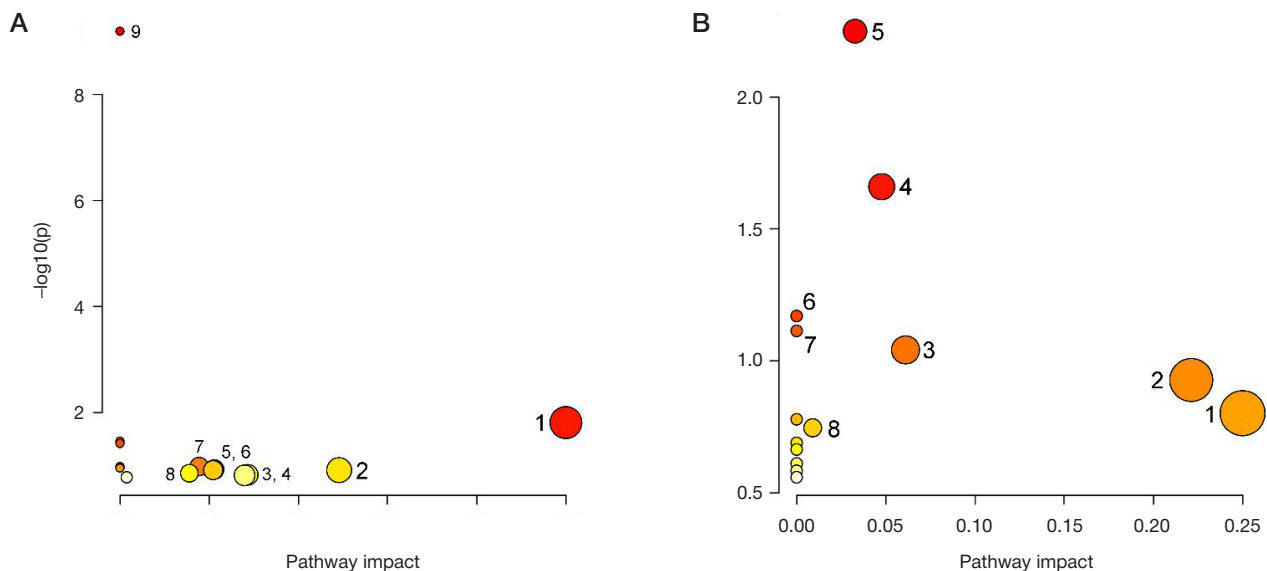| Metabolic pathway	Total number of metabolites involved	Number of metabolites that matched the experimental data	P	$-\text{Log}(P)$	Impact on the pathway
Aspartate metabolism	34	1	0.158	0.802	0.25
Phenylalanine and tyrosine metabolism	25	1	0.118	0.928	0.221
Glutathione metabolism	19	1	0.091	1.042	0.061
Glycine and serine metabolism	50	2	0.022	1.66	0.048
Ammonia recycling	25	2	0.006	2.249	0.033
Methionine metabolism	39	1	0.179	0.747	0.009

Fig. 2. Result of an analysis of the metabolic pathways involving amino acids with significant differences in levels in monocytes from patients in the "normal" group and from those in the BC group. **A**. Analysis using the KEGG database: 1 — phenylalanine, tyrosine and tryptophan biosynthesis; 2 — glycine, serine and threonine metabolism; 3 — tryptophan metabolism; 4 — tyrosine metabolism; 5 — glyoxylate and dicarboxylate metabolism; 6 — cysteine and methionine metabolism; 7 — glutathione metabolism; 8 — arginine and proline metabolism; 9 — aminoacyl-tRNA biosynthesis. **B**. Analysis using the SMPDB database: 1 — aspartate metabolism; 2 — phenylalanine and tyrosine metabolism; 3 — glutathione metabolism; 4 — glycine and serine metabolism; 5 — ammonia recycling; 6 — alanine metabolism; 7 — carnitine synthesis; 8 — methionine metabolism

were able to identify pathways ordered by levels of significance (pathway enrichment analysis — *y*-axis in Fig. 2) and the values of the influence of the metabolites in question on the pathway (pathway topology analysis — *x*-axis in Fig. 2). The color of the node corresponds to the level of significance, and the radius of the node correlates with the amount of influence on the path. The effect on the pathway was calculated as the sum of the significance values of the corresponding metabolites divided by the sum of the significance values of all metabolites in each pathway. Metabolic pathway enrichment was assessed by Over representation analysis (ORA) using a hypergeometric test.

To test the feasibility of diagnosing RBCs by amino acid levels in monocytes, we developed logistic regression models for each of the significant amino acids (Fig. 3A). We also considered models using a combination of amino acids and selected the four with the highest area under the operating curve (AUC) by ROC analysis (Fig. 3B). Table 5 shows the

results of the quality assessment of the single amino acid models. Models built on a combination of amino acids had AUC = 1 and 100% sensitivity and specificity (Fig. 3B).

DISCUSSION

Of the 26 amino acids analyzed, only six amino acids had significant differences in monocyte levels between healthy donors and BC patients. Of these six amino acids, glycine, tryptophan and asparagine are of particular interest because disturbances in the metabolic pathways associated with them are associated with tumor-induced changes [11, 13, 14, 18, 27, 31].

The availability over time of the essential amino acid tryptophan is an important determinant of the strength and quality of the immune response. Proliferation and activation of human T cells were strongly inhibited in tryptophan-free media compared to conventional nutrient media [32, 33]. Cancer cells, TAM and
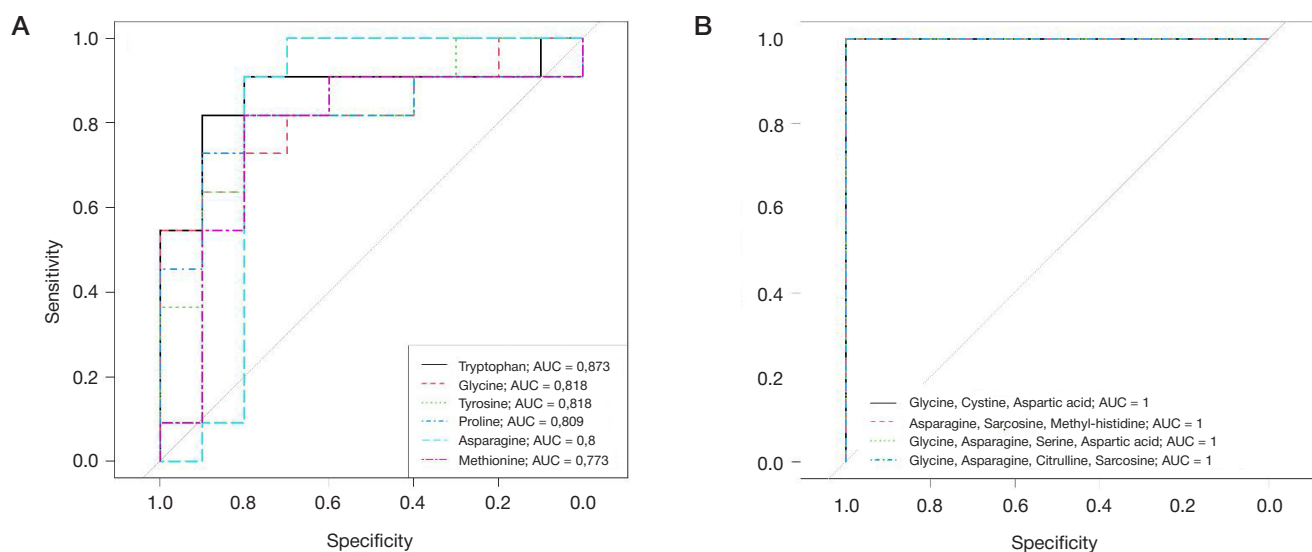
Fig. 3. ROC-curves of logistic regression models with monocyte amino acid levels as the independent variable and whether the sample belongs to the 'normal' or BC group as the dependent variable. The insets show the amino acids whose levels are taken as the independent variable, as well as the area under the operating curve for the corresponding logistic regression model. ROC curves are plotted for each of the statistically significantly different amino acids (**A**) as well as a combination of amino acids (**B**)

Table 5. Characteristics of logistic regression models predicting BC according to the content of selected amino acids whose levels in monocytes differ significantly between the "normal" group and BC

Amino acids	AUC	Threshold value	Sensitivity	Specificity	Positive predictive value
Tryptophan	0.87	0.53	0.91 (0.55; 1)	0.9 (0.7; 1)	0.92 (0.77; 1)
Glycine	0.82	0.74	0.73 (0.36; 1)	1 (0.6; 1)	1 (0.71; 1)
Tyrosine	0.82	0.46	0.82 (0.45; 1)	0.9 (0.5; 1)	0.9 (0.67; 1)
Proline	0.81	0.57	0.82 (0.45; 1)	0.9 (0.7; 1)	0.91 (0.73; 1)
Asparagine	0.8	0.45	1 (0.82; 1)	0.8 (0.5; 1)	0.85 (0.69; 1)
Methionine	0.77	0.51	0.82 (0.55; 1)	0.8 (0.5; 1)	0.83 (0.67; 1)

cancer-associated fibroblasts can reduce tryptophan levels through the enzymatic activity of indoleamine-2,3-dioxygenase (IDO) [13]. TAM, and sometimes tumor cells themselves, increase IDO levels and create an immunosuppressive microenvironment via at least two mechanisms: tryptophan depletion and accumulation of tryptophan catabolites such as kynurenine, 3-hydroxyanthranilate and quinolinate [34, 35]. Tryptophan depletion inhibits the proliferation of activated T cells, and tryptophan-derived catabolites act as ligands for aromatic hydrocarbon receptors [36]. Kinurenine is a suppressor of T-cell immunity. By stimulating aromatic hydrocarbon receptors, it directs naïve T cell differentiation towards regulatory T cells and inhibits Th17 cell differentiation [22, 37].

Biosynthesis of serine, glycine and one-carbon metabolism are crucial for maintaining cancer cell survival and proliferation and are of high clinical relevance. Excessive activation of serine and glycine biosynthesis leads to oncogenesis, providing a substrate for one-carbon metabolism. One-carbon metabolism, which is a cyclic metabolic network based on the chemical reaction of folic acid compounds, provides essential proteins, nucleic acids, lipids and other biological macromolecules to support tumor growth (31).

It was found that asparagine can affect cancer cell growth [38], leading to the use of the bacterial enzyme L-asparaginase to limit the availability of asparagine [14, 39]. Significant

efforts are being made to develop agents to deplete other amino acids and to act on central metabolic pathways that are dysregulated in cancer cells, including glycolysis, the tricarboxylic acid cycle and lipogenesis. Many of these drugs are still in preclinical stages, but some are currently being evaluated in clinical trials [14].

CONCLUSIONS

This study identified six amino acids whose levels differed significantly in the monocytes of breast cancer patients from those of healthy donors. Significant differences in metabolite levels were found for glycine (p-value = 0.0127), asparagine (p-value = 0.0197), proline (p-value = 0.0159), methionine (p-value = 0.0357), tryptophan (p-value = 0.0028), tyrosine (p-value = 0.0127). Bioinformatic analysis of metabolic pathways involving the discovered amino acids revealed biological networks that could potentially be involved in altering the phenotype of monocytes exposed to BC. The observed changes in the amino acid content of monocytes may indicate the influence of tumor processes not only on the microenvironment, but also indirectly on distant immune system participants. Based on the differences found, a model with 100% specificity and sensitivity has been proposed to diagnose BC according to the amino acid profile of monocytes.

References

1. Kzhyshkowska J, Gudima A, Moganti K, Gratchev A, Orekhov A. Perspectives for Monocyte/Macrophage-Based Diagnostics of Chronic Inflammation. Transfus Med Hemotherapy. 2016; 43 (2): 66–77.
2. Nikitina E, Larionova I, Choinzonov E, Kzhyshkowska J. Monocytes and macrophages as viral targets and reservoirs. Int J Mol Sci. 2018; 19 (9). DOI: 10.3390/ijms19092821.
3. Patysheva M, Larionova I, Stakheyeva M, Grigoryeva E, Iamshchikov P, Tarabanovskaya N, et al. Effect of Early-Stage Human Breast Carcinoma on Monocyte Programming. Front Oncol. 2022; 11 (February): 1–12.
4. Matuschik L, Riabov V, Schmuttermaier C, Sevastyanova T, Weiss C, Klüter H, et al. Hyperglycemia Induces Inflammatory Response of Human Macrophages to CD163-Mediated Scavenging of Hemoglobin-Haptoglobin Complexes. Int J Mol Sci. 2022; 23 (3): 1–19.
5. Patysheva M, Frolova A, Larionova I, Afanas'ev S, Tarasova A, Cherdyntseva N, et al. Monocyte programming by cancer therapy. Front Immunol. 2022; 13 (October): 1–21.
6. Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, Campion LR, et al. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. Nature. 2011; 475 (7355): 222–5.
7. Hanna RN, Cekic C, Sag D, Tacke R, Thomas GD, Nowyhed H, et al. Patrolling monocytes control tumor metastasis to the lung. Science (80-). 2015; 350 (6263): 985–90.
8. Shi C, Pamer EG. Monocyte recruitment during infection and

inflammation. Nat Rev Immunol. 2011; 11 (11): 762–74.
9. Engblom C, Pfirschke C, Pittet MJ. The role of myeloid cells in cancer therapies. Nat Rev Cancer. 2016; 16 (7): 447–62.
10. Fox CJ, Hammerman PS, Thompson CB. Fuel feeds function: Energy metabolism and the T-cell response. Nat Rev Immunol. 2005; 5 (11): 844–52.
11. Andrejeva G, Rathmell JC. Similarities and Distinctions of Cancer and Immune Metabolism in Inflammation and Tumors. Cell Metab. 2017; 26 (1): 49–70.
12. Bauer DE, Harris MH, Plas DR, Lum JJ, Hammerman PS, Rathmell JC, et al. Cytokine stimulation of aerobic glycolysis in hematopoietic cells exceeds proliferative demand. FASEB J. 2004; 18 (11): 1303–5.
13. Leone RD, Powell JD. Metabolism of immune cells in cancer. Nat Rev Cancer. 2020; 20 (9): 516–31.
14. Schmidt DR, Patel3 R, Kirsch DG, Lewis5 CA, Heiden MG Vander, Locasale4 JW. Metabolomics in Cancer Research and Emerging Applications in Clinical Oncology. CA Cancer J Clin. 2021; 71 (4): 333–58.
15. Odom JD, Sutton VR. Metabolomics in Clinical Practice: Improving Diagnosis and Informing Management. Clin Chem. 2021; 67 (12): 1606–17.
16. Clish CB. Metabolomics: an emerging but powerful tool for precision medicine. Mol Case Stud. 2015; 1 (1): a000588.
17. Wishart DS. Emerging applications of metabolomics in drug

discovery and precision medicine. Nat Rev Drug Discov. 2016; 15 (7): 473–84.

18. Viola A, Munari F, Sánchez-Rodríguez R, Scolaro T, Castegna A. The metabolic signature of macrophage responses. Front Immunol. 2019; 10 (JULY): 1–16.

19. Schairer DO, Chouake JS, Nosanchuk JD, Friedman AJ. The potential of nitric oxide releasing therapies as antimicrobial agents. Virulence. 2012; 3 (3): 271–9.

20. Van den Bossche J, Baardman J, Otto NA, van der Velden S, Neele AE, van den Berg SM, et al. Mitochondrial Dysfunction Prevents Repolarization of Inflammatory Macrophages. Cell Rep. 2016; 17 (3): 684–96.

21. Qualls JE, Subramanian C, Rafi W, Smith AM, Defreitas AA, Shirey KA, et al. Sustained generation of nitric oxide and control of mycobacterial infection requires argininosuccinate synthase 1. Cell Host Microbe. 2012; 12 (3): 313–23.

22. Kaprin AD, Starinskij VV, Petrova GV, redaktory. Zlokachestvennye novoobrazovaniya v Rossii v 2017 godu (zabolevaemost' i smertnost'). M.: MNIOI im. P. A. Gercena — filial FGBU «NMIC radiologii» Minzdrava Rossii, 2018; 250 s. Russian.

23. Cassetta L, Pollard JW. Repolarizing macrophages improves breast cancer therapy. Cell Res. 2017; 27 (8): 963–4.

24. Kuang DM, Zhao Q, Peng C, Xu J, Zhang JP, Wu C, et al. Activated monocytes in peritumoral stroma of hepatocellular carcinoma foster immune privilege and disease progression through PD-L1. J Exp Med. 2009; 206 (6): 1327–37.

25. De Sanctis F, Adamo A, Canè S, Ugel S. Targeting tumour-reprogrammed myeloid cells: the new battleground in cancer immunotherapy. Semin Immunopathol. 2022; (0123456789). DOI: 10.1007/s00281-022-00965-1.

26. Nguyen PHD, Wasser M, Tan CT, Lim CJ, Lai HLH, Seow JJW, et al. Trajectory of immune evasion and cancer progression in hepatocellular carcinoma. Nat Commun. 2022; 13 (1): 1–13.

27. Zhu Y, Li X, Wang L, Hong X, Yang J. Metabolic reprogramming and crosstalk of cancer-related fibroblasts and immune cells in the tumor microenvironment. Front Endocrinol (Lausanne). 2022; 13 (August): 1–26.

28. Larionova I, Tuguzbaeva G, Ponomaryova A, Stakheyeva M, Cherdyntseva N, Pavlov V, et al. Tumor-Associated Macrophages in Human Breast, Colorectal, Lung, Ovarian and Prostate Cancers. Front Oncol. 2020; 10 (October): 1–34.

29. Larionova I, Cherdyntseva N, Liu T, Patysheva M, Rakina M, Kzhyshkowska J. Interaction of tumor-associated macrophages and cancer chemotherapy. Oncoimmunology. 2019; 8 (7): 1–15.

30. Olingy CE, Dinh HQ, Hedrick CC. Monocyte heterogeneity and functions in cancer. J Leukoc Biol. 2019; 106 (2): 309–22.

31. Pan S, Fan M, Liu Z, Li X, Wang H. Serine, glycine and one-carbon metabolism in cancer (Review). Int J Oncol. 2021; 58 (2): 158–70.

32. Munn DH, Sharma MD, Baban B, Harding HP, Zhang Y, Ron D, et al. GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. Immunity. 2005; 22 (5): 633–42.

33. Munn BDH, Shafizadeh E, Attwood JT, Bondarev I, Pashine A, Mellor AL. Inhibition of T Cell Proliferation by Macrophage. 1999; 189 (9): 1363–72.

34. Platten M, Wick W, Van Den Eynde BJ. Tryptophan catabolism in cancer: Beyond IDO and tryptophan depletion. Cancer Res. 2012; 72 (21): 5435–40.

35. Moffett JR, Namboodiri MA. Tryptophan and the immune response. Immunol Cell Biol. 2003; 81 (4): 247–65.

36. Opitz CA, Litzenburger UM, Sahm F, Ott M, Tritschler I, Trump S, et al. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. Nature. 2011; 478 (7368): 197–203.

37. Stephens GL, Wang Q, Swerdlow B, Bhat G, Kolbeck R, Fung M. Kynurenine 3-monooxygenase mediates inhibition of Th17 differentiation via catabolism of endogenous aryl hydrocarbon receptor ligands. Eur J Immunol. 2013. 43 (7): 1727–34. DOI: 10.1002/eji.201242779.

38. RE N, TA M. Dual Requirement of Walker Carcinosarcoma 256 in vitro for Asparagine and Glutamine. Science. 1956; 124 (3212): 124–5.

39. Clavell LA, Gelber RD, Cohen HJ, Suzanne Hitchcock-Bryan RN, Cassady JR, Tarbel NJ, et al. Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. N Engl J Med. 1986; 315: 657–63.

Литература

1. Kzhyshkowska J, Gudima A, Moganti K, Gratchev A, Orekhov A. Perspectives for Monocyte/Macrophage-Based Diagnostics of Chronic Inflammation. Transfus Med Hemotherapy. 2016; 43 (2): 66–77.

2. Nikitina E, Larionova I, Choinzonov E, Kzhyshkowska J. Monocytes and macrophages as viral targets and reservoirs. Int J Mol Sci. 2018; 19 (9). DOI: 10.3390/ijms19092821.

3. Patysheva M, Larionova I, Stakheyeva M, Grigoryeva E, Iamshchikov P, Tarabanovskaya N, et al. Effect of Early-Stage Human Breast Carcinoma on Monocyte Programming. Front Oncol. 2022; 11 (February): 1–12.

4. Matuschik L, Riabov V, Schmuttermaier C, Sevastyanova T, Weiss C, Klüter H, et al. Hyperglycemia Induces Inflammatory Response of Human Macrophages to CD163-Mediated Scavenging of Hemoglobin-Haptoglobin Complexes. Int J Mol Sci. 2022; 23 (3): 1–19.

5. Patysheva M, Frolova A, Larionova I, Afanas'ev S, Tarasova A, Cherdyntseva N, et al. Monocyte programming by cancer therapy. Front Immunol. 2022; 13 (October): 1–21.

6. Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, Campion LR, et al. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. Nature. 2011; 475 (7355): 222–5.

7. Hanna RN, Cekic C, Sag D, Tacke R, Thomas GD, Nowyhed H, et al. Patrolling monocytes control tumor metastasis to the lung. Science (80-). 2015; 350 (6263): 985–90.

8. Shi C, Pamer EG. Monocyte recruitment during infection and inflammation. Nat Rev Immunol. 2011; 11 (11): 762–74.

9. Engblom C, Pfirschke C, Pittet MJ. The role of myeloid cells in cancer therapies. Nat Rev Cancer. 2016; 16 (7): 447–62.

10. Fox CJ, Hammerman PS, Thompson CB. Fuel feeds function: Energy metabolism and the T-cell response. Nat Rev Immunol.

2005; 5 (11): 844–52.

11. Andrejeva G, Rathmell JC. Similarities and Distinctions of Cancer and Immune Metabolism in Inflammation and Tumors. Cell Metab. 2017; 26 (1): 49–70.

12. Bauer DE, Harris MH, Plas DR, Lum JJ, Hammerman PS, Rathmell JC, et al. Cytokine stimulation of aerobic glycolysis in hematopoietic cells exceeds proliferative demand. FASEB J. 2004; 18 (11): 1303–5.

13. Leone RD, Powell JD. Metabolism of immune cells in cancer. Nat Rev Cancer. 2020; 20 (9): 516–31.

14. Schmidt DR, Patel3 R, Kirsch DG, Lewis5 CA, Heiden MG Vander, Locasale4 JW. Metabolomics in Cancer Research and Emerging Applications in Clinical Oncology. CA Cancer J Clin. 2021; 71 (4): 333–58.

15. Odom JD, Sutton VR. Metabolomics in Clinical Practice: Improving Diagnosis and Informing Management. Clin Chem. 2021; 67 (12): 1606–17.

16. Clish CB. Metabolomics: an emerging but powerful tool for precision medicine. Mol Case Stud. 2015; 1 (1): a000588.

17. Wishart DS. Emerging applications of metabolomics in drug discovery and precision medicine. Nat Rev Drug Discov. 2016; 15 (7): 473–84.

18. Viola A, Munari F, Sánchez-Rodríguez R, Scolaro T, Castegna A. The metabolic signature of macrophage responses. Front Immunol. 2019; 10 (JULY): 1–16.

19. Schairer DO, Chouake JS, Nosanchuk JD, Friedman AJ. The potential of nitric oxide releasing therapies as antimicrobial agents. Virulence. 2012; 3 (3): 271–9.

20. Van den Bossche J, Baardman J, Otto NA, van der Velden S, Neele AE, van den Berg SM, et al. Mitochondrial Dysfunction Prevents Repolarization of Inflammatory Macrophages. Cell Rep.

2016; 17 (3): 684–96.

21. Qualls JE, Subramanian C, Rafi W, Smith AM, Defreitas AA, Shirey KA, et al. Sustained generation of nitric oxide and control of mycobacterial infection requires argininosuccinate synthase 1. Cell Host Microbe. 2012; 12 (3): 313–23.

22. Каприн А. Д., Старинский В. В., Петрова Г. В., редакторы. Злокачественные новообразования в России в 2017 году (заболеваемость и смертность). М.: МНИОИ им. П.А. Герцена — филиал ФГБУ «НМИЦ радиологии» Минздрава России, 2018; 250 с.

23. Cassetta L, Pollard JW. Repolarizing macrophages improves breast cancer therapy. Cell Res. 2017; 27 (8): 963–4.

24. Kuang DM, Zhao Q, Peng C, Xu J, Zhang JP, Wu C, et al. Activated monocytes in peritumoral stroma of hepatocellular carcinoma foster immune privilege and disease progression through PD-L1. J Exp Med. 2009; 206 (6): 1327–37.

25. De Sanctis F, Adamo A, Canè S, Ugel S. Targeting tumour-reprogrammed myeloid cells: the new battleground in cancer immunotherapy. Semin Immunopathol. 2022; (0123456789). DOI: 10.1007/s00281-022-00965-1.

26. Nguyen PHD, Wasser M, Tan CT, Lim CJ, Lai HLH, Seow JJW, et al. Trajectory of immune evasion and cancer progression in hepatocellular carcinoma. Nat Commun. 2022; 13 (1): 1–13.

27. Zhu Y, Li X, Wang L, Hong X, Yang J. Metabolic reprogramming and crosstalk of cancer-related fibroblasts and immune cells in the tumor microenvironment. Front Endocrinol (Lausanne). 2022; 13 (August): 1–26.

28. Larionova I, Tuguzbaeva G, Ponomaryova A, Stakheyeva M, Cherdyntseva N, Pavlov V, et al. Tumor-Associated Macrophages in Human Breast, Colorectal, Lung, Ovarian and Prostate Cancers. Front Oncol. 2020; 10 (October): 1–34.

29. Larionova I, Cherdyntseva N, Liu T, Patysheva M, Rakina M, Kzhyshkowska J. Interaction of tumor-associated macrophages and cancer chemotherapy. Oncoimmunology. 2019; 8 (7): 1–15.

30. Olingy CE, Dinh HQ, Hedrick CC. Monocyte heterogeneity and functions in cancer. J Leukoc Biol. 2019; 106 (2): 309–22.

31. Pan S, Fan M, Liu Z, Li X, Wang H. Serine, glycine and one-carbon metabolism in cancer (Review). Int J Oncol. 2021; 58 (2): 158–70.

32. Munn DH, Sharma MD, Baban B, Harding HP, Zhang Y, Ron D, et al. GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. Immunity. 2005; 22 (5): 633–42.

33. Munn BDH, Shafizadeh E, Attwood JT, Bondarev I, Pashine A, Mellor AL. Inhibition of T Cell Proliferation by Macrophage. 1999; 189 (9): 1363–72.

34. Platten M, Wick W, Van Den Eynde BJ. Tryptophan catabolism in cancer: Beyond IDO and tryptophan depletion. Cancer Res. 2012; 72 (21): 5435–40.

35. Moffett JR, Namboodiri MA. Tryptophan and the immune response. Immunol Cell Biol. 2003; 81 (4): 247–65.

36. Opitz CA, Litzenburger UM, Sahm F, Ott M, Tritschler I, Trump S, et al. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. Nature. 2011; 478 (7368): 197–203.

37. Stephens GL, Wang Q, Swerdlow B, Bhat G, Kolbeck R, Fung M. Kynurenine 3-monooxygenase mediates inhibition of Th17 differentiation via catabolism of endogenous aryl hydrocarbon receptor ligands. Eur J Immunol. 2013. 43 (7): 1727–34. DOI: 10.1002/eji.201242779.

38. RE N, TA M. Dual Requirement of Walker Carcinosarcoma 256 in vitro for Asparagine and Glutamine. Science. 1956; 124 (3212): 124–5.

39. Clavell LA, Gelber RD, Cohen HJ, Suzanne Hitchcock-Bryan RN, Cassady JR, Tarbel NJ, et al. Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. N Engl J Med. 1986; 315: 657–63.