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Trends in Precision Diagnosis and Monitoring of Inflammatory Bowel Diseases: the Potential of Proteomic and Metabolomic Biomarkers

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ABSTRACT

Omics technologies, including proteomics and metabolomics approaches, provide promising opportunities to improve the accuracy of diagnosis and monitoring of the course of inflammatory bowel disease (IBD). Integration of these advanced research areas into clinical medicine not only allows for a more in-depth assessment of the pathogenesis of IBD, but also opens avenues for innovative therapeutic strategies adapted to individual patient profiles and patient cohorts.

The lecture analyzes trends in the identification of biomarkers with high sensitivity and specificity that can be used both for diagnosis and prognosis of the course of IBD subtypes, and for predicting the response to therapy, which, ultimately, will contribute not only to improved treatment outcomes, but also to an increase in the quality of life of patients.

The authors conducted a non-systematic, descriptive review of the literature with a search depth of 10 years, aimed at systematizing data on the achievements of proteomics and metabolomics approaches for the diagnosis, monitoring of the IBD course, and personalization of therapeutic strategies. The search for literary references was carried out using Scopus, Web of Science, MedLine, the Cochrane Library, EMBASE, Global Health, CyberLeninka, and RSCI databases.

The analysis of the results of experimental and clinical studies allowed to identify a number of biomarkers – candidates for testing and potential implementation in routine clinical practice. Convincing data were obtained on the potential benefits of integrating proteomics and metabolomics studies with other omics approaches. The importance of an interdisciplinary approach combining the results of clinical studies with modern approaches in bioinformatics and molecular biology for the development of more effective diagnostic tools and strategies is obvious.

Keywords: inflammatory bowel disease, Crohn's disease, ulcerative colitis, omics technologies, metabolome, proteome

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Тренды прецизионной диагностики и мониторинга воспалительных заболеваний кишечника: потенциал протеомных и метаболомных биомаркеров

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РЕЗЮМЕ

Омиксные технологии, в том числе протеомные и метаболомные подходы, предоставляют многообещающие возможности для повышения точности диагностики и мониторинга течения воспалительных заболеваний кишечника (ВЗК). Интеграция этих передовых направлений исследований в клиническую медицину не только позволяет более углубленно оценить патогенез ВЗК, но и открывает путь к инновационным терапевтическим стратегиям, адаптированным к индивидуальным профилям пациентов и когорт пациентов.

Лекция посвящена анализу трендов выявления биомаркеров с высокой чувствительностью и специфичностью, которые могут быть использованы как для диагностики и предикции течения подтипов ВЗК, так и прогнозировать ответную реакцию на терапию, что в конечном итоге будет способствовать не только улучшению результатов лечения, но и повышению качества жизни пациентов.

Авторами проведен несистематический, описательный поиск литературы с глубиной 10 лет, направленный на систематизацию данных о достижениях подходов протеомики и метаболомики для целей диагностики, мониторинга течения ВЗК и персонализации терапевтических стратегий. Поиск литературных источников проводился по базам данных Scopus, Web of Science, MedLine, The Cochrane Library, EMBASE, Global Health, CyberLeninka, РИНЦ.

Анализ результатов экспериментальных и клинических исследований позволил выделить ряд биомаркеров – кандидатов для тестирования и потенциального внедрения в рутинную клиническую практику. Получены убедительные данные о потенциальных преимуществах интеграции протеомных и метаболомных исследований с другими омиксными подходами. Очевидна значимость междисциплинарного подхода, объединяющего результаты клинических исследований, современные подходы биоинформатики и молекулярной биологии для разработки более эффективных диагностических инструментов и стратегий.

Ключевые слова: воспалительные заболевания кишечника, болезнь Крона, язвенный колит, омиксные технологии, метаболом, протеом

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Searching for disease biomarkers dates back to the formation of medicine as a science. The search for biomarkers in inflammatory bowel disease (IBD) is of no exception (Fig. 1). Precision medicine and diagnostic approaches associated with targeting interventions are becoming new hotspots and trends in modern medicine (Fig. 1). At the early stage of diagnostic research in IBD, the focus was placed on general characteristics and classical diagnostic approaches. Currently, the trend in research is increasingly shifting toward targeting IBD therapy and improving the quality of life of patients [1].

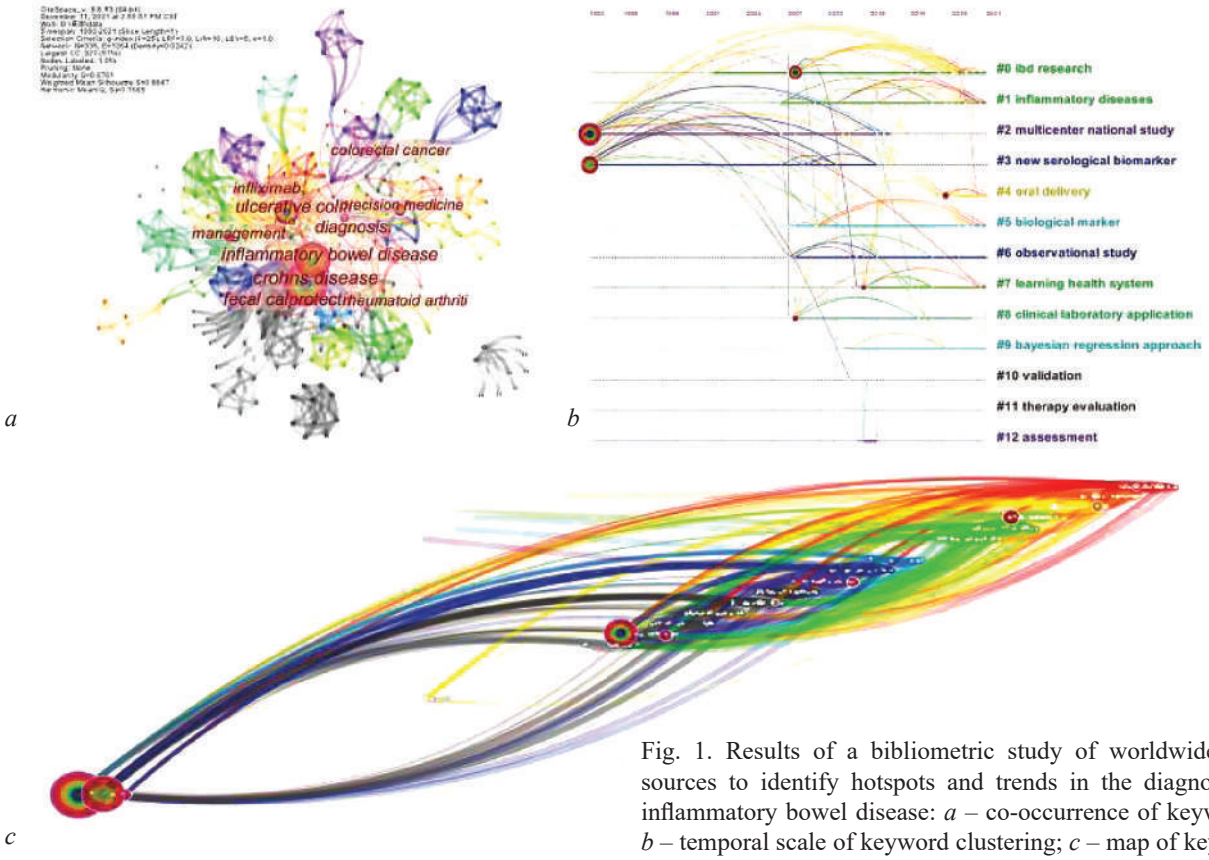

Fig. 1. Results of a bibliometric study of worldwide data sources to identify hotspots and trends in the diagnosis of inflammatory bowel disease: *a* – co-occurrence of keywords; *b* – temporal scale of keyword clustering; *c* – map of keyword time zones in the literature on accurate diagnosis and treatment of inflammatory bowel disease [1]

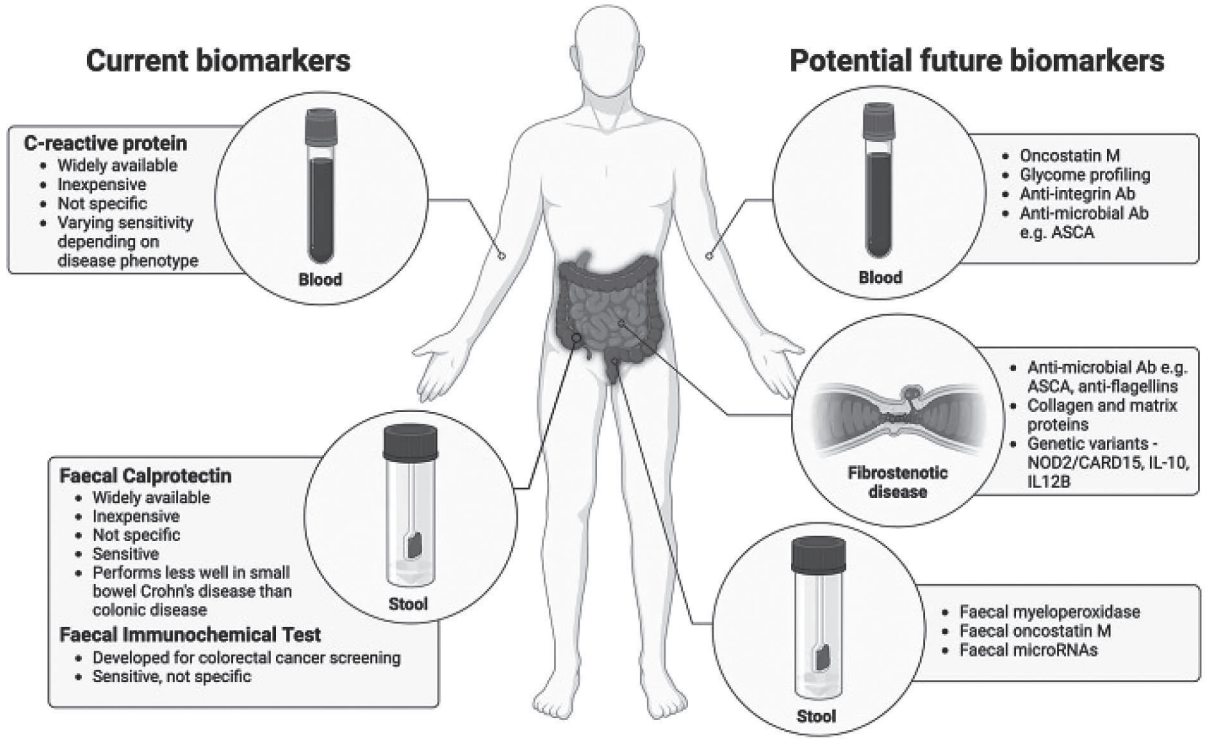

Fig. 2. Current and potential biomarkers in inflammatory bowel disease, adapted from [3]

Some of the most common keyword search markers for the diagnosis and management in IBD are C-reactive protein (CRP) and fecal calprotectin. However, they are obviously not true biomarkers of IBD, as they merely reflect the presence of inflammation and its severity, but are not specific, and changes in the values of these indicators are typical of many other conditions. They have relatively low sensitivity and specificity in patients with IBD [2]. Similarly, the evaluation of serologic biomarkers is of uncertain value in predicting disease progression or a response to treatment.

Today, omics biomarkers provide significant additional advantages for the diagnosis and management in IBD, including Crohn's disease (CD) and ulcerative colitis (UC) (Fig. 2). The introduction of omics technologies, the identification of genomic, proteomic, and metabolomic markers, and the in-depth assessment of the intestinal microbiome allow not only to assess the probability of disease development, but also to provide in-depth and comprehensive evaluation of the molecular basis and pathogenesis in IBD. Early diagnosis and understanding of the pathogenesis of CD and UC are extremely valuable for the choice of reasonable personalized pathogen-specific therapy in a variety of clinical manifestations.

Among omics biomarkers, the results of proteomics and metabolomics studies attract the attention of researchers and clinicians. Their significance as promising tools for the diagnosis, management, and control of IBD therapy in modern personalized and precision medicine is undoubted.

Proteomics and metabolomics are among the most dynamically developing areas of molecular diagnosis. The undeniable advantage of these approaches is the possibility of non-invasive assessment of a significant number of indicators.

A proteomics analysis has already identified some candidate IBD biomarkers for testing in clinical practice, such as oncostatin M and αvβ6 antibodies [4]. In addition, proteomics approaches have been actively used for identifying stool protein and peptide biomarker panels in patients at risk of IBD and in treatment strategy adjustment [5].

Metabolomic profiling also allows to differentiate IBD patients from healthy individuals and to identify CD and UC with high accuracy. Such metabolites as tryptophan and indole-3-acetic acid have been identified as potential biomarkers in IBD, with ROC curves showing high discriminatory power (AUC: 0.9738 for CD and 0.9887 for UC) [6]. Data from metabolomics studies also identify a number of biomarkers with a potential diagnostic value [7]. Simultaneuosly, , the integration of metabolomics data with other potential molecular biomarkers, such as lipidomics, can be used as an additional diagnostic advantage in IBD [8].

This work focuses on analyzing the results of current omics studies evaluating proteomic and metabolomic indices to identify potential biomarkers for the diagnosis, monitoring, and potential assessment of the response to therapy in patients with IBD.

OMICS BIOMARKER POTENTIAL

Currently, the study of omics biomarker potential and the integration of various omics data in IBD has focused on three areas of interest: identification of new diagnostic proteomic biomarkers, in-depth characteristics of disease pathogenesis, and response to treatment.

Proteomic and metabolomic biomarkers provide a holistic view of the disease, identifying molecular networks and pathways involved in the IBD pathogenesis (Fig. 3). This approach significantly helps to develop prognostic criteria for early detection of the disease and monitoring of clinical outcomes [9].

Proteome Analysis

Considering the presence of proven strong correlations between the level of protein expression and disease activity, proteomics attracts special attention as a diagnostic tool [10]. At the same time, a current trend in proteomics is the formation of diagnostic panels for the most accurate CD and UC signatures.

Diagnostic and Monitoring Capabilities

It is obvious that the diversity of clinical manifestations and insufficient sensitivity and specificity of existing biomarkers indicate the special significance of potential biomarkers for the differential diagnosis of IBD. Proteomics studies allow to differentiate IBD and other intestinal diseases with high sensitivity and specificity [11]. Proteomics approaches in IBD were first used in the works of U. Berndt et al. The studies revealed differences in protein expression by different T cell populations in CD and UC [12]. This experimental approach demonstrated high sensitivity (70%) and specificity (72.5%) in CD.

The results of the study on MMP-12 and oncostatin M are of great interest. They allowed to effectively differentiate IBD from other intestinal diseases [13].

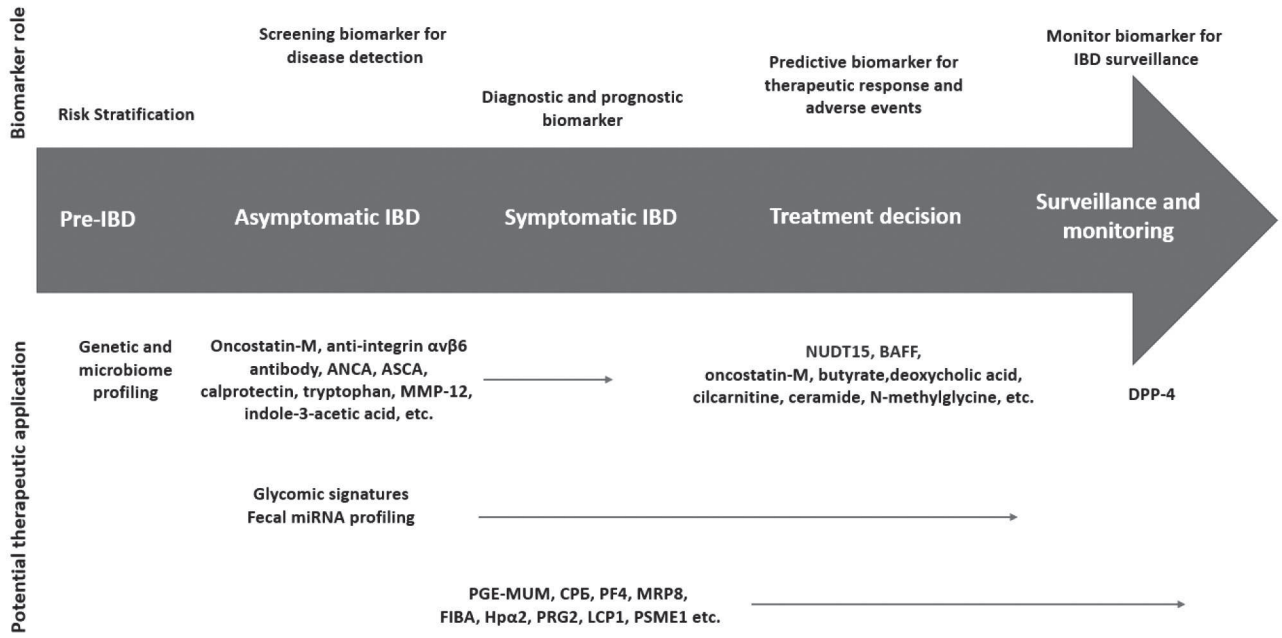

Fig. 3. Potential roles of biomarkers in IBD, examples of existing and new biomarkers that could perform these functions, adapted from [3]

Serum antibodies to αvβ6 integrin determined in the blood serum are now considered as another promising biomarker in IBD and, especially, UC [14]. The loss of intestinal epithelial barrier integrity precedes clinical manifestations of the disease, which explains the possibility of detecting antibodies to αvβ6 in the preclinical period of IBD, as well as the possible association of the level of antibodies to αvβ6 with the severity of the disease course, which is potentially prognostically significant.

Another candidate for application in clinical practice is PGE-MUM, which is determined in urine and correlates with endoscopic and histologic activity in IBD, especially in UC. PGE-MUM has a great diagnostic potential because of its better correlation with endoscopic parameters compared to CRP. In addition, threshold values for PGE-MUM were proposed to predict endoscopic and histologic activity with a reported sensitivity of 81–82% [15].

A significant trend in molecular diagnosis of IBD is the formation of diagnostic panels to evaluate protein expression in biological material of different types. Thus, four most diagnostically significant protein biomarkers were identified in serum: platelet factor 4 (PF4), calgranulin A (MRP8), fibrinogen A (α-chain) (FIBA), and haptoglobin alpha-2 (Hpα2). Hpα2 was particularly significant in differentiating UC and CD with accuracy similar to or higher than that in ANCA and ASCA serologic tests [16]. The analysis of colonic mucosal tissue samples from adult and pediatric patients allowed to form two candidate protein panels [17].

These panels were effective in the diagnosis of IBD and the differential diagnosis of CD and UC, respectively. The diagnostic panel included fatty acid binding protein 5 (FABP5), uridine diphosphate-α-d-glucose-6-dehydrogenase (UGDH), leucine-rich mitochondrial protein containing PPR motifs (LRPPRC), visfatin/NAMPT, and inorganic pyrophosphatase 1 (PPA1). Elevated levels of NAMPT and PPA1 were particularly significant in IBD. The differential diagnostic panel included mitochondrial trifunctional enzyme subunit beta (HADHB), cytosol aminopeptidase (LAP3), leukotriene-A-4 hydrolase (LTA4H), metallothionein-2 (MT2A), mitochondrial tricarboxylate transport protein (SLC25A1), heterogeneous nuclear ribonucleoprotein H3 (HNRNPH3), mitochondrial delta(3,5)-delta(2,4)-dienoyl-CoA isomerase (ECH1), transferrin receptor protein 1 (TFRC), beta-2-microglobulin (B2M), SEC61 transmembrane channel complex protein, subunit alpha 1 (SEC61A1), staphylococcal nuclease domain-containing protein 1 (SND1), , and transferrin (TF). The first nine proteins of the panel were significantly elevated in CD compared to UC patients. Thus, they can be considered as candidates for an

in-depth evaluation in the differential diagnosis of CD and UC regardless of the age of patients. In the analysis of colonic biopsy proteome, there are three newly identified biomarkers, including eosinophil major basic protein (PRG2), laminin 2 (LCP1), and proteasome activator complex subunit 1 (PSME1), that are clearly associated with active CD [18].

It is of particular interest that many biomarkers are mainly components of fatty acid metabolism [17]. This allows to consider the prospect of a possible combination of proteomics studies with the assessment of the lipid profile in IBD patients.

The proteome analysis also suggests the pathogenetic significance of mitochondrial dysfunction in the development of IBD, especially UC [19]. Decreased expression of eight mitochondrial proteins (ATP synthase subunit beta (ATP5B), mitochondrial malate dehydrogenase 2 (MDH2), heat shock protein 90 (HSPA9B), voltage-dependent anion-selective channel protein 1 (VDAC1), peroxiredoxin 1 (PRDX1), heat shock protein 60 (HSPD1), peroxiredoxin 2 (PRDX2), and prohibitin (PHB)), was particularly significant in UC. The key protein of mitochondrial complex, PHB, was decreased in biopsy specimens of colonic mucosa in UC both in remission and relapse. This allows to suggest possible early mitochondrial changes during disease formation.

B cell-activating factor (BAFF), a member of the tumor necrosis factor (TNF) superfamily, attracts special attention among proteomic biomarkers. It is produced by most cells of the innate and adaptive immunity and is of great importance for immune regulation and inflammatory changes in the intestine in IBD [20]. In IBD, BAFF levels are elevated in serum, feces, and colonic tissues and are associated with inflammation in the intestinal mucosa [21]. Pathogenetically relevant BAFF overexpression, in turn, exacerbates the proinflammatory activity of immune cells in IBD, including through the NF-κB signaling pathway and the NLRP3 inflammasome [22]. These data allow us to consider BAFF as a candidate biomarker for monitoring the course of IBD, including in the context of therapy.

Potential for Personalized Therapy and Assessment of a Treatment Response

In addition to diagnostic biomarkers, proteomics approaches can potentially be used to assess the response of IBD patients to ongoing therapy. For example, an elevated serum BAFF level, mentioned in the previous section, was initially associated with a better response to infliximab treatment in CD patients. Those with a clinical response to infliximab treatment showed a decrease in its levels after treatment, whereas those who did not respond to therapy showed an increase in the parameter [23]. In addition, specific single nucleotide polymorphisms (SNPs) in the BAFF gene, such as rs1041569, have been associated with CD susceptibility and a response to treatment [24].

The potential of BAFF blockade is now considered as one of the therapeutic strategies. It has been shown in experimental models that BAFF blockade reduces the severity of inflammation, weight loss, and histopathologic damage in colitis [25, 26]. Thus, BAFF may not only be a potential diagnostic and therapeutically predictive biomarker, but also may be considered as one of the targets for the IBD treatment.

The dynamic assessment of circulating chemokine levels and the assessment of monocyte activation have also been used as candidate biomarkers for the response to treatment with TNF inhibitors, particularly infliximab. Within 2 weeks after the initiation of therapy in patients without a clinical response, there was an obvious decrease in the level of protein from CD14+/CD86+ macrophages and the level of the chemokine CCL2 [27].

In another study, proteomics approaches were used for the response management of infliximab and prednisolone therapy in IBD children. The study proposed a candidate panel with 18 proteins and 3 microRNAs [28].

Thus, the potential of the proteomics data obtained allows to consider this approach as promising for the differential diagnosis of IBD, research on IBD pathogenesis, as well as monitoring and prediction of the treatment response. At the same time, the results of the proteome analysis in a number of cases demonstrate associative links with other areas of omics diagnosis, such as lipidomics, which allows to speak about the possibility of more in-depth studies in IBD.

Metabolomic Biomarkers

Metabolomic biomarkers have also become promising tools for diagnosing and evaluating the response to treatment of IBD, including CD and UC. Metabolomic biomarkers can be used not only to identify pathogenetic features of the disease and, as expected, diagnostic targets, but can potentially guide therapeutic decisions. Metabolomics is increasingly being used to identify biomarkers to predict a treatment response and to distinguish IBD subtypes.

Diagnostic Potential

Today, metabolomic biomarkers are used in the differential diagnosis of IBD subtypes and to identify key differences between IBD patients and healthy persons. Serum and plasma, feces, and urine are considered as the main biological samples for metabolomic biomarkers. Thus, a group of five serum metabolites – pyruvate, phenylacetylglutamine, isolithocholic acid, taurodeoxycholic acid, and glycolithocholic acid – showed high accuracy (AUC = 0.861) in the differential diagnosis between CD and UC groups. High diagnostic accuracy rates allow us to consider them as a non-invasive diagnostic alternative to the tests used in routine clinical practice [29].

Serum metabolomics studies have demonstrated an increase in tryptophan and indole-3-acetic acid levels in both CD and UC patients, while kynurenine and indole-3-propionic acid levels were elevated only in CD [6]. A study by T.Vakhitov et al. identified 14 serum metabolites, including 2-hydroxybutyric acid and creatinine, as potential biomarkers of UC [30]. Other plasma metabolites – acylcarnitine, 3-indoleacetic acid, and dehydroepiandrosterone sulfate – were associated with intestinal microbiota and immune response formation. They were highlighted as candidate markers for further in-depth analysis [31].

The analysis and identification of fecal metabolites are also being used to develop metabolic profiles of individuals with IBD. Among 78 metabolites identified by L. Ning et al. all, metabolites were classified into three major categories of nutrient metabolism, including amino acids, carbohydrates, and fatty acids [7]. According to the results, the increase in the levels of amino acids, such as tryptophan, glutamine, arginine, 5-hydroxytryptophan, and histidine, was worth noting. These data go in line with the previous results [32]. Various organic acids related to the tricarboxylic acid cycle, such as pyruvic acid, fumaric acid, malonic acid, and oxoglutaric acid, were elevated in the feces of patients with IBD, indicating abnormal energy metabolism of the intestinal microbiota.

In addition to the possibility of using fecal metabolites to identify IBD, it is also possible to perform differential diagnosis of their subtypes. For example, significant changes in fecal metabolome profiles have been described in patients with UC and CD. The metabolic signature of fecal IBD includes alterations in short-chain fatty acids, tryptophan metabolites, sphingolipids, and vitamin levels. Although there is a considerable overlap between the metabolic signatures of the two subtypes of IBD, CD is primarily characterized by enrichment of primary bile acids, whereas UC is characterized by higher levels of proteolytic fermentation products [33].

The analysis of metabolomic pathways is also of particular importance for the formation of diagnostic strategies in IBD. Studies have demonstrated that glyoxylate and dicarboxylate metabolism, alanine, aspartate and glutamate metabolism, as well as glycerolipid metabolism in patients with IBD are associated with disease activity and can be used in the differential diagnosis of IBD subtypes [6]. A decrease in the ratio of primary and secondary bile acids in IBD compared to healthy individuals is worth noting. The metabolomics analysis also associated metabolism of beta-alanine, arginine, and proline with IBD, while glycerolipid metabolism in UC and CD differed significantly [6].

Correlations between IBD activity and changes in amino acid metabolism and β-oxidation of fatty acids have been described [34]. Amino acids, such as L-glutamine, glycine, and L-arginine, have been shown to support intestinal redox balance and immune homeostasis and can potentially alleviate the severity of IBD symptoms.

In addition, the metabolomics analysis also confirms the significance of the relationships between amino acids and various signaling pathways, including mTOR and NF-kB, involved in the implementation of inflammatory responses. These pathways play an important role in regulating the balance of pro-inflammatory and anti-inflammatory cytokines in the gut [35]. Alterations in fatty acid metabolism, especially polyunsaturated fatty acids (PUFAs), are also closely associated with IBD. Changes in PUFA ω-6 and ω-3 levels correlate with inflammatory markers, suggesting their role in modulating inflammation in IBD [36]. An approach involving the evaluation of ratios between pro-inflammatory and anti-inflammatory mediators and fatty acid derivatives can also be used for diagnostic purposes in IBD. For example, an increased arachidonic acid-to-eicosadienoic acid ratio is indicative of a proinflammatory state in UC patients.

Metabolome as a Biomarker of a Treatment Response

Metabolomic profiles can be used to predict the response to a number of biological drugs. The significant role of the intestinal microbiota and its

endogenous metabolites in the IBD development is known. It is suggested that the analysis of metabolites, including endogenous metabolites, may serve as predictors of the response to biological therapy in patients with IBD. According to a systematic review that included 38 studies investigating the potential of fecal and intestinal wall microbiota and endogenous metabolomic markers as predictors of a response to biologic therapy in patients with IBD, the data on the significance of metabolomic signatures in assessing the response of patients with IBD to various biological agents were confirmed [37]. In the future, these data can be used for precision and personalized therapy. Thus, the levels of endogenous metabolites, such as butyrate and deoxycholic acid, were significantly associated with clinical remission after anti-TNF alpha drug therapy.

So, higher levels of butyrate-producing bacteria and specific metabolites, such as acetamide, have been shown to be associated with a positive response to vedolizumab [37]. In addition, lower baseline levels of acylcarnitine and ceramide and increased levels of N-methylglycine were positively associated with the response to vedolizumab [38].

CD patients with a positive clinical response to ustekinumab also showed specific bacterial signatures of the gut microbiota – the increase in *Faecalibacterium* and lower levels of *Escherichia/shigella*. This supports the suggestion that bacterial profiles can be used as predictors of a treatment response in IBD [37].

Therefore, it is clear that metabolomic profiling is of particular interest and importance in the context of precision and personalized medicine for patients with IBD.

CONCLUSION

Proteomics and metabolomics studies open significant perspectives for further study of IBD. The results of experimental and clinical studies have already identified a number of biomarkers – candidates for testing and introduction into routine clinical practice. There is compelling evidence of the potential benefits of integrating these areas with other omics approaches, such as lipidomics. The integrative biomarker analysis can be used both to assess IBD pathogenesis and to personalize patient management approaches and treatment strategy selection. The integration of multi-omics data, including those using artificial intelligence, can also be considered as a basis for tools to predict IBD development and the course of the disease [39]. Data integration and IBD datasets and biomarker atlases are of great use for predicting specific features of the disease [40].

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