https://doi.org/10.22416/1382-4376-2022-32-1-46-52

Metabolomic profiles as a new understanding of disease processes

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Aim. This review will demonstrate possibilities of using metabolomic profiling to identify biomarkers of various internal organs diseases.
Key points. A new diagnostic direction is associated with high-sensitive spectral analysis of biomarker molecules. This review will discuss some of the latest advances with an emphasis on the use of metabolomics to identify major metabolic changes in various diseases. The possibility of finding diagnostic markers in diseases of the gastrointestinal tract, respiratory and cardiovascular systems, in oncology, endocrinology, neurology are discussed. These results define new potential therapeutic strategies, making metabolomics useful for a wide range of biomedical and pharmaceutical research.
Conclusion. Metabolomic profile changes in different types of diseases will help to improve understanding of the pathogenesis. New therapeutic approaches may be developed. They will take into account individual characteristics of the patient, identified by using current molecular technologies. The results of metabolomic studies can be used to monitor treatment outcomes.
Keywords: metabolites, metabolomic profiling, biomarkers, mass spectrometry, liquid chromatography, treatment monitoring
Conflict of interest: The authors declare no conflict of interest.

For citation: Zolnikova O.Yu., Reshetova M.S., Ivanova M.N., Ivashkin V.T. Metabolomic profiles as a new understanding of disease processes. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2022;32(1):46–52. https://doi.org/10.22416/1382-4376-2022-32-1-46-52

Метаболомные профили как новое понимание процессов болезни

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Цель обзора: представить информацию о возможностях применения метаболомного профилирования для выявления биомаркеров различных заболеваний внутренних органов.
Основные положения. Новое диагностическое направление связано с высокочувствительным спектральным анализом молекул-биомаркеров. В обзоре литературы обсуждаются некоторые из последних достижений с акцентом на применение метаболомики для выявления основных метаболомных изменений при различных заболеваниях. Обсуждается возможность поиска диагностических маркеров при заболеваниях желудочно-кишечного тракта, респираторной и сердечно-сосудистой систем, в онкологии, эндокринологии, неврологии. Эти результаты определяют и новые потенциальные терапевтические стратегии, делая метаболомику полезной для широкого круга биомедицинских и фармацевтических исследований.
Заключение. Новые данные об изменении метаболомного профиля при разных нозологических формах помогут улучшить понимание патогенеза заболеваний. И разработать новые терапевтические подходы в лечении, учитывая данные индивидуальных характеристик пациента, выявляемые с помощью актуальных молекулярных технологий. Результаты метаболомных исследований могут быть применимы и в качестве мониторинга результатов лечения.
Ключевые слова: метаболиты, метаболомное профилирование, биомаркеры, масс-спектрометрия, жидкостная хроматография, мониторинг лечения
Конфликт интересов: Авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Зольникова О.Ю., Решетова М.С., Иванова М.Н., Ивашкин В.Т. Метаболомные профили как новое понимание процессов болезни. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2022;32(1):46–52. https://doi.org/10.22416/1382-4376-2022-32-1-46-52

Metabolomic studies are relatively new and rapidly developing scientific direction. It uses advanced analytical chemistry and computational technologies to describe complex biochemical processes. Currently, metabolomics has applications in various fields of science, including human health, drug development, microbiology, and the food industry. The variety of metabolomic studies application fields is due to possibility to analyze a wide range of substrates, including solids (tissues, soil, etc.), liquids (biological fluids, water) and gases (exhaled air, odors). These researches can be carried out in vivo (with visualization of a specific group of cells) and in vitro (using extracts and biofluids) [1–4]. Nuclear magnetic resonance spectroscopy (NMR), gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) serve as major analytics platforms to examine metabolome [2]. Combination of research types allows to accurately identify metabolites in different biosamples and significantly broaden their studied range. Metabolomic studies are conventionally subdivided into metabolomic profiling and metabolomic target analysis [3]. Metabolomic profiling is generally used to identify metabolomic differences in various nosologies. Target analysis is conducted to determine specific metabolites [4, 5]. In practice, metabolomic profiling precedes further targeted research. The fundamental basis of this diagnostic approach includes the following fact: the production of each metabolite is caused by particular biochemical reactions in the body. This allows the use of certain highly specific molecules as biomarkers.

Metabolomic researches in gastroenterology

Using high-resolution magnetic resonance imaging (MRI) with high resolution magic-angle spinning (HR-MAS) the level of metabolites in chronic and acute pancreatitis was assessed. The study demonstrated a correlation between changes in the metabolomic profile and inflammatory changes in the pancreas. In acute necrotizing pancreatitis, an increase in the level of amino acids (leucine, isoleucine, valine) and a decrease in the level of taurine and fatty acids compared with chronic pancreatitis were observed. The authors suggested that these changes may be potential metabolomic markers in the differential diagnosis between chronic and acute pancreatitis [6]. Also, a work devoted to the isolation of exocrine pancreatic insufficiency biomarkers is described (EPI). According to the analysis results, in the group of patients with EPI, an increase in the levels of phosphatidylserine, phosphatidylcholine, pentazine and a peptide consisting of arginine, threonine and proline was observed [7].

A search was carried out for specific serum metabolites that can help predict the onset and progression of inflammatory bowel disease (IBD). The changes in gut microbiota and metabolomic profiles of patients with Crohn's disease, ulcerative colitis and healthy control were compared. Each stool sample was subjected to metagenomic sequencing and metabolomic analysis using GC-MS. As a result of the study, the difference between the metabolome in patients with IBD and in the group of healthy controls was demonstrated. Based on the generalization of sequencing data and metabolomic analysis, 122 associations between bacterial and metabolomic profiles were identified. One of the important findings was the revealed correlation of changes in metabolites with a decrease in taxonomic biodiversity of the gut microbiota in patients with IBD [8]. In a systematic review, published in 2020, observations from 64 studies, aimed at studying the metabolome of various biological environments of the body in patients with IBD, were summarized. The authors point to the fact that when choosing a material for research, it is necessary to take into account the high lability of the metabolomic indicators of urine and feces, which vary depending on the patient's diet. In this case, serum and blood plasma react more slowly to changes in the diet and can carry more static information about the metabolomic profile and about systemic metabolism in general (Table 1). In studies describing the analysis of blood metabolites of patients with IBD, changes in the level of branched-chain amino acids were observed. Thus, in the groups of patients with Crohn's disease and ulcerative colitis, an increase in the levels of isoleucine, leucine and valine was observed compared with the control group. 3-hydroxybutyrate, a breakdown product of the amino acids listed above, was increased in 5 cases in patients with ulcerative colitis. At the same time, the level of glutamine in IBD was reduced, which, according to the authors, indicates a defect in the process of tight junction proteins synthesis and the intestinal wall integrity loss. An increase in the ratio of kynurenine and tryptophan levels was observed. The levels of lipids, arachidonic acid and arachidonate varied in different directions in blood and feces samples, showing lower values in blood and increasing in stool samples [9].

In a study of patients with celiac disease, an increase in the content of indolecarboxylic (indoleacetic acid, indolepropionic acid) and dicarboxylic acids (succinic and fumaric acids) was determined. Indolic acids are metabolites of tryptophan with potential neuroprotective effects and are designed to prevent the development of oxidative stress. An increase in dicarboxylic acids is considered by the authors as a marker of hypoxia [10].

The study of the metabolomic profile in patients with liver diseases is of great interest. It is noted that the level of glycocholic acid, taurocholic acid, phenylalanine, branched-chain amino acids increases with more severity disease from steatosis to non-alcoholic steatohepatitis (NASH), NASH cirrhosis, while the values of glutathione in these nosological forms decrease ($p < 0.001$ for each state) [11, 12].

Table. 1. Metabolomic profiles in IBD

Biological substrate	Identified changes in the metabolome
Stool	↑ Acylcarnitines, Lysophospho-choline, Triacylglycerides ↓ Primary and Secondary bile acids ↓ SCFA Amino Acids: ↑ Leucine, Isoleucine, Valine ↑ Alanine, Glycine, Lysine, Phenylalanine, Taurine, Tyrosine
Urine	↑ Citrate, Succinate ↓ Formate, Hippurate, Trigonelline ↓ SCFA Amino Acids: ↓ Alanine, Taurine Asparagine, Glycine
Blood	↑ 3-Hydroxbutyrate ↑ Tryptophan Catabolites ↓ Arachidonic acid Amino Acids: ↑ Isoleucine ↓ Tryptophan ↓ Glutamine, Histidine ↓ Leucine, Isoleucine, Valine
Biopsy material	↓ Choline, Gliatilin ↓ Myoinositol Amino Acids: ↑ Aspartate ↓ Leucine, Isoleucine, Valine ↓ Alanine, Glutamine, Glutamate
Breath	↑ Pentane ↓ Hydrogen sulfide

Metabolomic researches in pulmonology

To date, few metabolomic researches in patients with respiratory system diseases have been described. Usually, they deal with the study of volatile organic compounds in the concentrate of exhaled air. In samples of exhaled air from patients with chronic obstructive pulmonary disease (COPD), bronchial asthma (BA) and healthy controls, 9 compounds were identified (2,3-dihydro-1-inden-1-one, ethyl citrate, decanol-1, 2-phenoxyethanol and others), which are of the greatest importance in the differential diagnosis of groups. Mathematical analysis of the obtained data allowed us to distinguish between healthy and patients with BA with an accuracy of 75 %, healthy and patients with COPD with an accuracy of 85 %, patients with BA and COPD with an accuracy of 83 % [13]. In the view of Bowerman K. et al., the spectrum of the metabolomic profile of blood serum in COPD combines 46 % of lipids, 20 % of xenobiotics and 20 % of metabolites associated with amino acids, including N-acetylglutamate and its analogue N-carbamoylglutamate [14]. Statistically significant negative correlations between metabolites of glycerophospholipids and three products of oxidative stress (superoxide dismutase (SOD), myelopyroxidase (MPO), and 8-isoprostaglandin F2α (8-iso-PGF2α)) have been revealed in studies. Along with that, it was found that the diagnostic values of SOD, MPO and 8-iso-PGF2α in sputum exhibit high sensitivity and specificity in predicting the severity of COPD [15].

In a number of studies in patients with BA, the most altered metabolomic pathways were the biosynthesis of omega-6 or omega-3 fatty acids, including arachidonic, linoleic, eicosapentaenoic and docosahexaenoic acids, as well as the metabolism of galactose and citrate [16, 17].

Altered levels of γ-tocopherol / β-tocopherol, positively correlated with the composition of the gut microbiota (family Christensenellaceae) [18]. A significant decrease in the content of short-chain fatty acids (acetate, propionate, and butyrates) produced by the microbiota, a change in their spectrum and isoforms was found [19]. An inverse correlation was found between the content of dicarboxylic acids (suberic (octanedioic) and sebacic (decandioic)) with the forced expiratory volume of patients [20–22].

Hasegawa K. et al. performed a metabolomic analysis of the blood serum of infants with severe bronchiolitis. Scientists investigated the relationship of serum 25-hydroxycalciferol (25OHD) levels with the metabolome and the severity of bronchiolitis. It was found that metabolites (fibrinopeptide A, N1-methyladenosine, sphingomyelin) correlated with a low level of 25OHD are significantly associated with more frequent use of invasive mechanical ventilation in these patients. At the same time, 6 metabolites were identified (1-(1-enylstearoyl)-2oleoylglycerophosphorylethanolamine (GPE); 1-(1-enylstearoyl)-linoleyl-GPE; isoursodeoxycholate; 1-linoleoyl-glycerophosphate (GPA); glycerate; glycylvalin

correlating with a higher level of 25OHD and a lower frequency of use of invasive mechanical ventilation [23].

Mass spectrometry confirmed the differences in the metabolomic spectrum of exhaled air in patients with acute respiratory distress syndrome (ARDS) with COVID-19 (28 patients) and in healthy controls (12 patients). In a multivariate analysis with an accuracy of 93 % (sensitivity: 90 %, specificity: 94 %), a characteristic "breath print" for COVID-19 was determined. The three most distinct notable volatiles in COVID-19 ARDS patients were methylpent-2-enal, 2,4-octadiene-1-chloroheptane, and nonanal [24].

Metabolomic researches in cardiology

Using metabolomic profiling, trimethylamine-N-oxide (TMAO) has been identified, which is associated with a higher risk of developing cardiovascular diseases [25–27]. Subsequent targeted metabolomic studies have established that TMAO is a by-product of trimethylamine. Trimethylamine, in turn, is a product of the microbial degradation of carnitine, betaine and choline obtained from meat and contained in food phospholipids [28–30]. TMAO alters the cholesterol balance by dysfunction of flavin monooxygenase 3 [31]. Although the role of TMAO in human physiology is still being elucidated, there is ample evidence that endogenously produced TMAO in sufficiently large quantities is a metabolite that provokes the development of diseases of the cardiovascular system. A study by Chen X. et al. the relationship between the progression of atherosclerosis and impaired metabolism of fatty acids, primarily palmitic acid, has been demonstrated, which significantly accelerates the development of atherosclerotic changes due to the activation of inflammation and apoptosis [32].

Changes in the metabolomic profile correlate with the severity of chronic heart failure (CHF) and systolic myocardial dysfunction. The most important metabolites in this pathogenetic combination are 2-hydroxybutyrate, glycine, methylmalonate, and myo-inositol [33]. In patients with low LV ejection fraction, higher serum concentrations of acylcarnitines, carnitine, betaine, and amino acids were found, with low levels of phosphatidylcholines, lysophosphatidylcholines, and sphingomyelins [34].

Metaboliomics research in oncology

Cancer is widely recognized as a genetic disorder resulting from mutations in key oncogenes or tumor suppressors. However, over the last few years, there have been significant changes in the understanding of this disease. This is partly due to the "rediscovery" of two metabolic processes, aerobic glycolysis and glutaminolysis, which are found in almost all tumors, and are also closely associated with a number of known oncogenes and tumor suppressors [35, 36]. Oncomolecules identified by metabolomic studies are endogenous metabolites, the accumulation of which initiates and/or supports tumor growth and metastasis. The first confirmed oncometabolite was 2-hydroxyglutarate, found in high concentrations in gliomas [37, 38]. This compound appears to indirectly alter histone methylation patterns, which ultimately leads to tumorigenesis. Later, fumarate, succinate, sarcasin, glutamine, asparagine, and lactate were also identified as oncometabolites [35–38]. Halfenprox, permethrin, and biotin sulfone, which is oxidized biotin (also known as vitamin H), are recognized as metabolites associated with the risk of lung cancer. It is discussed that the reason for the increase in the activity of these metabolites is associated with smoking [39]. The literature presents an analysis of the urine metabolome in patients with oncological and precancerous diseases of the upper gastrointestinal tract [40]. This study involved 44 patients with esophageal carcinoma, 31 patients with Barrett's esophagus, and 75 healthy controls. The results of the study demonstrated clear differences in the metabolomic profile of the studied groups [40]. Much attention is currently paid to the role of short-chain fatty (butyrate), indolecarboxylic (indoleacetic, indolepropionic) and dicarboxylic acids (succinic, fumaric) produced by gut microbiota in the pathogenesis of colon cancer. These metabolites, according to researchers, have tumor suppressive properties, and their levels are significantly reduced in case of intestinal tumor lesions [10, 41]. With further study of the causal relationships, it becomes clear that many of the oncometabolites act as signaling molecules or structural regulators that affect immune cells, activate pro-carcinogenic inflammatory pathways, and control cell division processes.

Metabolomics research in endocrynology

Metabolomic profiling made it possible to establish a change in the level of amino acids as a prognostic marker for the development of diabetes mellitus (DM). In particular, elevations in serum of branched-chain amino acids (leucine, isoleucine, valine), aromatic amino acids (phenylalanine, tyrosine) and a little-known amino acid (aminoadipic acid) can be used to identify people at risk of developing type 2 diabetes. It is assumed that the levels of these markers have a prognostic potential long before the onset of the disease, and on the one hand they may be associated with dietary factors, while on the other hand, they may be caused by the changes in the composition of the gut microbiota (a decrease in the content of Propionibacterium, Bifidobacterium). The latter factor, in turn, can contribute to the development of insulin resistance and diabetes [42–44].

Metabolomics research in neurology

Neurodegenerative diseases such as Parkinson's and Alzheimer's are mediated by the development of mitochondrial dysfunction and oxidative stress. Along with this, the patients showed a number

of characteristic changes in the metabolomic profile. Thus, in Parkinson's disease, the metabolism of amino acids, fatty acids, and glutathione is impaired. This is evidence in favor of increased oxidative stress, the presence of neuroinflammation, as well as impaired glucose regulation [45]. In the work of He R. et al., correlations were established between the levels of homovanillic acid (a metabolite of dopamine) and movement disorders in patients [46]. Changes in serum levels of ceramide, sphingomyelin and phosphatidylcholine are discussed to be the predictors of Alzheimer's disease development. Some of these metabolites correlate with the severity of cognitive impairment and may act as markers of disease progression [47]. In demyelinating diseases, in particular in multiple sclerosis, the metabolomic profile is characterized by an increase in the content of ketone bodies (β-hydroxybutyrate, acetoacetate, acetone), which is associated with impaired metabolism of tricarboxylic fatty acids in mitochondria. An increase in the content of choline and phospholipids was noted, as well as a decrease in tryptophan and its neuroactive metabolite kynurenine [47–50]. Interesting findings concern patients with schizophrenia. It is known that this disease is associated with the presence of insulin resistance and an increased content of triglycerides with long-chain saturated fatty acids (with 16 or more carbon atoms), as well as branched-chain amino acids (phenylalanine, tyrosine, proline, glutamic acid, lactic acid, pyruvic acid). Initially, these metabolomic changes were associated with the side effects of antipsychotic drugs. It has now been proven that these changes are characteristic for all patients with schizophrenia, regardless of the medication being administered, and act as biomarkers of the disease. In general, it is known that all psychoses are characterized by glutamate-dependent developmental mechanisms. However, the characteristic and distinguishing feature of schizophrenia is an increase in the content of proline formed from glutamate [47].

Conclusion

Modern medicine combines a strategy of prevention, timely diagnosis and treatment of internal organs diseases. Metabolomic studies, which include comprehensive characterization of metabolites, are being conducted on increasing rates in order to understand the mechanisms of disease development, search for disease biomarkers, identify new therapeutic strategies and monitor treatment outcomes.

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Submitted: 17.11.2021 Accepted: 22.12.2021 Published: 28.02.2022
Поступила: 17.11.2021 Принята: 22.12.2021 Опубликована: 28.02.2022

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