



# Metabolomics and Its Role in Inflammatory Bowel Disease: What Do We Know?

N. Tsonev \*, D. Zvezdov, D. Gashkova, D. Andreeva, M. Stefanova

Department of Gastroenterology, Second Multiprofile Hospital for Active Treatment, Sofia, Bulgaria

\*Corresponding author: N. Tsonev; ORCID: 0000-0002-0604-3824; [dr.n.tsonev@abv.bg](mailto:dr.n.tsonev@abv.bg)

Received 25 October 2022;

Accepted 16 November 2022;

Published 20 November 2022

## Abstract

Inflammatory bowel diseases comprise of ulcerative colitis and Crohn's disease, both of which have increasing incidence. Despite not having completely understood pathogenesis, genetic factors, environmental factors and microbiota are thought to play a role in a predisposed individual. Common symptoms include abdominal pain, diarrhea, fever, weight loss and rectal bleeding. Diagnosis is made by clinical, laboratory, endoscopic, radiologic and histologic examinations. Nevertheless, about 15% of patients do not have a definitive diagnosis. Metabolomics measures metabolites in a biological sample (feces, serum, urine, tissue and air) thereby having the potential to clarify disease pathogenesis and find new biomarkers, which will then aid in diagnosis, guide therapy and give prognosis.

**Keywords:** *IBD, Crohn's disease, Ulcerative colitis, microbiome, metabolome, metabolomics, biomarkers*

## Introduction

Crohn's disease and Ulcerative colitis are forms of chronic inflammatory diseases, characterized by transmural intestinal inflammation and stricture formation (Crohn's disease) or continuous inflammation involving the rectum (ulcerative colitis). There is increasing incidence of both forms of IBD in developed countries with one of the proposed factors being adopting the so-called Western diet [1]. The pathogenesis of IBD is not fully understood, but microbiome and environmental factors play a role in genetically susceptible individuals [2,3]. Diagnosis of IBD is complex and is based on clinical, biochemical, endoscopic, radiologic and histologic findings. It is important to discriminate between both IBD phenotypes in order to form a therapeutic strategy and predict prognosis.

Several biomarkers associated with IBD have been studied, such as perinuclear antineutrophil cytoplasmic (pANCA), anti-Saccharomyces cerevisiae antibodies (ASCAs), antibodies to exocrine pancreas (PABs), circulating noncoding RNAs such as miRNA and lncRNA, cathelicidin, CRP, and trefoil factor 3, but their use is not well adopted [4,5] and new biomarkers are needed in order to support diagnosis and aid therapy in IBD patients.

## Role of the microbiome

The human microbiome is defined as community of microorganisms living in different parts of the human body. More than 1000 species have been described [85]. The biggest concentration of microorganisms is in the colon and distal ileum, 99% of them are of bacterial origin and 90% are of phylotypes Bacteroidetes and Firmicutes [6,7]. One of the main changes in the gut microbiome in IBD patients is on one side increasing number of phylum Proteobacteria, most of which are pathogens, including Escherichia coli (a variant called adherent-invasive), Enterobacteriaceae, Klebsiella and Proteus spp, and reduced number of phylum

Firmicutes on the other [8-11]. Faecalibacterium prausnitzii and Roseburia hominis, which are butyrate-producing microorganisms are reported to be reduced in IBD patients. Butyrate is a short chain fatty acid, which is a main energy source for colonocytes and its lower concentrations in IBD patients aid inflammation and disrupts intestinal barrier integrity [12-16]. On the other hand, Ruminococcus gnavus, also from phylum Firmicutes has mucin-degrading properties and is reported in increased concentrations in IBD patients, mainly in Crohn's disease, which aids in intestinal barrier integrity disruption [16,17].

Paneth cell dysfunction is also reported in IBD individuals. These cells play a key role in maintaining intestinal homeostasis by producing and secreting antimicrobial peptides such as lysosym and alpha-defensins [18,19].

Change in gut microbiome is also associated in many trials with autoimmune conditions such as type 1 diabetes and rheumatoid arthritis [20,21], type 2 diabetes and obesity [22,23], colorectal cancer [24], heart disease [25] and IBD [26]. A key step in IBD pathogenesis is believed to be loss of immune tolerance to gut antigens of bacterial origin, which causes an abnormal immune response in a susceptible individual.

Oral dysbiosis is also reported in IBD represented by change in Streptococcus and Prevotella in saliva. Furthermore, a positive correlation is observed with increased fecal calprotectin and interleukins [16,27-29]. In normal conditions gut microbiome has direct and indirect effect due to its metabolite diversity, thus aiding normal physiological processes, as well as other metabolic processes outside of the GI tract.

## What is metabolomics?

Metabolites are products of many biological processes in the body. Their presence and quantitative measurement in different biological substrates in the human organism (urine, feces, serum, tissue) can provide detailed information about the specific state, which the body

represents, reflecting a specific metabolic phenotype [42]. Metabolomics is the study of these metabolites. It can be beneficial for diagnosis, monitoring therapy and determining the natural course of disease. The initiation of various metabolic reactions leads to the formation of the so-called metabolic markers that could subsequently be used to differentiate healthy from diseased [42].

There are two types of metabolomics - targeted analysis, where a particular metabolite is searched for and its concentration is measured, and untargeted, measuring the largest possible number of metabolites in a biological sample. Multiple methods are used to measure metabolites, but the main ones are proton nuclear magnetic resonance spectroscopy (H-NMR), liquid chromatography (LC), gas chromatography in combination with mass spectroscopy (MS), due to their high specificity and reproducibility of results.

Metabolites can be entirely of bacterial origin, but some of them after they are absorbed in the gastrointestinal tract, are processed (by hepatorenal conjugation, for example) and are then expelled from the body as co-metabolites.

## Metabolomics in IBD - change in lipid metabolism

Altered metabolism has already been established in some diseases, such as type 1 and type 2 diabetes mellitus, liver diseases (bile acids), neurodegenerative diseases (tryptophan metabolites), cardiovascular diseases and colorectal cancer (long-chain fatty acids) [16,30,31].

In some of the patients with IBD (about 15%), despite having performed the necessary tests to establish the diagnosis, it is impossible to distinguish Crohn's disease from ulcerative colitis. In this context, metabolomics could distinguish healthy from diseased, as well as Crohn's disease from ulcerative colitis, by examining metabolites in various biological products such as urine [32-34], serum [35-40], and feces [34,40,41,42]. In a study by Elizabeth A. Scoville et al. from 2012 a total of 173 metabolites were found that differed in patients with IBD from healthy controls, 27 of them were increased and 146 were decreased, mainly affecting metabolites related to lipid metabolism - fatty acids, acylcarnitine, sphingolipids and bile acids. This difference was more pronounced in patients with Crohn's disease than in those with ulcerative colitis [62].

Fatty acids are important for maintaining intestinal homeostasis and have a role in inflammatory processes - some have a pro-inflammatory, others anti-inflammatory effect. Therefore, a change in their levels affects intestinal inflammation [43]. Short-chain fatty acids (SCFA) such as butyrate, acetate and propionate also have a trophic effect on the colonic mucosa and are a source of energy for colonocytes. Butyrate is also an important immunomodulator, inducing production of Tregs and mucus, thereby suppressing inflammation [44].

Short-chain fatty acids (SCFA) are one of the first identified abnormal metabolites in IBD. Decreased levels have been reported in a number of studies [33,41,45,40]. One of the first by Marchesi et al from 2007 succeeded in differentiating healthy subjects from controls as well as Crohn's disease from ulcerative colitis. They reported low fecal levels of SCFA, including dimethylamine and trimethylamine [41,42].

Low levels of SCFA butyrate and propionate are associated with dysbiosis in Crohn's disease which is due to reduced levels of butyrate-producing organisms *Fecalibacterium prausnitzii* and *Roseburia hominis* [46]. In this regard, in a study in which patients with Crohn's disease were treated with prebiotics (inulin and butyrate) a decrease in the levels of *Ruminococcus gnavus* was observed, high levels of which are associated with dysbiosis in IBD [46] and an increase in the levels of *Bifidobacterium longum*, leading to a reduction in disease activity [47,16]. In a study by Pal et al from 2015 in children with IBD, treatment with butyrate resulted in a positive effect on intestinal disease activity [48]. The intake of food

rich in fiber increases the level of SCFA, improves dysbiosis and quality of life in patients with UC [49,7]. Another important energy source for colonocytes, responsible for about 30% of their energy needs, is glutamine, which also has altered levels, mostly reduced, which enabled Hisamatsu et al from 2012 in their study, calculating AminoIndex based on multivariate analysis of amino acid profiles from the serum of patients with IBD, to differentiate CD from UC [50,42].

Polyunsaturated fatty acids are also metabolites found at abnormal levels in patients with IBD. They are associated with intestinal inflammation through eicosanoids derived from arachidonic acid [51-54] and also correlate with inflammatory cytokines [55]. A 2019 study by Lai et al reported decreased levels of long-chain fatty acids such as docosahexaenoic, linolenic, and arachidonic acids and medium-chain fatty acids such as pelargonic and caprylic acids in the serum of patients with Crohn's disease [43,5]. Increased levels of eicosatrienoic, omega-3-, docosapentaenoic, and omega-6 fatty acids, which are thought to have anti-inflammatory activity, have also been reported [45]. This increase could be due to malabsorption caused by the inflammation.

Another lipid-associated change is in LDL, HDL and VLDL. Patients with Crohn's disease have lower fecal cholesterol levels compared to healthy controls [45], as well as lower serum LDL and HDL levels, more pronounced in CD. The reason for this is that pro-inflammatory cytokines such as TNF-alpha, IL-1 and INF-gamma inhibit the expression of lipoprotein lipase [56,57,5].

Closely related to lipid metabolism are prostaglandins, which are produced from arachidonic acid. Low levels of prostaglandins have been found in CD, with the exception of PGE2, which activates Th17 lymphocytes, which in turn activate dendritic cells and increase IL-23 production [5,58]. Bile acids -another altered metabolites, mainly secondary bile acids deoxycholic acid and lithocholic acid, are significantly reduced in UC patients. They suppress inflammation by inhibiting the synthesis of proinflammatory mediators and suppressing intestinal epithelial apoptosis [7,59,60]. They also exert an antimicrobial effect and their absence contributes to dysbiosis [61,16].

## Alteration in the tricarboxylic acid (TCA) cycle and its metabolites

Tricarboxylic acid (TCA) cycle, also known as the Krebs cycle, is the final process in the oxidation of proteins, lipids, and carbohydrates. A significant reduction of intermediate metabolites such as citrate, aconitate, alpha-ketoglutarate, succinate, fumarate and malate was found in the serum of CD patients compared to controls and UC patients. Moreover, the metabolite reported in lowest levels in CD patients (11-fold compared to controls and 18-fold compared to CD patients) is beta-hydroxybutyrate, which is synthesized from acetyl-CoA [62]. In addition to serum, low levels of succinate and citrate are also observed in urine [63,37,33]. Alonso et al even suggested citrate as a potential biomarker, mainly in CD patients, as its levels correlate with disease activity [65,5].

## Alterations in other metabolites

Alterations in essential amino acid levels has also been reported. An example of this is the altered level of tryptophan, which was elevated in the feces of patients with IBD compared to controls [66,5]. On the other hand, Nikolaus et al found low levels of this amino acid in the serum of patients with IBD [67]. In some studies, administration of tryptophan and its metabolites (indole-3-aldehyde, indole-3-propionic acid, and indole-3-acetic acid) suppresses colonic inflammation, protects epithelial integrity, and reverses colitis-associated microbial dysbiosis [68-71,7].

Phenylalanine, another amino acid with anti-inflammatory effects (suppresses TNF production) [72], was increased in serum and decreased in feces, reported by two different authors [43,40]. High

levels of taurine, glycine, lysine, alanine were also found in feces. This is most likely due to impaired epithelial absorption due to intestinal inflammation, but could also be due to dysbiosis, as some bacteria use amino acids for their metabolism [73,74, 16]. An increase in some polyamines - putrescine and cadaverine - was observed in the feces of patients with CD and UC, which suggests that these polyamines have a negative effect on disease [75,7]. An increase in fecal and serum taurine levels has also been reported [46,40,34,76-79,7].

Also of interest is the co-metabolite of mixed origin (mammalian and microbial) hippurate, or N-benzoylglycine. It is produced by bacterial fermentation of aromatic compounds introduced from the diet (aromatic amino acids, polyphenols and purines) to benzoic acid with subsequent conjugation with glycine in the liver. It was found to be significantly lower in the urine of patients with IBD compared to controls. Similar to it is formate, which is also in low amounts [35,37,33,32,80,16]. This suggests its potential use as a biomarker. A similar co-metabolite reported in low concentrations in urine is p-cresol sulfate, which is derived from bacterial metabolism of tyrosine, primarily by Clostridia spp [32,81,44].

Histidine metabolism is also altered. It is converted by the microbiota into ergothioneine. This metabolite has antioxidant and neuroprotective properties. It was also found in low amounts reported by Lai et al. from 2019. It is assumed that this is due to the damage or lack of its transporter (OCTN1), which is expressed only in the small intestine, which suggests its use for the differentiation of CD from UC [43, 82,83,84,5].

## Conclusion

Based on all above, it can be seen that a number of metabolites in patients with IBD are altered to varying degrees. There is data for some of them that have the potential to be used as biological markers to differentiate Crohn's disease from ulcerative colitis, and some correlate with the activity of the inflammatory process. Commensal microbiota and their metabolites are candidates for the production of new probiotics containing *F. prausnitzii*, *Akkermansia muciniphila*, *Bacteroides fragilis* due to their butyrate-producing properties. However, more data is needed in order for these finding to be standardized and implemented in routine clinical practice.

## References

- [1] Kaplan, G.G.; Ng, S.C. Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. *Gastroenterology* 2017,152, 313-321.e2.
- [2] Dupaul-Chicoine J, Dagenais M, Saleh M: Crosstalk between the intestinal microbiota and the innate immune system in intestinal homeostasis and inflammatory bowel disease. *Inflamm Bowel Dis* 2013; 19: 2227-2237.
- [3] Strober W, Fuss I, Mannon P: The fundamental basis of inflammatory bowel disease. *J Clin Invest* 2007; 117: 514-521.
- [4] Peyrin-Biroulet, L.; Reinisch, W.; Colombel, J.F.; Mantzaris, G.J.; Kornbluth, A.; Diamond, R.; Rutgeerts, P.; Tang, L.K.; Cornillie, F.J.; Sandborn, W.J. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. *Gut* 2014, 63, 88-95
- [5] Bauset, C.; Gisbert-Ferrándiz, L.; Cosín-Roger, J. Metabolomics as a Promising Resource Identifying Potential Biomarkers for Inflammatory Bowel Disease. *J. Clin. Med.* 2021, 10, 622. <https://doi.org/10.3390/jcm10040622>
- [6] Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 2010;464:59-65
- [7] Mengfan Li et al, Gut microbial metabolome in inflammatory bowel disease: From association to therapeutic perspectives
- [8] Lloyd-Price J, Arze C, Ananthakrishnan AN, Schirmer M, Avila-Pacheco J, et al. Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. *Nature* 2019;569:655-62
- [9] Santoru ML, Piras C, Murgia A, Palmas V, Camboni T, et al. Cross-sectional evaluation of the gut-microbiome metabolome axis in an Italian cohort of IBD patients. *Sci Rep* 2017;7:9523
- [10] Matsuoka K, Kanai T. The gut microbiota and inflammatory bowel disease. *Semin Immunopathol* 2015;37:47-55
- [11] Nagao-Kitamoto H, Kamada N. Host-microbial cross-talk in inflammatory bowel disease. *Immune Netw* 2017;17:1-12.
- [12] Wang W, Chen L, Zhou R, et al. Increased proportions of Bifidobacterium and the Lactobacillus group and loss of butyrate-producing bacteria in inflammatory bowel disease. *J Clin Microbiol* 2014;52:398-406.
- [13] Lopez-Siles M, Enrich-Capy N, Aldeguer X, et al. Alterations in the abundance and co-occurrence of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* in the colonic mucosa of inflammatory bowel disease subjects. *Front Cell Infect Microbiol* 2018;7:281
- [14] Machiels K, Joossens M, Sabino J, et al. A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. *Gut* 2014;63:1275-83
- [15] Frank DN, Robertson CE, Hamm CM, et al. Disease phenotype and genotype are associated with shifts in intestinal-associated microbiota in inflammatory bowel diseases. *Inflamm Bowel Dis* 2011;17:179-84
- [16] Kate Gallagher,a, Alexandra Catesson,a Julian L. Griffin,a Elaine Holmes,a,c Horace R. T. Williamsa,b, Metabolomic Analysis in Inflammatory Bowel Disease: A Systematic Review, *Journal of Crohn's and Colitis*, 2021, 813-826 doi:10.1093/ecco-jcc/ijaa227
- [17] Henke MT, Kenny DJ, Cassilly CD, Vlamakis H, Xavier RJ, Clardy J. *Ruminococcus gnavus*, a member of the human gut microbiome associated with Crohn's disease, produces an inflammatory polysaccharide. *Proc Natl Acad Sci U S A* 2019;116:12672-7
- [18] Wang SL, Shao BZ, Zhao SB, et al. Impact of paneth cell autophagy on inflammatory bowel disease. *Front Immunol* 2018;9:693
- [19] Lueschow SR, McElroy SJ. The paneth cell: the curator and defender of the immature small intestine. *Front Immunol* 2020;11:587
- [20] B.P. Boerner, N.E. Sarvetnick, Type 1 diabetes: role of intestinal microbiome in humans and mice, *Ann. N.Y. Acad. Sci.* 1243 (1) (2011) 103-118
- [21] S. Abdollahi-Roodsaz, S.B. Abramson, J.U. Scher, The metabolic role of the gut microbiota in health and rheumatic disease: mechanisms and interventions, *Nat. Rev. Rheumatol.* 12 (8) (2016) 446-455
- [22] H.K. Pedersen, V. Gudmundsdottir, H.B. Nielsen, T. Hyotylainen, T. Nielsen, B.A. Jensen, K. Forslund, F. Hildebrand, E. Prifti, G. Falony, E. Le Chatelier, F. Levenez, J. Dore, I. Mattila, D.R. Plichta, P. Poho, L.I. Hellgren, M. Arumugam, S. Sunagawa, S. Vieira-Silva, T. Jorgensen, J.B. Holm, K. Trost, H.I.T.C. Meta, K. Kristiansen, S. Brix, J. Raes, J. Wang, T. Hansen, P. Bork, S. Brunak, M. Oresic, S.D. Ehrlich, O. Pedersen, Human gut microbes impact host serum metabolome and insulin sensitivity, *Nature* 535 (7612) (2016) 376-381

- [23] S. Shoaie, P. Ghaffari, P. Kovatcheva-Datchary, A. Mardinoglu, P. Sen, E. Pujos-Guillot, T. de Wouters, C. Juste, S. Rizkalla, J. Chilloux, Quantifying diet-induced metabolic changes of the human gut microbiome, *Cell Metab.* 22 (2) (2015) 320-331
- [24] C.L. Sears, W.S. Garrett, Microbes, microbiota, and colon cancer, *Cell Host Microbe* 15 (3) (2014) 317-328
- [25] A.L. Jonsson, F. Backhed, Role of gut microbiota in atherosclerosis, *Nat. Rev. Cardiol.* 14 (2) (2017) 79-87
- [26] M. Wlodarska, A.D. Kostic, R.J. Xavier, An integrative view of microbiome-host interactions in inflammatory bowel diseases, *Cell Host Microbe* 17 (5) (2015) 577-591
- [27] Qi Y, Zang S, Wei J, et al. High-throughput sequencing provides insights into oral microbiota dysbiosis in association with inflammatory bowel disease. *Genomics* 2020. doi:10.1016/j.ygeno.2020.09.063
- [28] Said HS, Suda W, Nakagome S, et al. Dysbiosis of salivary microbiota in inflammatory bowel disease and its association with oral immunological biomarkers. *DNA Res* 2014;21:15-25
- [29] Xun Z, Zhang Q, Xu T, Chen N, Chen F. Dysbiosis and ecotypes of the salivary microbiome associated with inflammatory bowel diseases and the assistance in diagnosis of diseases using oral bacterial profiles. *Front Microbiol* 2018;9:1136
- [30] Davies NW, Guillemin G, Brew BJ. Tryptophan, neurodegeneration and HIV-associated neurocognitive disorder. *Int J Tryptophan Res* 2010;3:121-40
- [31] Trivedi DK, Hollywood KA, Goodacre R. Metabolomics for the masses: the future of metabolomics in a personalized world. *New Horiz Transl Med* 2017;3:294-305
- [32] Williams, H. R., Cox, I. J., Walker, D. G., North, B. V., Patel, V. M., Marshall, S. E., et al. (2009). Characterization of inflammatory bowel disease with urinary metabolic profiling. *The American Journal of Gastroenterology*, 104(6), 1435-1444. <https://doi.org/10.1038/ajg.2009.175>
- [33] Stephens, N. S., Siffledeen, J., Su, X., Murdoch, T. B., Fedorak, R. N., & Slupsky, C. M. (2013). Urinary NMR metabolomic profiles discriminate inflammatory bowel disease from healthy. *Journal of Crohn's and Colitis*, 7(2), e42-e48. <https://doi.org/10.1016/j.crohns.2012.04.019>
- [34] Kolho, K. L., Pessia, A., Jaakkola, T., de Vos, W. M., & Velagapudi, V. (2017). Faecal and serum metabolomics in paediatric inflammatory bowel disease. *Journal of Crohn's and Colitis*, 11(3), 321-334. <https://doi.org/10.1093/ecco-jcc/jjw158>
- [35] Dawiskiba, T., Deja, S., Mulak, A., Zabek, A., Jawien, E., Pawelka, D., et al. (2014). Serum and urine metabolomic fingerprinting in diagnostics of inflammatory bowel diseases. *World Journal of Gastroenterol*, 20(1), 163-174. <https://doi.org/10.3748/wjg.v20.11.163>
- [36] Ooi, M., Nishiumi, S., Yoshie, T., Shiomi, Y., Kohashi, M., Fukunaga, K., et al. (2011). GC/MS-based profiling of amino acids and TCA cycle-related molecules in ulcerative colitis. *Inflammation Research*, 60(9), 831-840. <https://doi.org/10.1007/s00011-011-0340-7>
- [37] Schicho, R., Shaykhtudinov, R., Ngo, J., Nazyrova, A., Schneider, C., Panaccione, R., et al. (2012). Quantitative metabolomic profiling of serum, plasma, and urine by 1H NMR spectroscopy discriminates between patients with inflammatory bowel disease and healthy individuals. *Journal of Proteome Research*, 11(6), 3344-3357. <https://doi.org/10.1021/pr300139q>
- [38] Williams, H. R., Willmore, J. D., Cox, I. J., Walker, D. G., Cobbold, J. F., Taylor-Robinson, S. D., et al. (2012). Serum metabolic profiling in inflammatory bowel disease. *Digestive Diseases and Sciences*, 57(8), 2157-2165. <https://doi.org/10.1007/s10620-012-2127-2>
- [39] Zhang, Y., Lin, L., Xu, Y., Lin, Y., Jin, Y., & Zheng, C. (2013). 1H NMR-based spectroscopy detects metabolic alterations in serum of patients with early-stage ulcerative colitis. *Biochemical and Biophysical Research Communications*, 433(4), 547-551. <https://doi.org/10.1016/j.bbrc.2013.03.012>
- [40] Bjerrum, J. T., Wang, Y., Hao, F., Coskun, M., Ludwig, C., Gunther, U., et al. (2015). Metabonomics of human fecal extracts characterize ulcerative colitis, Crohn's disease and healthy individuals. *Metabolomics*, 11, 122-133. <https://doi.org/10.1007/s11306-014-0677-3>
- [41] Marchesi, J. R., Holmes, E., Khan, F., Kochhar, S., Scanlan, P., Shanahan, F., et al. (2007). Rapid and noninvasive metabonomic characterization of inflammatory bowel disease. *Journal of Proteome Research*, 6(2), 546-551. <https://doi.org/10.1021/pr060470d>
- [42] De Preter, V., Machiels, K., Joossens, M., Arijs, I., Matthys, C., Vermeire, S., et al. (2015). Faecal metabolite profiling identifies medium-chain fatty acids as discriminating compounds in IBD. *Gut*, 64(3), 447-458. <https://doi.org/10.1136/gutjnl-2013-306423>
- [43] Lai, Y.; Xue, J.; Liu, C.W.; Gao, B.; Chi, L.; Tu, P.; Lu, K.; Ru, H. Serum Metabolomics Identifies Altered Bioenergetics, Signaling Cascades in Parallel with Exposome Markers in Crohn's Disease. *Molecules* 2019, 24, 449
- [44] Aldars-García, L.; Gisbert, J.P.; Chaparro, M. Metabolomics Insights into Inflammatory Bowel Disease: A Comprehensive Review. *Pharmaceuticals* 2021, 14, 1190. <https://doi.org/10.3390/ph14111190>
- [45] Franzosa, E.A.; Sirota-Madi, A.; Avila-Pacheco, J.; Fornelos, N.; Haiser, H.J.; Reinker, S.; Vatanen, T.; Hall, A.B.; Mallick, H.; McIver, L.J.; et al. Gut microbiome structure and metabolic activity in inflammatory bowel disease. *Nat. Microbiol.* 2019, 4, 293-305
- [46] Lloyd-Price J, Arze C, Ananthakrishnan AN, et al.; IBDMDB Investigators. Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. *Nature* 2019;569:655-62.
- [47] De Preter V, Joossens M, Ballet V, et al. Metabolic profiling of the impact of oligofructose-enriched inulin in Crohn's disease patients: a double-blinded randomized controlled trial. *Clin Transl Gastroenterol* 2013;4:e30.
- [48] Pal K, Tinalal S, Al Buainain H, Singh VP. Diversion proctocolitis and response to treatment with short-chain fatty acids-a clinicopathological study in children. *Indian J Gastroenterol* 2015;34:292-9
- [49] Fritsch J, Garces L, Quintero MA, Pignac-Kobinger J, Santander AM, et al. Low-Fat, high-fiber diet reduces markers of inflammation and dysbiosis and improves quality of life in patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2021;19:1189-1199.e1130
- [50] Hisamatsu T, Okamoto S, Hashimoto M, Muramatsu T, Andou A, Uo M, Kitazume MT, Matsuoka K, Yajima T, Inoue N, Kanai T, Ogata H, Iwao Y, Yamakado M, Sakai R, Ono N, Ando T, Suzuki M, Hibi T. Novel, objective, multivariate biomarkers composed of plasma amino acid profiles for the diagnosis and assessment of inflammatory bowel disease. *PLoS One* 2012; 7: e31131 [PMID: 22303484 DOI: 10.1371/journal.pone.0031131]
- [51] Sharon, P., & Stenson, W. F. (1984). Enhanced synthesis of leukotriene B4 by colonic mucosa in inflammatory bowel disease. *Gastroenterology*, 86(3), 453-460.

- [52] Ueda, Y., Kawakami, Y., Kunii, D., Okada, H., Azuma, M., Le, D. S., et al. (2008). Elevated concentrations of linoleic acid in erythrocyte membrane phospholipids in patients with inflammatory bowel disease. *Nutrition Research*, 28(4), 239-244. <https://doi.org/10.1016/j.nutres.2008.02.005>.
- [53] Esteve-Comas, M., Ramirez, M., Fernandez-Banares, F., Abad-Lacruz, A., Gil, A., Cabre, E., et al. (1992). Plasma polyunsaturated fatty acid pattern in active inflammatory bowel disease. *Gut*, 33(10), 1365-1369.
- [54] Marion-Letellier, R., Savoye, G., Beck, P. L., Panaccione, R., & Ghosh, S. (2013). Polyunsaturated fatty acids in inflammatory bowel diseases: A reappraisal of effects and therapeutic approaches. *Inflammatory Bowel Diseases*, 19(3), 650-661. <https://doi.org/10.1097/MIB.0b013e3182810122>
- [55] Wiese, D. M., Horst, S. N., Brown, C. T., Allaman, M. M., Hodges, M. E., Slaughter, J. C., et al. (2016). Serum fatty acids are correlated with inflammatory cytokines in ulcerative colitis. *PLoS ONE*, 11(5), e0156387. <https://doi.org/10.1371/journal.pone.0156387>.
- [56] Querfeld, U.; Ong, J.M.; Prehn, J.; Carty, J.; Saffari, B.; Jordan, S.C.; Kern, P.A. Effects of cytokines on the production of lipoprotein lipase in cultured human macrophages. *J. Lipid Res.* 1990, 31, 1379-1386
- [57] Friedman, G.; Barak, V.; Chajek-Shaul, T.; Etienne, J.; Treves, A.J.; Stein, O.; Stein, Y. Recombinant human interleukin-1 suppresses lipoprotein lipase activity, but not expression of lipoprotein lipase mRNA in mesenchymal rat heart cell cultures. *Biochim. Biophys. Acta* 1991, 1089, 83-87.
- [58] Sheibanie, A.F.; Yen, J.H.; Khayrullina, T.; Emig, F.; Zhang, M.; Tuma, R.; Ganea, D. The proinflammatory effect of prostaglandin E2 in experimental inflammatory bowel disease is mediated through the IL-23->IL-17 axis. *J. Immunol.* 2007, 178, 8138-8147
- [59] Ward JBJ, Lajczak NK, Kelly OB, O'Dwyer AM, Giddam AK, et al. Ursodeoxycholic acid and lithocholic acid exert anti-inflammatory actions in the colon. *Am J Physiol Gastrointest Liver Physiol* 2017;312:G550-8
- [60] Lajczak-McGinley NK, Porru E, Fallon CM, Smyth J, Curley C, et al. The secondary bile acids, ursodeoxycholic acid and lithocholic acid, protect against intestinal inflammation by inhibition of epithelial apoptosis. *Physiol Rep* 2020;8:e14456
- [61] Ocvirk S, O'Keefe SJ. Influence of bile acids on colorectal cancer risk: potential mechanisms mediated by diet-gut microbiota interactions. *Curr Nutr Rep* 2017;6:315-22.
- [62] Scoville, E.A.; Allaman, M.M.; Brown, C.T.; Motley, A.K.; Horst, S.N.; Williams, C.S.; Koyama, T.; Zhao, Z.; Adams, D.W.; Beaulieu, D.B.; et al. Alterations in Lipid, Amino Acid, and Energy Metabolism Distinguish Crohn's Disease from Ulcerative Colitis and Control Subjects by Serum Metabolomic Profiling. *Metabolomics* 2018, 14, 17.
- [63] Julia A, Vinaixa M, Domenech E, et al. Urine metabolome profiling of immune-mediated inflammatory diseases. *BMC Med* 2016;14:133.
- [64] Dawiskiba T, Deja S, Mulak A, et al. Serum and urine metabolomic fingerprinting in diagnostics of inflammatory bowel diseases. *World J Gastroenterol* 2014;20:163-74. 54.
- [65] Alonso, A.; Julia, A.; Vinaixa, M.; Domenech, E.; Fernandez-Nebro, A.; Canete, J.D.; Ferrandiz, C.; Tornero, J.; Gisbert, J.P.; Nos, P.; et al. Urine metabolome profiling of immune-mediated inflammatory diseases. *BMC Med.* 2016, 14, 133
- [66] Jansson, J.; Willing, B.; Lucio, M.; Fekete, A.; Dicksved, J.; Halfvarson, J.; Tysk, C.; Schmitt-Kopplin, P. Metabolomics reveals metabolic biomarkers of Crohn's disease. *PLoS ONE* 2009, 4, e6386.
- [67] Nikolaus, S.; Schulte, B.; Al-Massad, N.; Thieme, F.; Schulte, D.M.; Bethge, J.; Rehman, A.; Tran, F.; Aden, K.; Hasler, R.; et al. Increased Tryptophan Metabolism Is Associated with Activity of Inflammatory Bowel Diseases. *Gastroenterology* 2017, 153, 1504-1516.e2
- [68] Scott SA, Fu J, Chang PV. Microbial tryptophan metabolites regulate gut barrier function via the aryl hydrocarbon receptor. *Proc Natl Acad Sci U S A* 2020.
- [69] Cervantes-Barragan L, Chai JN, Tianero MD, Di Luccia B, Ahern PP, et al. Lactobacillus reuteri induces gut intraepithelial CD4(+) CD8alphaalpha(+) T cells. *Science* 2017;357:806-10.
- [70] Busbee PB, Menzel L, Alrafas HR, Dopkins N, Becker W, et al. Indole-3-carbinol prevents colitis and associated microbial dysbiosis in an IL-22-dependent manner. *JCI Insight* 2020;5.
- [71] Zelante T, Iannitti RG, Cunha C, De Luca A, Giovannini G, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity* 2013;39:372-85
- [72] He, F.; Wu, C.; Li, P.; Li, N.; Zhang, D.; Zhu, Q.; Ren, W.; Peng, Y. Functions and Signaling Pathways of Amino Acids in Intestinal Inflammation. *Biomed. Res. Int.* 2018, 2018, 9171905.
- [73] Ma N, Ma X. Dietary amino acids and the gut-microbiome-immune axis: physiological metabolism and therapeutic prospects. *Compr Rev Food Sci Food Saf* 2019;18:221-42 90.
- [74] Mojtahed A, Gee MS. Magnetic resonance enterography evaluation of Crohn disease activity and mucosal healing in young patients. *Pediatr Radiol* 2018;48:1273-9
- [75] Santoru ML, Piras C, Murgia A, Palmas V, Camboni T, et al. Cross sectional evaluation of the gut-microbiome metabolome axis in an Italian cohort of IBD patients. *Sci Rep* 2017;7:9523
- [76] Bushman FD, Conrad M, Ren Y, Zhao C, Gu C, et al. Multi-omic analysis of the interaction between clostridioides difficile infection and pediatric inflammatory bowel disease. *Cell Host Microbe* 2020;28:422-433.e427
- [77] Alghamdi A, Gerasimidis K, Blackburn G, Akinci D, Edwards C, et al. Untargeted metabolomics of extracts from faecal samples demonstrates distinct differences between paediatric crohn's disease patients and healthy controls but no significant changes resulting from exclusive enteral nutrition treatment. *Metabolites* 2018;8
- [78] Diederens K, Li JV, Donachie GE, de Meij TG, de Waart DR, et al. Exclusive enteral nutrition mediates gut microbial and metabolic changes that are associated with remission in children with Crohn's disease. *Sci Rep* 2020;10:18879
- [79] Sinniger V, Pellissier S, Fauvelle F, Trocmé C, Hoffmann D, et al. A 12-month pilot study outcomes of vagus nerve stimulation in Crohn's disease. *Neurogastroenterol Motil* 2020;32:e13911
- [80] Williams HR, Cox IJ, Walker DG, et al. Differences in gut microbial metabolism are responsible for reduced hippurate synthesis in Crohn's disease. *BMC Gastroenterol* 2010;10:108
- [81] Saito, Y.; Sato, T.; Nomoto, K.; Tsuji, H. Identification of phenol- and p-cresol-producing intestinal bacteria by using media supplemented with tyrosine and its metabolites. *FEMS Microbiol. Ecol.* 2018, 94, fiy125.

- [82] Paul, B.D.; Snyder, S.H. The unusual amino acid L-ergothioneine is a physiologic cytoprotectant. *Cell Death Differ.* 2010, 17, 1134-1140.
- [83] Shimizu, T.; Masuo, Y.; Takahashi, S.; Nakamichi, N.; Kato, Y. Organic cation transporter Octn1-mediated uptake of food-derived antioxidant ergothioneine into infiltrating macrophages during intestinal inflammation in mice. *Drug Metab. Pharm.* 2015, 30, 231-239.
- [84] Kato, Y.; Kubo, Y.; Iwata, D.; Kato, S.; Sudo, T.; Sugiura, T.; Kagaya, T.; Wakayama, T.; Hirayama, A.; Sugimoto, M.; et al. Gene knockout and metabolome analysis of carnitine/organic cation transporter OCTN1. *Pharm. Res.* 2010, 27, 832-840.
- [85] Rajilić-Stojanović M, de Vos WM. The first 1000 cultured species of the human gastrointestinal microbiota. *FEMS Microbiol Rev* 2014;38:996-1047.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third-party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2022