Role of metabolites derived from gut microbiota in inflammatory bowel disease

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Abstract

Over the past two decades, it is improved gut microbiota plays an important role in the health and disease pathogenesis. Metabolites, small molecules produced as intermediate or end products of microbial metabolism, is considered as one of the major interaction way for gut microbiota with the host. Bacterial metabolisms of dietary substrates, modification of host molecules or bacteria are the major source of metabolites. Signals from microbial metabolites affect immune maturation and homeostasis, host energy metabolism as well as mucosal integrity maintenance. Based on many researches, the composition and function of the microbiota can be changed, which is also seen in the metabolite profiles of patients with inflammatory bowel disease (IBD). Additionally, some specific classes of metabolites also can trigger IBD. In this paper, definition of the key classes of microbial-derived metabolites which are changed in IBD, description of the pathophysiological basis of association and identification of the precision therapeutic modulation in the future are the major contents.

Core Tip: In the gastrointestinal tract of the human, a variety of microorganisms such as bacteria, fungi, viruses, archaea and protozoa are collected and considered as a community, containing a genome, suitable to the environment and the host. Microbiome, with wide functions, can ferment dietary fibres, defence pathogen, synthesize vitamin and promote immune maturation and metabolic homeostasis, which indicates microbiome is deeply integrated with human biology. However, because gut microbiota is associated with ancestral diet high in fibre, the dietary alteration resulted from western diet causes maladaptive change for this association, and products of microbial metabolism exist at a nexus between host and microbiome.

INTRODUCTION

In recent years, metabolomics based evaluation system has been used to search for biomarkers of inflammatory bowel disease (IBD) and explore its pathogenesis. It is becoming an important method of IBD research[1]. In the gastrointestinal tract of the human, a variety of microorganisms such as bacteria, fungi, viruses, archaea and protozoa are collected and considered as a community, containing a genome, suitable to the environment and the host[2]. Microbiome can ferment dietary fibres, defence pathogen, synthesize vitamin and promote immune maturation and metabolic homeostasis, which indicates microbiome is deeply integrated with human biology[3]. However, because gut microbiota is associated with ancestral diet high in fibre, the dietary alteration resulted from western diet causes maladaptive change for this association[4].

Researchers have begun to investigate the metabolites of IBD using metabonomics to explain the undetermined etiology and improve treatment outcomes[5]. In terms of diagnosis and evaluation, to date, there is no reliable laboratory test that can distinguish between the two subtypes of IBD, namely ulcerative colitis and Crohn's disease; Conventional inflammatory hematological indicators, such as platelet parameters, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), can be used to judge the correlation with IBD inflammatory activity and predict treatment effect and prognosis[6]. However, such tests cannot screen IBD patients in a timely and effective manner. Therefore, new biomarkers for IBD are still being sought, and the emergence of metabolomics techniques can help better analyze and solve these key questions.

As an integral part of systems biology, metabolomics is a method of quantitative analysis of all metabolites in a living organism, imitating the research ideas of genomics and proteomics, and searching for the relative relationship between metabolites and physiological and pathological changes [7]. The research objects are mostly small molecules with a relative molecular weight of less than 1000.

Microbial metabolites are found in a variety of biological tissues such as faeces, urine, serum, and have diversized effects on these host physiology[8]. IBD patients can be classified based on the alterations in faecal, urinary and serum metabolomes, which shows a new mechanism and association is found[9]. Additionally, several metabolite classes become the key research, for finding the association with intestinal inflammation and IBD, such as bile acid erivatives[10]. It is noted that these may affect the host, and association is found among the host, dysbiotic microbiota and an altered metabolite milieu through the inflammation model involving diet, genetic risk and the microbiota[11].

A metabolome is a collection of metabolites in a cell, tissue, or organ, consisting of a series of molecules of different chemical types, such as peptides, carbohydrates, lipids, nucleic acids, and the catalytic products of foreign substances[12]. Metabolomics studies evaluate the effects of exogenous stimuli and explore their mechanisms by quantitatively analyzing the changes of endogenous metabolites in biological systems[13]. Complete metabolomics includes sample collection and preparation; Detection and identification of metabolites; Data analysis and modeling; To establish the relationship between temporal and spatial variation of metabolites and characteristics of organisms[14]. Metabonomics is the genomics, proteomics, transcriptome study after emerging "omics", metabonomics has the advantage of the medium and small molecular substances is the study of the biology to produce the final results and metabolism, while genome and proteome have a cumulative and compensation effect, they are effective tiny changes in metabolites is amplified, therefore, The identification of metabolites is easier and more accurate to reflect the state of biological system[15].

In this review, the characteristics description of gut metabolome, and the description of the integration of metabolomics with other data are involved[16]. Furthermore, untargeted researches of IBD, targeted metabolomics with the focus on short chain fatty acids (SCFAs), bile acids and tryptophan metabolism are included[17]. In final, small molecule discovery, diagnostic potential and therapeutic manipulation of the gut microbiome–metabolome axis as the future directions is dicussed[18].

CHARACTERIZATION OF THE GUT METABOLOME

Metabolites are comprehensive products of physiological processes, and metabolic phenotypes can reflect the organism's life state. Metabolomics technology reflects the body's response to physiological stimulation or gene modification through qualitative and quantitative analysis of real-time changes in endogenous substances[19]. Compared with other omics, it detects a relatively small number of substances, but amplifies small differences at the level of genes and proteins. At the same time, effectively reduce the interference of inactive genes and inactive proteins, higher accuracy. Therefore, metabolomics has developed rapidly in the last 20 years[20].

The human body is a super organism composed of host and microorganism. Intestinal flora participates in absorption, metabolism, immunity, defense and maintenance of intestinal stability[21]. However, for a long time, the important role of intestinal flora in maintaining human balance has been underestimated due to the large variety and number, complex interrelationship and lack of efficient and convenient analysis methods[22]. In addition to maintaining intestinal homeostasis through self-formation of mucosal barrier and multi-signaling pathway regulation, co-metabolites of host and intestinal flora are also a major regulation mode. Intestinal flora participates in host metabolism, producing a large number of small molecules and hormones, and metabolites enter the host body to participate in body circulation and affect host homeostasis[23]. For example, flagellin and lip-polysac-charide produced by intestinal flora regulate human fat metabolism through nuclear factor interleukin-3 and biological clock, so intestinal flora is both metabolic participant and regulator[24]. Changes in metabolites can also predict abnormalities in the gut microbiota, For example, the increase of organic acid content in urine suggests that *Clostridium difficile*, *Faecalibacterium prausnitzii* and *Bifidobacterium SPP.*, *Subdoligranulum SPP.*, and *Lactobacillus SPP*[25].

For metabolomics, there are several analytical techniques and platforms on the basis of mass spectrometry [26]. Metabolomics research strategies can be pursued in either targeted or untargeted ways. Targeted metabolomics accurately quantifies a group of known metabolites, whereas untargeted approaches cover as many metabolites as possible[27].

Metabolomics has the advantages of high throughput, high accuracy and high sensitivity, which can detect the changes of small molecule metabolites produced by the body in the dynamic process of metabolism qualitatively or quantitatively[28]. The analysis process of metabonomics includes three parts: sample preparation, data collection and data analysis and interpretation[29]. The samples for metabonomics analysis are mainly biological specimens, which are commonly used in urine, blood, saliva, feces extract, and local pathological tissues such as colon tissue. The metabolites in the samples are usually 1H-NMR and gas chromatography[30].

Gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry (LIQUID chromatography-mass spectrometry) Lc-ms) and other methods. Bioinformatics platform is used for data processing for data analysis and interpretation, and principal Component analysis (PCA) is the most commonly used method[31]. PCA and Partial least squares discriminant analysis (PLS-DA). Since the 1990s. Since the emergence of the late Era, metabolomics has been widely used in the study of drug toxicity and mechanism, microbial and plant metabolomics, nutrition science and disease diagnosis and other fields[32].

Notably, attention should be taken to the untargeted metabolomics, though this method is a promising method to discover program[33]. Firstly, no universal method exists in sample preprocessing and extraction, particular methods in allusion to particular families of metabolites[34]. As a result, several methods can be combined. Consequently, considering different sample matrix and molecules, extraction methods show different efficacy so that it is difficult to obtain precise quantification. Secondly, there are various pitfalls when spectral data from mass spectrometry experiments are converted into to chemically annotated compounds[35]. According to different levels of evidences, various compounds are still classified as unknowns[36]. To understand them, it requires manual expertise and computational algorithms. Thirdly, it is not enough to take databases such as Metlin as the references, because it only contains a small fraction of compounds[37]. Based on estimation, higher than 90% of spectral features in a microbiome study is not known. But, according to a recent study, a molecular class can be assigned from Human Metabolome Database based on 43% of metabolite features[38]. Additionally, it is a great challenge to annotate the unknown compound. Finally, various intermediate- or low-concentration compounds or proximally produced ones in the intestine, can not be well represented in the faecal metabolome[39]. Consequently, special requirements in the sample collection and standardization, annotation and data integration at a systematic biology level as well as careful design are needed when integrating discovery projects that incorporate untargeted metabolomics with other omics technologies[40].

However, targeted metabolomics own several strongpoints in extraction, known internal standards and more precise absolute quantification, even though it is limited to spectrum[41].

UNTARGRTED METABOLOMICS IN IBD

A large number of untargeted faecal metabolomic researches among the patients with IBD are published [42]. Though these researches involve different groups, including adults and children, and different subtypes and using different metabolomics approaches, some common themes are considered[43]. metabolomics can be used to classify the groups who are healthy and with IBD[44]. However, metabolomics is not an ideal approach to discriminate Crohn's disease and ulcerative colitis.

From metabolite group, the description of dysregulation of bile acid metabolism, changes in the levels of amino acids, sphingolipids, polyaminesand reductions in levels of medium-chain fatty acids and SCFAs is consistent in faecal samples[45]. At the same time, variation in the metabolome is associated with the variation of microbiome between the healthy subjects and patients groups[46].

Bile acids can be divided into primary bile acids and secondary bile acids according to their sources, and free bile acids and conjugated bile acids according to their structural types[47]. Primary bile acids are produced in the liver and bind to taurine or glycine to form the corresponding conjugated bile acids, which are then released into the gallbladder by bile Salt export Pump for storage and further concentration[48]. After eating, bile acids are released into the duodenum, facilitating emulsification and absorption of lipids in the small intestine. At the terminal ileum, about 95% of the bile acids are reabsorbed and returned to the liver *via* the portal vein[49]. The cycle in which bile acids are secreted from the liver to the intestine, reabsorbed in the ileum, and then returned to the liver *via* the portal vein is called hepatoenteric circulation. 400-800 mg of unabsorbed bile acids enter the colon daily for further dissociation, hydroxylation, differential isomerization, and dehydroxylation, and the enzymes catalyzing these reactions are mostly produced by intestinal microorganisms[50]. The biliary saline hydrolysates involved in bile acid dissociation are mainly produced by B*acteroides, Clostridium, Lactobacillus, Bifidobacterium* and *Listeria*. Dehydrogenase or heteroisomerase involved in Bile acids oxidation or heteroisomerase reaction are mainly *Bacteroides*, *Eubacterium, Clostridium*, *Escherichia*, *Eggerthella*., *Peptostreptococcus* and *Ruminococcus*[51]. A series of reactions of bile acids in colon play an important role in maintaining the diversity and dynamic balance of bile acid pools. It is worth noting that bile acids can also affect the composition of intestinal microorganisms through bacteriostasis while intestinal microorganisms produce enzymes catalyzing the metabolism of bile acids[52].

The pathogenesis of IBD is not completely clear, genetic factors and environmental factors are important factors leading to mucosal immune response disorders. With the development of metabolomics, the researchers observed significant changes in a variety of metabolites in IBD patients compared with healthy subjects, such as fecal amino acids, bile acids, sphinomyelic acid, medium chain fatty acids, short chain fatty acids, and polyamines[53]. The change of intestinal bile acid profile is closely related to the development of IBD. A study involving 155 patients with IBD and 65 healthy controls showed that more than 2700 metabolites differed between patients with IBD and healthy people[54]. The metabolites of IBD patients were mainly manifested as sphenolipids and bile acids, while the bile acids enriched in feces of IBD patients were mainly conjugated bile acids and sulphated bile acids, while the content of secondary bile acids decreased. The analysis of serum bile acid content in patients with IBD showed that the serum bile acid metabolism was disorder, especially the secondary bile acid content in patients with active stage was significantly reduced[55].

The diversity of intestinal bile acids is closely related to intestinal microbes. Although the causal relationship between intestinal flora and IBD is still unclear, the disorder of bile acid metabolism in IBD patients is often accompanied by changes in intestinal microbial composition[56]. The diversity of intestinal flora in IBD patients decreased, and the composition ratio of intestinal flora also changed, which was mainly manifested as the decreased abundance of *Firmicutes*[57]. The proportion of Clostridia changed significantly, the abundance of *Roseburia* and *Faecalibacterium* decreased, while that of *Ruminococcus gnavus* increased. The ratio of *Faecalibacterium prausntizii* and *Escherichia coli* decreased. In turn, increased bile acid content in the gut promotes the growth of biliary tolerant bacteria such as Bilophila Wadsworthi and promotes TH1-mediated mucosal immune response[58].

Untargeted metabolomics researches are also carried out among the human biological samples, involving urine, serum and/or plasma and intestinal biopsy samples[59]. Compared with control group, the level of urinary mammalian–microbial co-metabolite hippurate is reduced, and tricarboxylic acid cycle intermediates and amino acid metabolism in IBD group are altered[60]. Generally, it is possible to distinguish the healthy subjects and the controlled ones, even though it is not completely clear to know the differences between metabolomes of patients with Crohn's disease and those with ulcerative colitis[61].

The new research results involve loss of secondary bile acids, vitamins B3 and B5 and SCFAs, and expansion of acylcarnitines and polyunsaturated fatty acids[62]. But, it is found that the result is associated with dysbiotic subset of samples. This dysbiotic subset was defined as being outside the ninetieth percentile of the healthy cohort, and 'excursions' into this state were weakly correlated with inflammatory activity[63]. This indicates that multimodal functional assessment is important in explaining the longitudinal relationship, with a higher understanding than a single classification[64]. The study on the mechanism in the future can answer the question of clinical relevance involving the determination of biomarkers of treatment response and disease course[65].

TARGETED METABOLOMICS IN IBD

Biles acids

Bile acids is synthesized from cholesterol by the liver in a multi-enzyme process, involving two products[66]. These primary bile acids exhibit amphipathic properties, which are beneficial for the lipid digestion and absorption in the small intestine[67]. When reaching the distal ileum, 95% of them are reabsorbed, and the rest is recycled and replaced, which are controlled by fibroblast growth factor[68]. Bile acids not only can regulate own synthesis, but also can exert many metabolic and immune effects through binding a series of receptors such as farnesoid X receptor (FXR), TGR5 as well as constitutive androstane receptor[69]. TGR5 is beneficial for improving insulin sensitivity, reduce energy expenditure in muscle and brown adipose tissue, and relax the gallbladder[70]. TGR5 also reduces Kupffer cell response to lipopolysaccharide by nuclear factor-κB inhibition and release of IL-1, IL-6 and tumor necrosis factor (TNF) from peripheral blood monocytes in humans. Activation of FXR has diverse effects on host metabolism[71].

Hepatic bile acid synthesis is regulated by the FXR-FGF15/19 signaling pathway. Activation of this signaling pathway reduces the expression of enzymes related to hepatic bile acid synthesis and reduces bile acid synthesis[72]. It has been found that reduced FGF19 levels in Crohn's disease (CD) patients lead to reduced activation of FXR, which inhibits the FXR-FGF15/19 pathway and leads to increased bile acid synthesis in the liver, leading to the development of intestinal inflammation[73]. Therefore, compared with the normal population, the enterohepatic circulation is blocked in IBD patients, and the activation of signal pathways that negatively regulate the synthesis of intrahepatic bile acids is reduced, leading to an increase in the total amount of bile acids in the intestinal lumen, which is also one of the causes of intestinal inflammation[73].

Restoration of bile acid pools was found to increase colon RORγ Treg cell numbers and improve host susceptibility to inflammatory colitis through bile acid nuclear receptors[74]. Recent studies have shown that ursodeoxycholic acid, as a candidate drug for nonalcoholic fatty liver disease[75], can improve intestinal barrier function, reduce intestinal inflammation, and regulate intestinal microbiota composition. Ursodeoxycholic acid and its metabolite, shicholic acid, can reduce the severity of intestinal inflammation and inhibit the expression of mucosal cytokines in a DSS-induced mouse model of colitis[76]. It has also been found that ursodeoxycholic acid and shicholic acid can inhibit the cleavage of caspase-3, a protease related to colon epithelial apoptosis[77]. Therefore, ursodeoxycholic acid may improve intestinal inflammation by inhibiting the apoptosis of epithelial cells. However, long-term high dose (28-30 mg/kg/d) ursodeoxycholic acid exposure is not protective for Ulcerative colitis (UC) patients and may increase the risk of colorectal cancer[78]. The role of ursodeoxycholic acid in the treatment of IBD is still controversial and has not been confirmed by strong clinical evidence, so further studies are needed.

Although some reports suggest that secondary bile acids such as deoxycholic acid and shicholic acid may be cytotoxic molecules that cause oxidative stress, membrane damage, interference with DNA repair, mucosal inflammation and colon cancer[79], some studies have found that Clostridium hiranonis promotes the production of secondary bile acids[80]. Relieves DSS-induced colitis because secondary bile acids at physiological concentrations inhibit the growth of *E. coli* and *B. perfringens in vitro*[81]. Clostridium scindens may also be involved in the induction of CD relief in children by producing secondary bile acids. Therefore, secondary bile acids may be a promising therapeutic agent for IBD and deserve further study[82].

MICROBIALLY TRANSFORMED BILE ACIDS IN IBD

The pathogenesis of IBD is related to genetics, environment, intestinal microecology and immunity, but the specific biological mechanism is still unclear. As an important part of intestinal microecology, intestinal flora can directly affect intestinal environmental homeostasis and participate in bile acid metabolism, while the abnormal bile acid metabolism also affects the quality and quantity of intestinal flora, and both of them are involved in the occurrence and development of intestinal inflammation[83].

For IBD patients, due to bile acid malabsorption and the inherently bidirectional nature of such interaction, it is not easy to observe the effect of dysbiosis on bile acid dysmetabolism[84]. Some researchers including Devkota carry out a ground-breaking study find that the propotion of taurine-conjugated bile acids in the mice with the diet high in milk-derived fat is higher than that in the ones with low-fat diet, which leads to the bloom of B. wadsworthia[85]. Due to the development of colitis, the change happens on IL10$^{-/-}$ mice, which indicates that western diet, altered host metabolites, dysbiosis are associated with inflammation in the genetically susceptible host[86].

Recent studies have found that bile acids are a powerful driver of intestinal microbiota maturation in newborns[87]. The effects of bile acids on intestinal flora are bidirectional, promoting the growth of bacteria dependent on bile acid metabolism on the one hand, and inhibiting the growth of bacteria sensitive to bile on the other hand[88]. Bile acids have a direct lactating effect on bacterial cell membranes and can also play an antibacterial role by activating the synthesis of antimicrobial

substances mediated by FXR[89]. FXR is expressed in liver, intestine, fat, vascular wall, pancreas, kidney and other tissues[90]. Activation of intestinal FXR can induce the encoding of antimicrobial target genes including angiogenin, carbonic anhydrase 12 and inducible nitric oxide synthase, thus exerting antibacterial effect[91]. In the process of deoxycholic acid induced intestinal inflammation, the diversity of intestinal flora decreased significantly[92]. At the level of bacteroidetes, the proportion of Firmicutes increased while the proportion of Bacteroidetes decreased. At the genus level, the proportion of Bacteroidetes increased, while the proportion of Clostridium XIVA decreased, indicating that high concentration of deoxycholic acid could aggravate the imbalance of intestinal flora[93].

Additionally, using synthetic agonist to directly stimulating FXR shows anti-inflammatory effect, and shows protection function in chemically induced colitis, but susceptibility to chemical injury is increased as the result of FXR−/− mice exhibit[94]. It should be noted that if microbial bile acid metabolizing genes is lost, the cell subtype in vivo may be reduced[95].

Repeated exposure of intestinal epithelial cells to high concentrations of bile acids is an important risk factor for IBD, and IBD patients have high levels of deoxycholic acid in the intestine[96]. In rats with colitis induced by Trinitrobenzenesulfonic acid (TNBS), apical sodium-dependent bile acid transporter (ASBT) expression decreased[97]. In IBD patients, ileal inflammation blocks hepatoenteric circulation of bile acids, leading to reduced ileal reabsorption, which may be due to inhibition of ASBT promoter expression by inflammatory cytokines, thus increasing fecal bile acids[98].

In recent years, intestinal flora has been regarded as an "endocrine organ" that regulates host physiological functions by producing metabolites such as bile acids and short-chain fatty acids. Bile acid metabolism mainly occurs in hepatocytes and intestinal flora[99].

Animal studies have shown that deoxycholic acid reduces intestinal abundance of Clostridium, a species that produces bile acid hydrolases that convert Tauro-Muricholic acid into cholic acid[100]. The decrease of this genus resulted in the accumulation of taurocholic acid, which is an FXR antagonist and inhibits the FXR-mediated signaling pathway[101]. FXR interacts with downstream fibroblast growth factor15/19 (FGF15/19) to regulate bile acid metabolism through the enterohepatic signaling pathway [102]. Once FXR and FGF15/19 signal pathways are interfered, the intestinal liver circulation of bile acids in the body is disturbed, resulting in increased bile acid levels in the intestinal lumen. High concentration of bile acids can promote the occurrence of gastrointestinal inflammation by damaging the DNA of intestinal cells[103].

In many studies, the altered faecal bile acid in IBD is described repeatedly. Considering potential confounders, Ganesan *et al*[104] perform a study and focus on the patients with isolated colonic IBD. Recent studies have shown that deoxycholic acid mediates intestinal ecological imbalance, damages the intestinal mucosal barrier, and ultimately leads to intestinal inflammation. The disturbance of intestinal microbiome - bile acid dialogue can damage intestinal barrier function and activate inflammatory signaling pathway, leading to the occurrence and development of intestinal inflammation[105].

TRYPTOPHAN

Through eating poultry, fish and dairy foods, the humans obtain tryptophan. This is an essential, aromatic amino acid and the precursor for the synthesis of several important bioactive molecules. Tryptophan metabolism is mainly produced in the gastrointestinal tract[106]. Amino acids play an important role in keeping your gut healthy. Tryptophan is an essential amino acid associated with autoimmune, and its metabolic pathway is related to the pathogenesis of inflammatory bowel disease [107].

Dietary tryptophan can be metabolized by intestinal flora into a series of indole-metabolites, such as indole-acetic acid, indole-3-acetaldehyde, indole-3-aldehydes, indole-acrylics, and indole-3-propionic acid, which act as ligands for aromatic hydrocarbon receptors, which have been implicated in the pathogenesis of IBD[108]. Indoles, indoles propionic acid and indoles acrylic acid may reduce intestinal permeability and affect mucosal homeostasis by binding progesterone X receptor. Indoleformaldehyde can activate aromatic hydrocarbon receptors on intestinal immune cells and increase IL-22 production. Indole derivatives bind to aromatic hydrocarbon receptors to produce IL-10, so oral indole-3-propionic acid protects mice from DSS-induced colitis[108]. Therefore, the disorder of intestinal flora can destroy immune regulation through its metabolites and promote the progress of intestinal inflammation.

Dietary tryptophan follows one of three main routes, and the majority is metabolized in the kynurenine pathway. and its rate-limiting enzymes include indoleamine 2,3-dioxygenase 1 in mucosal and immune cells and tryptophan 2,3-dioxygenase in the liver[109]. Serotonin pathway is considered as the second major host route, of which, the rate-limiting enzyme tryptophan hydroxylase 1 in enterochromaffin cell plays a controlled role. In final, tryptophan can be metabolized by the gut microbiota into a range of indole metabolites[110]. It is important that microbiota and microbial metabolite also play a regulation role for both host tryptophan pathways[111].

In allusion to metabolites from gut microbiome,GLP1 is released due to the stimulation of indole, but indole derivatives can act as agonists for AhR.Diet-derived AhR agonists has a great effect on maintaining the microbial load and composition and immune tolerance in the proximal small intestine

[112]. On contrary, in the distal small intestine and colon, microbiotaderived AhR agonists has a great effect. Existing researches show that limited mount of bacteria can produce AhR agonists, whereas when *C. sporogenes* is produced, which triggers IPA. Its production is associated with fldAIBC phenyl-lactate gene cluster, beneficial for maintaining barrier function and inhibiting mucosal TNF production [113].

TRYPTOPHAN METABOLISM

A study involving 535 patients with IBD shows that tryptophan metabolism is increased, and disease activity is inversely correlated with tryptophan levels[114]. Based on this analysis, it is suggested metabolism is increased through kynurenine pathway[115]. The result is also observed in the previous studies. Previous studies have reported that the expression of AhR in inflamed mucosal samples from patients with Crohn's disease is decreased, and lack of dietary tryptophan has the association with worsening colitis in mouse models[116].

Tryptophan is one of the eight essential amino acids in the human body. When tryptophan is ingested, it enters different metabolic pathways, including protein anabolism and tryptophan catabolism[117]. The tryptophan catabolism pathway includes: 5-ht pathway (about 95%), canisurine pathway (about 1%-2%), and bacterial decomposition pathway[118]. These pathways work together to maintain the balance of the body's environment and keep the body healthy. At the same time, as a drug, tryptophan is widely used in the treatment of many diseases[119]. For example, tryptophan supple-mentation can reduce mood swings and irritability in women with premenstrual syndrome, improve sleep quality in patients with sleep disorders, treat depression, and may be used as an adjunct therapy for smokers to quit smoking. Recent studies have confirmed that the metabolic pathway of tryptophan regulates gastrointestinal function[120], and changes in tryptophan metabolism can lead to gastrointestinal dysfunction and disease, such as inflammatory bowel disease, irritable bowel syndrome, celiac disease and diverticulitis. In previous studies, tryptophan levels in UC patients were significantly lower than those in healthy volunteers. The same results were seen in UC animal models. However, the researchers did not make a strict distinction between the active stage and the remission stage[121]. By comparing the differences of tryptophan in different periods of UC patients (active stage, remission stage) and healthy volunteers, this study further demonstrated that tryptophan plays a key role in the occurrence and development of UC[122]. In the experiment, we also found that serum tryptophan level was negatively correlated with inflammatory markers ESR and CRP in active UC patients ($P < 0.05$). Based on the changes of serum tryptophan in active and remission stages of UC, as well as the correlation between serum tryptophan level in active stage and inflammatory markers, serum tryptophan level in patients with UC may have important significance for monitoring the activity of UC. This also fully demonstrates the value of tryptophan in UC research[123].

Additionally, researchers carry out a research to examine the effect of mucinutilizing bacteria, and confirm that commensal *P. russellii* plays a role in reducing the susceptibility to colitis by metabolizing tryptophan to IA, through which, goblet cell differentiation is improved and inflammatory signal is reduced[124]. The same pathway occurs for IA in *P. russellii*. A novel finding that fldAIBC phenyllactate gene cluster was also identified in *P. russellii* is described. This is a new finding, making a link between a bacterium with mucin- and tryptophan-metabolizing abilities to improved epithelial integrity, so that the researchers can know the decrease in phenyllactate gene cluster in ulcerative colitis in the condition of metagenomics study involving IBD and non-IBD control individuals[125].

Intestinal flora involved in tryptophan metabolism is also an important signal pathway to regulate the immune system. It has been confirmed that tryptophan metabolism is weakened in the absence of intestinal bacteria, which is manifested as increased tryptophan content and decreased active metabolites. Intestinal tryptophan metabolites can regulate the activity of Aryl hydrocarbon receptor (AhR) in immune cells, which is a key factor to maintain immune balance[126]. Ah R can effectively balance T regulatory cells and Th17. Indole is a product of tryptophan expressed by enterobacteriaceae tryptophan enzyme, which can protect the integrity of intestinal bacterial membrane, reduce the adhesion of pathogenic bacteria, promote the production of anti-inflammatory factor interleukin-10, and reduce the production of inflammatory factors. Indole-3-propionic acid (INdole-3-propionic acid) is a product of indoles under the action of intestinal flora, and its production requires the participation of Clostridium sporogenes. Indole-3-propionic acid can inhibit inflammatory signals through progesterone X receptors and improve the integrity of the intestinal barrier[127].

SCFAs

SCFAs is a kind of beneficial metabolite and derived from microbiota-accessible carbohydrates[128]. After microbial fermentation, acetate, propionate and butyrate are produced, also other gases such as gases methane and hydrogen sulfide are included[129]. Different diets affect the proportions 50%-70% for acetate, 10%-20% for propionate and the biggest for butyrate. In allusion to dietary intervention, if the humans take more animal-based diets, the protein fermentation is rapidly changed and dysbiosis is caused[130].

SCFAs are organic fatty acids composed of one to six carbon atoms. The main production site of SCFAs is the colon. SCFAs are mostly produced by the enzymatic hydrolysis of carbohydrates in undigested and absorbed food residues by anaerobic bacteria in the colon, mainly including acetic acid, propionic acid and butyric acid, with a concentration of about 20-140 in the colon The type and quantity of mmol/L. sccfAs were mainly determined by the composition of intestinal flora, digestion time, host-microbial metabolic flux and fiber content in host food[131]. SCFAs produced by fermentation participate in the metabolism of different organs in human body and play different functions. Acetic acid produced by bacterial fermentation can be absorbed and utilized by the host and is an important source of host energy, providing about 10% of the total daily energy of the human body. After absorbed by blood, propionic acid catabolizes in the liver, participating in the process of pyruvate reversal into glucose, and may inhibit the synthesis of fat; Butyric acid is mainly used by epithelial cells and is the main energy source of epithelial cells[132].

Notably, it is observed typical dysbiosis in IBD is correlated with the lost bacterial species, which is consistent with the general result that faecal SCFA level is reduced in the metabolomics studies of human IBD[133]. If the section of colon is surgically failed, diversion colitis is caused and can be treated with SCFA enemas. Butyrate by enema is effective to treat ulcerative colitis to a certain degree, and butyrate-producing dietary fibre additives may be beneficial for the maintenance of remission[134].

SCFAs and IBD

If the butyrate-producing species in IBD patients is lost, it is observed that butyrate oxidation is impaired. On the basis off some researches, among the patients with IBD, the level of faecal SCFAs is reduced at different degrees[135]. This result is consistent with the research on the quantitative PCR targeting the butyryl-CoA: Acetate-CoA-transferase gene[136]. While the result for active ulcerative colitis and Crohn's disease indicates that the intermediate molecule lactate is increased[137]. But, due to the fact that only approximately 5% of SCFAs remain in faeces, there is no significant difference in the alterations in transit, absorption and utilization between the controlled subjects and healthy ones[138]. As a result, to know that anti-inflammatory associations with butyrateproducing bacteria may be caused by other mechanisms is also beneficial for the further study[139].

SCFAs are endogenous substances that have been widely studied for the correlation between IBD metabolomics and intestinal flora. SCFAs are products of indigestible carbohydrates under the action of *Clostridium plusseri, Rothberry, Eubacterium* and *Bifidobacteria*, mainly including acetic acid, propionic acid, butyric acid and isobutyric acid[140]. The content of SCFAs in feces can reflect the status of intestinal flora. It has been reported that the fecal butyric acid, isobutyric acid and acetic acid in patients with active IBD decreased significantly, and the contents of *Clostridium coccoides, Clostridium leptum, Clostridium pralei* and *R.i. Ntestinalis* decreased. Correlation analysis showed that *butyric-producing bacteria Clostridium plerii* and *enterorothburiae* were positively correlated with butyric acid, isobutyric acid and acetic acid, while abnormal enterobacteria tended to be normal during remission[141]. Therefore, this study suggested that the decrease of SCFAs content caused by intestinal flora disturbance was related to the incidence of IBD. The abnormal metabolism of butyric acid, which is the energy source of colon epithelial cells, and acetic acid, which is involved in adipogenesis and gluconeogenesis, suggests that inflammation leads to disturbance of intestinal energy metabolism. Acetic acid and butyric acid exert anti-inflammatory effects by activating G protein receptor 41 (GPR41) and GPR43 and inhibiting histone deacetylases. Regulating intestinal production of short-chain fatty acids has become a new target for the treatment of IBD[142].

According to a mouse study, the association between the low level and dietary fibre and susceptibility to dextran sulfate sodium (DSS)-induced colitis is constructed, in which, diet-derived SCFAs plays an important role[143]. Based on the result of DSS model, if the fatty acid receptor GPR43 in mice is lost, refractory colitis is triggered[144]. The same finding is seen in the constituents of the gut microbiota[145]. It is indicated that overactivation of the NLRP1A receptor in mice leads to loss of butyrate-producing Clostridiales, with increased IL-18 and IFNγ production[146]. In final, it is observed the gene expression of NLRP1 in inflamed regions of the distal colon in patients with ulcerative colitis is increased, and a majority of bacterial operational taxonomic units were of the order Clostridiales, which is consist with the mechanistic observation in a human cohort[147] (Figure 1).

OTHER ASSOCIATED METABOLITES

Fatty acids showed significant changes in faeces of UC patients, including a significant decrease in short chain fatty acids (SCFA, such as acetic acid, propionic acid and butyric acid) and medium chain fatty acids (valeric acid, hexanoic acid, heptanic acid, captanic acid and nonanoic acid)[148]. Fatty acids participate in energy supply through β -oxidation, and butyric acid oxidation can provide 60% energy for colon cells, again suggesting abnormal energy metabolism in UC state. SCFA plays an anti-inflammatory role through tumor necrosis factor α and NF-κB pathways and the activation of GPR41 and GPR43. The decrease of SCFA induced by inflammation can make inflammation persist. Medium chain fatty acids activate peroxisome proliferators to activate receptors for anti-inflammatory effects[149].
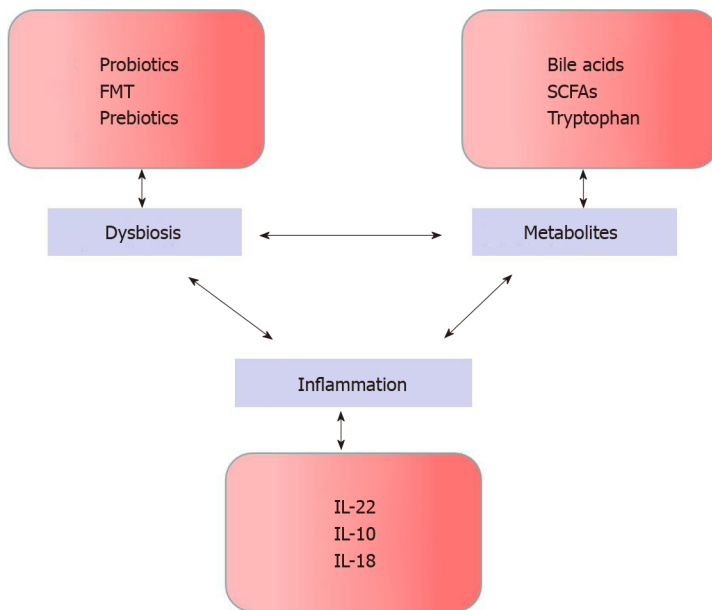
Figure 1 The cycle of circular causality in inflammatory bowel disease. FMT: Fecal microbiota transplantation; SCFAs: Short chain fatty acids.

Methylamine, trimethylamine, and trimethylamine oxide are products of choline action by gastrointestinal flora, and their reduction indicates that choline metabolism is disturbed[150]. Choline is an important component of cell membrane and the key to maintaining cell membrane integrity. Choline increases in feces of UC patients, while glycerophosphoryl choline decreases as a choline metabolite, indicating that the integrity of intestinal cell membrane changes in UC patients and inflammation may lead to intestinal mucosal damage[151]. Low density lipoprotein (LDL) and very low densit lipoprotein (VLDL) are products of fat metabolism in the liver. The decrease in serum levels of both is caused by inflammation that increases the activity of phospholipase A2, promotes the hydrolysis of phospholipids in LDL and VLDL, and inhibits the expression of lipase that hydrolyzes triglycerides[152].

Succinate metabolism in IBD is a promising direction. Succinate is the intermediate of host cells and the microbiota. In the host, succinate acts as an important pro-inflammatory signal and has been shown to be a key mediator, *via* IL-1β, of macrophage response to lipopolysaccharide[153]. For the patients with Crohn's disease, the level of succinate in the serum is increased, and increased result is obtained for the expression of the SUCNR1, Sucnr1$^{-/-}$ mice are protected against fibrosis and 2,4,6-trinitrobenzene sulfonic acid-induced colitis[154]. On contrary, the level of urinary succinate among the IBD patients is decreased, lower than that of the controlled subjects[155]. The level of faecal succinate in the patients with ulcerative colitis and Crohn's disease is higher than that in the subjects with no IBD and in DSS-induced colitis at the peak period of weight loss[156]. It is analyzed from the perspective of microbiota that succinate-utilizing Phascolarctobacterium is less abundant in both ulcerative colitis and Crohn's disease than in healthy subjects. Some researchers make efforts to find the effect of important metabolite and the role of gut microbiota[157].

FUTURE DIRECTIONS

Small-molecule discovery

The family involving G protein-coupled receptor (GPCR) ligands, N-acyl amides, is identified[158]. These are encoded by the microbiota and that are agonists to receptors that have important implications for gastrointestinal and metabolic physiology, such as the endocannabinoid receptor GPR119[159]. A study carried out by Settanni *et al*[160] uses bioinformatics mining to identify biologically conserved gene clusters in metagenomes by the computational and synthetic biology pipeline.

Using another different 'chemistry forward' method and relying on a high-throughput GPCR reporter platform, human gut microbiota is derived from 11 patients with IBD, aiming to identify relevant metabolites. This study not only identify the activation of GPCRs in a wide range based on the constituents analysis of the human gut microbiota, but also identify *Morganella morganii* converted the aromatic amino acid l-phenylalanine into phenethylamine, and the clear in vivo association between *M. morganiiproduced* and *Lactobacillus reuteri*-produced histamine and colonic transit time[161]. By relying on Human Microbiome Project dataset, these research results are obtained based on the deep mining of metagenomic assemblies, so as to determine the increase level of histidine decarboxylase genes in the

patients with Crohn's disease[162]. Using these methods, information as well as techniques from different sources to examine the microbiota for novel compounds, it is of great significance to identify bioactive molecules relevant to IBD[162].

THERAPEUTIC OPTIONS

Next-generation probiotics. Studies have shown that dysbiosis has the association with disease, which motivate the researchers to perform combined therapy involving the host process and microbiome[163]. Intestinal probiotics Akkermansia Muciniphila can induce homeostasis IgG production and antigen-specific T cell response in mice, regulate immune homeostasis, and improve the symptoms of DSS induced colitis in mice.

A recent study found that a hydrolyzed protein diet alleviates DSS-induced colitis by regulating the imbalance of intestinal flora and increasing the production of secondary bile acids by Clostridium hiranonis[164]. Other studies found that exogenous fucose can significantly reduce the inflammatory response of DSS colitis mice, and it was found that after the administration of fucose, the imbalance of intestinal flora was improved, so as to restore the normal synthesis of bile acid pools in the body and liver, and then reduce the colitis of mice.

However, potential next-generation probiotics (NGPs) invove commensals in the gut of adults, so researchers pay more attention to its metabolite production. Candidate NGPs, according to the identification of its role in specific condition based on the analysis of gut microbiome, is featured with fastidiousness, or extreme sensitiveness of oxygen[165]. As a result, how to isolate, cultivate characterize and formulate them is of a great challenge. It is possible for NGPs and other similar products performed with evaluation under the regulation of LBPs, so that investigation for the new drug procedures based on FDA152 is required[165].

In the previous studies, the potential of targeted microbiome–metabolite therapeutics in the form of the colonization resistance is found[162]. Some studies show *C. difficile* spore germination receptor binds to the primary bile acid CA derivatives and is inhibited by the secondary bile acid deoxycholic acid (DCA). When *C. scindens* to mice at risk of Clostridium difficile infection (CDI) is administrated, the resistance to CDI is improved[162].

Faecal microbiota transplantation

It is interesting that bile acid profiles show marked alteration in CDI and restored after successful fecal microbiota transplantation (FMT) which is effective in treating recurred CDI[158]. some studies demonstrate that FMT is effective in reducing the remission in ulcerative colitis. Fecal microbiota transplantation is the transplantation of faecal flora from a healthy donor into the gastrointestinal tract of a patient and can correct IBD-related intestinal flora disorders. Some scholars have found that fecal bacteria transplantation may be a safe and effective method for the treatment of refractory CD. Six weeks after receiving fecal bacteria transplantation, the severity index of Crohn's disease under endoscopy decreased significantly with CD, and the level of C-reactive protein also decreased significantly compared with the control group[162]. Patients who were in remission after fecal bacteria transplantation had more *Eubacterium Hallii* and *Roseburia Inulivorans* in their faeces and colon, which increased short-chain fatty acid biosynthesis and secondary bile acid levels. Specific bacterial and metabolic pathways in fecal bacteria transplantation are involved in inducing remission, and these findings may be of great reference value for the design of microbial therapies for IBD. The sample size may also affect the experimental results. Therefore, whether fecal transplantation is effective in alleviating symptoms of IBD patients needs to be verified by clinical studies with larger samples.

Metabolites

LBPs is a partially attractive due to its ability in getting high concentration of metabolites in the intestine, so oral metabolites or their precursors may be a great challenge in pharmacology[154]. At present, a placebo-controlled, crossover trial in allusion to tryptophan metabolites is undergoing, aiming to determine the efficiency of oral 5-hydroxytryptophan administration on fatigue among the patients with IBD[165]. For diabetes, niacin is delivered to the gut microbiota by microcapsules, which indicates that the level of gut Bacteroidetes is increased, and the marker of insulin resistance in healthy control volunteers is improved. This is an interesting finding, which demonstrates some preclinical and clinical promise is effective in treating ulcerative colitis.

CONCLUSION

Based on analysis involving technology, observational data and experimental insight, it is illuminated that microbial metabolites is beneficial for the pathogenesis of IBD. With the change of lifestyle and dietary pattern, the incidence of IBD is increasing year by year. High-fat diet changes the intestinal

microecological homeostasis and also affects the metabolism of bile acids in the body, so that the role of the dialogue mechanism between intestinal flora and bile acids in gastrointestinal diseases has attracted more and more attention. In conclusion, existing studies have shown that intestinal flora imbalance or bile acid metabolism disorder caused by various external factors can make intestinal flora, bile acid metabolism and IBD form a vicious circle of mutual influence. For the prevention and treatment of IBD, it is necessary to further explore the mechanism of intestinal flora, bile acids and their receptors in IBD. The scientific and reasonable application of probiotics, antibiotics, bile acids and their derivatives to prevent IBD will be the key problem to be solved in the future.

In this review, untargeted metabolomics and microbiome analyses are summarized, suggesting that the pattern of alteration for metabolite profiles is consisteds. Among of them, bile acids, SCFAs and tryptophan metabolites are analyzed in details. This study emphasizes the unknowns in the faecal metabolome, so creating large multinational cohorts of patients with IBD and controls, and of pipelines for microorganism–metabolite discovery and evaluation is encouraged. From the perspective of future direction, some promising fields are identified to achieve the objective. It is noted that how to integrate dietary and targeted microbiota manipulation or even microbiota reconstitution to realize the goals is a great challenge. Gut microbiota-derived metabolites is possible to become a promising direction.

FOOTNOTES

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