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REVIEW

New insights into the interplay between intestinal flora and bile acids in inflammatory bowel disease

Lie Zheng

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Abstract

Intestinal flora plays a key role in nutrient absorption, metabolism and immune defense, and is considered to be the cornerstone of maintaining the health of human hosts. Bile acids synthesized in the liver can not only promote the absorption of fat-soluble substances in the intestine, but also directly or indirectly affect the structure and function of intestinal flora. Under the action of intestinal flora, bile acids can be converted into secondary bile acids, which can be reabsorbed back to the liver through the enterohepatic circulation. The complex dialogue mechanism between intestinal flora and bile acids is involved in the development of intestinal inflammation such as inflammatory bowel disease (IBD). In this review, the effects of intestinal flora, bile acids and their interactions on IBD and the progress of treatment were reviewed.

Key Words: Intestinal flora; Bile acids; Inflammatory bowel disease; Fecal microbiota transplantation; Prebiotics

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Core Tip: With the increase of economic level and the improvement of people's living standard, the incidence of inflammatory bowel disease (IBD) in China is gradually increasing, causing a heavy burden to the society. 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 (BA) metabolism, while the abnormal BA metabolism also affects the quality and quantity of intestinal flora, and both of them are involved in the occurrence and development of intestinal inflammation.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic relapsing disease, including Crohn's disease (CD) and ulcerative colitis (UC), which has become a public health problem worldwide. With changes in diet and lifestyle, the incidence of IBD is rising rapidly worldwide. The composition of intestinal flora is considered to be the main driver of intestinal immune dysfunction in IBD, but this concept has not been fully proven[1]. Bile acids (BAs) are steroid molecules produced by interaction between the host and gut flora. It is one of the largest bioactive substances found in mammals and acts on the G protein and nuclear receptor families^[2]. In this review, we reviewed the effects of intestinal flora, BA receptors and their interactions on IBD and the progress of its treatment.

INTESTINAL FLORA AND IBD

IBD patients were found to have intestinal microbiota imbalance, which was mainly characterized by decreased intestinal microbiota diversity. The anti-inflammatory bacteria in feces of IBD patients, such as Faecalibacterium prausnitzii and Roseburia, have decreased. In the intestinal mucus layer, Roseburia can convert acetate to butyrate and produce secondary BAs, which may have anti-inflammatory effects^[3]. The proportion of Bacteroides Fragilis in IBD patients also decreased significantly. The polysaccharide A produced by The bacterium induces the development of CD4+ T cells and the anti-inflammatory function of regulatory T cells (Treg)[4]. A recent study found that the use of short-term antibiotics at an early age increased the susceptibility of mice to colitis induced by Dextran sulfate sodium (DSS), suggesting that the imbalance of intestinal flora is closely related to the incidence of IBD[5].

The intestinal flora metabolizes to produce many bioactive molecules that interact with the host. The typical representatives are short chain fatty acids, which mainly include acetic acid, propionic acid and butyric acid. These bioactive molecules not only serve as energy for intestinal epithelial cells, but also increase the secretion of anti-inflammatory cytokines such as interleukin (IL-10) and the number of Treg cells by activating the G protein-coupled receptor 5 (TGR5) on intestinal cells and immune cells[6]. It can reduce tissue inflammation and maintain the stability of intestinal mucosal barrier function. Studies have shown that butyrate can promote the recovery of intestinal barrier function and accelerate the repair of intestinal epithelial cell injury through synaptopoptin, while the loss of bacterial flora blocks the expression of synaptopoptin and increases the sensitivity to colitis and intestinal permeability in mice^[7].

Dietary tryptophan can be metabolized by intestinal flora into metabolites such as indoleacetic acid, indole3-acetaldehyde, indole3-aldehydes, indole3-acrylics and indole3-propionic acid, thus acting as ligands of aromatic hydrocarbon receptors, which are closely related to the pathogenesis of IBD[8].

Indoles, indoles propionic acid and indoles acrylic acid bind to progesterone X receptors, thereby reducing intestinal permeability and affecting mucosal homeostasis^[9]. Indoleformaldehyde secretes IL-22 by activating aromatic hydrocarbon receptors on intestinal immune cells. Indole-3-propionic acid protects mice from DSS-induced colitis by binding to aromatic hydrocarbon receptors to produce IL-10 [10]. Therefore, intestinal flora disorder can disrupt immune regulation and promote inflammation through its metabolites.

BA METABOLISM

BA is an important compound and structural component in human and animal Bile, and the liver is the main site of BA formation[11]. BA synthesis by the great influence of diet, the body from free cholic acid (CA), the primary BAs combined with secondary free CA and BA composition, type of free BA is by chenodeoxycholic acid (CDCA) and CA, primary BA combination type of cows sulfonated goose deoxycholic acid (DCA) and ammonia goose DCA, taurocholic acid as well as the composition of gca, Secondary free CA consists of CA and DCA[12]. BAs are a kind of important host-derived compounds, which have many important physiological functions and effects on the host and its intestinal flora. BAs are metabolites of cholesterol, and the transformation of BAs requires the help of intestinal microflora [13]. The classical pathway and the alternative pathway are two pathways of BA synthesis. It is regulated by cholesterol 7α-hydroxylase (CYP7A1), sterol 12α-hydroxylase (CYP8B1), cholesterol 27αhydroxylase (CYP27A1) and other enzymes related to BA synthesis[14]. It has been confirmed that in



the classical pathway of BA synthesis, cholesterol in human liver is catalyzed by CYP7A1 to produce 7α hydroxyl cholesterol, and then is catalyzed by 3β -hydroxyl- δ 5-C27-steroid dehydrogenase (3β -HSD), CYP8B1 and CYP27A1. 7α-hydroxyl cholesterol is catalyzed to produce primary BAs, free CA and goose DCA (CDCA)[15].

In the alternative pathway, cholesterol is catalyzed by CYP27A1 to produce 27α -hydroxyl cholesterol, followed by DCA in response to CYP7B1[16]. The free CA then binds to glycine and taurine by its own amide bond to form conjugated BAs which enter the intestinal tract of the body [17]. Taurocholic acid forms DCA after hydroxy release by intestinal bacteria. In the metabolism of goose DCA, goose DCA is a combination of glycine and goose DCA[18]. The intestinal bacteria of the body hydrolyze goose DCA and dehydroxyl to form stone CA[19]. Goose DCA can also react with taurine to form taurocholic acid. CYP7A1 is a rate-limiting enzyme of BA synthesis in the body, and its activity can regulate the rate of BA synthesis in the process of BA synthesis, which has been proved in an experimental study^[20]. Rats in the experimental group were fed BA, and the activity of 7α -hydroxylase was decreased and the rate of BA synthesis was also significantly decreased in the experimental group compared with normal rats [21]. After BA synthesis by bile salt export pump into the gall bladder stores, when the body after eating, in the gallbladder bile into the intestine to help the body absorb the lipid in food, the BA level in the body is not fixed, it is in the steady state environment, in the terminal ileum 95% BA enterohepatic circulation will be absorbed by weight, over 5% of conjugated BA eduction of excrement and urine, Limited BAs are reused through the enterohepatic circulatory system[22]. This process, called BA enterohepatic circulation, occurs about six times a day in the body. Most BAs are reabsorbed at the terminal ileum via the apical membrane sodium-dependent bile salt transporter (ASBT) of intestinal cells, where bile salts are transported from the intestinal epithelial cells to the basal outer membrane side into the blood with the help of intestinal BA proteins[23].

BA AND IBD

Repeated stimulation of intestinal epithelial cells with high concentration of BAs is an important risk factor for the pathogenesis of IBD, which will destroy host material metabolism and signal transduction [24]. In rats with colitis induced by Trinitrobenzenesulfonic acid, apical sodium-dependent BA transporter, ASBT expression decreased. When intestinal inflammation occurs, the intestinal barrier is damaged, which leads to the reduction of ASBT expression, and finally the destruction of enterohepatic circulation leads to the accumulation of BAs in the intestinal mucosa, and the intestinal inflammation is aggravated. In IBD patients, ileal inflammation blocks hepatoenteric circulation of BAs, leading to reduced ileal reabsorption, which may be due to inhibition of ASBT promoter expression by inflammatory cytokines, thus increasing fecal BAs[25].

Hepatic BA synthesis is regulated by the Farnesoid X receptor (FXR)-FGF15/19 signaling pathway. Activation of this signaling pathway reduces the expression of enzymes related to hepatic BA synthesis and reduces BA synthesis^[26]. Activation of FXR can improve colon inflammation, protect intestinal inflammation, reduce intestinal permeability, and reduce goblet cell extinction. The activation of FXR can also inhibit the secretion of tumor necrosis factor- α (TNF- α), interferon (IFN)- γ , IL-17 and other inflammatory cytokines in the mucosal cells of IBD patients, and up-regulate the expression of antiinflammatory factor IL-10 in the intestinal tract[27]. Therefore, compared with the healthy control group, the enterohepatic circulation of IBD patients is blocked, the negative regulatory pathway of intrahepatic BA synthesis is reduced, and the total amount of BAs in the intestinal lumen is increased, leading to intestinal inflammation[28].

BA-ACTIVATED RECEPTORS IN IBD

BA receptors mainly consist of TGR5, FXR, and pregnane X receptor (PXR), Constitutive Androstane receptor (CAR), Vitamin D receptor (VDR), PXR. It has the functions of regulating BA metabolism, glucose utilization, fatty acid synthesis and oxidation, energy homeostasis balance, immune cell function, nerve activity and so on.

TGR5 and IBD

TGR5 is a membrane receptor containing seven transmembrane regions. TGR5 mRNA expression was found in almost all human and rodent tissues, especially in gallbladder, ileum and colon[29]. Lithocholic acid (LCA) was the most effective in TGR5 stimulation. The rest were DCA, CDCA and CA. Activation of TGR5 can trigger the elevation of cyclic adenosine monophosphate (C-AMP) or epidermal factor growth. The activation of receptor (EGFR)-sarcoma (SRC) kinase affects the physiological state of cells [30].

IBD is caused by an overactive immune response to intestinal antigens. TGR5 deletion has been found to exacerbate intestinal inflammation in DSS-induced colitis mice[31]. There was no significant difference in TGR5 expression in colonic mucosa between patients with UC and the control group[32].



However, a recent study showed that TGR5 expression was significantly elevated in the colonic mucosa of children with UC, and was concentrated in lamina propria phagocytes[33]. TGR5-specific activation of macrophages isolated from the intestines of patients with CD significantly inhibited the production of TNF- α in macrophages, suggesting that the TGR5 signaling pathway may play an immunomodulatory role in IBD[34].

TGR5 is highly expressed in mononuclear macrophages, and intestinal macrophages, as the main source of cytokines, play an important role in immune homeostasis[35]. Polarization of macrophages is generally divided into two types, M1, which promotes inflammation, and M2, which suppresses inflammation. Rather than inducing macrophage activation to either phenotype alone, BA-activated TGR5 induces "mixed phenotype" macrophages, where an elevated IL-10/IL-12 ratio indicates the dominance of the immunosuppressive M2 phenotype[36]. TGR5 specific activation can reduce the production of pro-inflammatory cytokines such as IL-6, IL-1 β and TNF- α in THP1 cells, and TGR5 activation can inhibit the secretion of inflammatory cytokines in intestinal macrophages in a dose-dependent manner [37]. In terms of mechanism, TGR5 activates C-AMP and EGFR-SRC kinase pathways in response to BAs. On the one hand, BA-activated TGR5 mediated the activation of C-AMP, which further activated PKA, up-regulated the expression and activity of C-AMP binding element, and finally inhibited the translocation of NF-xB into the nucleus through a series of steps[38]. Meanwhile, the expression of antiinflammatory factor IL-10 was significantly increased after the activation of C-AMP binding element [39]. On the other hand, in M1-type macrophages, TGR5-dependent EGFR trans-activated SRC kinase activation leads to NF-KB activation through downstream protein kinase C, and increased expression of pro-inflammatory cytokines IL-1 β , IL-6, and TNF- α [40]. In summary, BA-TGR5 signal transduction regulates a complex balance between pro-inflammatory and anti-inflammatory cytokines in the gut.

FXR and IBD

A nuclear receptor superfamily member, FXR, with BA ligand activity was first identified in a 1995 study of rat liver C DNA[41]. FXR mainly exists in the intestine, liver and kidney, especially in the ileum, colon and liver, and is involved in the regulation of a large number of physiological activities of the human body. In addition to regulating BA metabolism and transport, FXR also plays a key role in regulating lipid and glucose homeostasis, inflammatory response, and barrier function[42].

BAs can be classified according to their affinity for binding FXR in vitro. CDCA has the highest excitatory effect on FXR, followed by CA, DCA and LCA[43]. Compared with their natural forms, the sugar-taurosulfo-conjugated forms of CDCA, DCA and LCA are more effective agonists. Among the synthesized FXR agonists, GW4064 selectively excites FXR with high affinity, which is widely used in experimental studies[44].

FXR plays an important role in the development and progression of IBD. Early colon cell tests showed that FXR gene knockout mice were more likely to develop severe intestinal inflammation than wild-type mice, suggesting that intestinal FXR could reduce intestinal inflammation[45]. It has been found that activation of intestinal FXR can inhibit NF-KB activation and reduce intestinal inflammation through multiple pathways [46]. FXR attenuates the translocation of NF- κ B subunit P65, thereby inhibiting NF-KB transcription, reducing the gene expression of pro-inflammatory factor IL-8, and alleviating intestinal inflammation^[47]. Activation of intestinal FXR expression can inhibit intestinal tolllike receptor 4-myeloid differentiation factor 88 signaling pathway, thereby down-regulating NF-KB expression and alleviating intestinal inflammation[48]. In addition, activation of FXR can up-regulate the expression of IL-10, an anti-inflammatory factor in the intestinal tract, thus exerting an anti-inflammatory effect. It is concluded that activation of intestinal FXR can reduce intestinal inflammation and play a protective role in IBD intestine, and FXR is expected to become a drug target for IBD treatment [49]. It is important to note that FXR has different functions in different tissues, and currently there are no intestinal FXR specific agonists. Therefore, when FXR is used as a treatment for IBD, it may activate hepatic FXR and cause adverse reactions^[50].

Intestinal BA accumulation can cause the proliferation and apoptosis of intestinal epithelial cells, leading to IBD. FXR can regulate BA synthesis and reabsorption to maintain intestinal BA homeostasis [51]. On the one hand, FXR can regulate the expression of fibroblast growth factor (FGF), thereby inhibiting the expression of CYP7A1 and reducing BA synthesis [52]. On the other hand, intestinal FXR also promotes the expression of organic solute transporter alpha-beta (OST α/β), Inhibit the expression of ASBT in ileum, thus promoting the excretion of intestinal BA and alleviating the injury of intestinal BA[53]. Therefore, intestinal FXR has a protective effect on the intestinal tract of IBD and can be used as a therapeutic target for IBD. As a synthetic FXR agonist, GS-9674 alleviates cholestatic intestinal injury by activating FXR in intestinal epithelial cells to up-regulate FGF19 expression[54]. Based on 6-alphaethyl-chenodeoxycholic acid (6-ECDCA), which is mainly used for the treatment of cholestatic diseases, the 6-ECDCA can activate FXR, regulate the expression of OST α/β and ASBT, and improve the intestinal cholestasis[55]. However, there is no clinical trial of 6-ECDCA as a treatment for IBD, but with the deepening of basic research, it is expected to become a treatment for IBD targeting FXR.

PXR and IBD

PXR is an important member of the nuclear receptor superfamily and is mainly expressed in colon and liver. Studies have shown that PXR plays an important role in maintaining intestinal homeostasis, and



its gene deletion leads to an increased risk of IBD[56]. Moreover, PXR not only participates in intestinal immune response by regulating inflammatory signaling pathways, but also can receive endogenous signals to regulate intestinal homeostasis, so it is expected to become a new therapeutic target.

Excessive inflammatory response is the most prominent feature of IBD. NF- κ B is the most classic inflammatory signaling pathway, and when activated, it releases a large number of inflammatory factors, exacerbating IBD[57]. The nuclear receptor PXR is an upstream regulatory factor of NF- κ B, and can regulate NF-kB through PXR to reduce intestinal inflammation. We found that compared with wildtype mice, NF-KB was activated in the colon of PXR knockout mice, resulting in the release of a large number of inflammatory factors (such as TNF- α , IL-6, etc.), and increased intestinal inflammation [58]. It is speculated that PXR gene deletion may activate NF-KB pathway and increase intestinal inflammation. Activation of PXR receptor can inhibit NF-KB expression in the intestinal tract, thereby reducing the level of downstream inflammatory factors and reducing intestinal inflammation[59]. PXR protects the intestine by regulating NF-KB signaling. In addition, PXR also regulates non-classical inflammatory pathways, such as transforming growth factor (TGF- β 1) expression, which plays a role in reducing intestinal inflammation. Therefore, PXR is considered as one of the most promising targets for IBD treatment[60].

Intestinal mucosal barrier is an important physical barrier to prevent toxic substances from invading the intestine, maintaining intestinal mucosal homeostasis and avoiding intestinal injury. When the intestinal permeability is increased, the intestinal mucosal barrier function is reduced, which can directly lead to the occurrence or exacerbation of IBD symptoms. Increased intestinal permeability in IBD patients is closely related to the abnormal expression of Myosin light-chain kinase (MLCK) and C-Jun n-terminal kinase 1/2 (JNK1/2)[61]. However, nuclear receptor PXR can reduce intestinal permeability by down-regulating the expression of MLCK and JNK1/2, and play a role in maintaining intestinal mucosal barrier function. It was found that MLCK expression and myosin II light chain phosphorylation level in colon tissue of IBD patients were significantly increased, and intestinal permeability was increased[62]. Pregnenolone 16-alpha carbonitrile (PCN), a PXR agonist, can inhibit MLCK and myosin II light chain phosphorylation, reduce the permeability of the intestinal barrier, and avoid intestinal injury. The up-regulation of JNK1/2 expression in intestinal cells of IBD patients increases intestinal permeability, while PCN can down-regulate intestinal JNK1/2 expression by inducing GADD45β protein transcription, reducing intestinal permeability and avoiding toxin invasion [63]. Therefore, PXR can maintain intestinal mucosal barrier function, and its ligand can be used to treat IBD. However, PXR receptor agonist PCN is only used in animal experimental studies, and has not been used for clinical treatment. The study of intestinal protective mechanism of PXR will promote the application of PXR agonists in clinical treatment[64].

In human body, metabolic enzymes and transporters are highly expressed in the intestine, among which metabolic enzymes are mainly involved in the detoxification process of intestinal toxic substances, such as CYP3A4 and CYP3A11[65]. Transporters are mainly involved in the excretion of intestinal cytotoxic substances, such as P-glycoprotein (P-GP)[66]. Studies have shown that the reduced expression of metabolic enzymes and transporters involved in the metabolism of heterogenic substances in the intestine of IBD patients leads to the accumulation of intestinal toxins, and PXR is an upstream regulatory factor of multiple metabolic enzymes and transporters, which can regulate their expression to play a detoxification role^[67]. Activation of PXR can significantly up-regulate the expression of CYP3A4 gene in wild-type mice, thus improving the symptoms of abdominal pain and diarrhea. The expression level of P-GP in colon tissues of IBD mice prepared by DSS was down-regulated, and the poison was accumulated in intestine. PXR could reduce the accumulation of poison by regulating the expression of P-GP[68]. PXR can up-regulate the expression of drug metabolism enzymes and transporters to eliminate intestinal toxicity, and has a protective effect on IBD intestinal tract. Tanshinone II A, the active ingredient of Salvia miltiorrhiza in labiaceae, is A highly active PXR agonist, which mainly upregulates the expression of PXR to increase the expression of downstream metabolic enzymes and transporters, thereby promoting intestinal toxin metabolism and efflux, and improving the symptoms of IBD[69]. PXR agonists speed up the metabolism of other drugs in the body, reducing the potential for adverse reactions to these drugs. However, large-scale activation of PXR can up-regulate the expression of metabolic enzymes and transporters, and then affect the metabolism of other drugs, leading to decreased efficacy and even induced drug interactions, which may limit the clinical application of PXR agonists in the treatment of IBD^[70]. It can be seen from the above that the protective effect of PXR on the intestinal tract of IBD has been preliminarily confirmed. Based on its protective mechanism, PXR can be used as a target for drug therapy of IBD, providing a new perspective for innovative drug research and IBD treatment.

CAR and IBD

CAR is a nuclear receptor for steroidal hormones, which is mostly expressed in intestinal epithelial cells. Although the protective mechanism of CAR against IBD is not fully understood, there is increasing evidence that it also plays a key role in regulating intestinal inflammation and protecting the intestinal mucosal barrier[71]. Biopsies of the intestinal mucosa of IBD patients showed that CAR gene expression was strongly associated with intestinal inflammation levels. In IBD mice, intestinal mucosal barrier was disrupted, and the activation of p38MAP kinase by CAR agonist CITCO enhanced IEC cell migration



and accelerated intestinal mucosal healing^[72]. In addition, CAR significantly regulates metabolic enzymes and transporters located in the intestine, and protects the intestine from toxic interference by inducing the expression of metabolic enzymes and transporters[73]. These results suggest that CAR, like PXR and FXR, can play a protective role in IBD by reducing intestinal inflammation and maintaining intestinal mucosal homeostasis, but the specific mechanism remains to be studied [74]. In conclusion, CAR is also a promising drug target for IBD treatment, and further study of its protective mechanism against IBD can provide reference for drug development targeting CAR.

VDR and IBD

VDR is a member of the nuclear hormone receptor superfamily, which exists in all the target tissues of vitamin D3, such as intestinal tract and liver[75]. VDR, as an important nuclear transcription factor, intervenes in many downstream genes through specific binding with ligands. Studies have confirmed that VDR gene polymorphism is associated with the risk of IBD, and there are differences in VDR genotypes among different genders and populations[76]. Human proteomics shows that VDR is highly expressed in the normal small intestine and colon, but reduced intestinal VDR expression and impaired VD/VDR signaling pathway were observed in patients with CD and UC[77]. Therefore, intestinal VDR plays an important role in the occurrence and development of IBD.

Loss of VDR in intestinal epithelial cells leads to activation of NF-KB signaling, which promotes production of pro-inflammatory cytokines [78]. A genome-wide association analysis showed that VDR binds to 42 disease-associated single nucleotide polymorphisms, of which one-third significantly affect transcription factor NF-KB binding and gene regulation. Immunoprecipitation results suggested that VDR had a protein-protein interaction with IKK β upstream of NF- κ B[79]. VDR inhibited ser-177 phosphorylation of IKKβ by binding to IKKβ, thereby inhibiting NF-κB activation and IL-6 elevation induced by TNF- α , and improving intestinal inflammation[80].

A meta-analysis shows that variations in the VDR gene significantly affect the human gut microbiome [81]. It was found that the protective effect of probiotics on IBD depends on the epithelial VDR signaling pathway. In the normal intestinal flora of mice, the distribution and abundance of bacteria in the intestinal epithelium after VDR knockout were significantly changed, mainly manifested as increased abundance of Bacteroides fragilis in mice with VDR deletion[82]. In addition, intestinal epithelial VDR deletion exacerbated the intestinal inflammatory damage caused by sodium glucan sulfate modeling in mice, while the intestinal epithelial VDR deletion mice and wild-type control mice were reared in the same cage for modeling, this difference in intestinal inflammation caused by different genotypes disappeared[83]. This indicates that VDR deficiency causes intestinal flora disorder and aggravates the occurrence and development of IBD. Another study showed that defective VDR expression in intestinal Panth cells leads to reduced lysozyme secretion, impaired antimicrobial activity of pathogenic bacteria, and thus increased inflammatory response[84]. Other studies have found that lack of VD in the diet of mice can cause intestinal microflora disorder, mainly manifested in increased abundance of Helicobacter hepaticus and decreased abundance of probiotics Akkermansia Muciniphila[85]. Therefore, VDR genes may play an important role in homeostasis and signal transduction between the microbiome and host in intestinal inflammation.

Some studies have speculated that metabolites of intestinal flora regulate intestinal immune responses in a VDR dependent manner[86]. Butyrate is a short-chain fatty acid produced by intestinal microorganisms. 2% sodium butyrate in drinking water increased intestinal VDR expression and inhibited inflammation in mice with colitis[87]. In addition, secondary BAs and shicholic acids produced by intestinal flora metabolism inhibit Th cell immune response by activating VDR of CD4+Th cells, thereby reducing IFN-γ and IL-2 production in intestinal inflammation[88]. In conclusion, VDR related basic studies provide many new ideas and explanations for the mechanism of intestinal flora in IBD.

Sphingosin1-phosphate receptor 2 and IBD

Sphingosine-1 (S1P) is an active sphingosine-1 that participates in the regulation of various cell functions under physiological and pathological conditions[89]. S1P can function directly as intracellular signaling molecules or extracellular by activating 5 G protein-coupled receptors (GPCRs). S1P has been shown to be a key regulator of proliferation, migration, and survival of many cell types. The expression of 5 S1PRs was different in different tissues or organs. All five S1PRs were detected in the human intestine, but the expression levels of S1PRs were different[90]. It has been reported that S1P regulates the expression of e-cadherin by activating S1PR2 to enhance intestinal epithelial cell barrier function. It has also been reported that S1P reduces intestinal epithelial cell apoptosis through the Akt dependent pathway[91,92]. These studies suggest that S1P and its receptor can promote intestinal epithelial cell proliferation and enhance epithelial cell barrier function, and play a protective role in intestinal mucosal barrier.

Retinoid-related orphan receptor gammar and IBD

Retinoid-related orphan receptor gammar (RORy T) is a specific transcription factor controlling Th17 cell differentiation. Treg cells are from the same source as Th17 cells, and they are closely related [93].



Treg cells play an important role in maintaining the body's immune tolerance state and the stability of internal environment, and preventing the occurrence of autoimmune diseases. Th17 cells, a new type of CD4+ cell subpopulation discovered in 2003, play a pro-inflammatory role mainly by secreting cytokines such as IL-17, IL-22 and IL-21[94]. RORY T is a transcriptional activator that plays a key role in the differentiation of Th17 cells. Inhibition of RORy T expression can inhibit the differentiation of nonsensitized T cells into Th17 cells[95]. It has been found that RORy T directs the differentiation of proinflammatory Th17 cells and regulates the production of IL-17 in peripheral blood[96]. Therefore, it is reasonable to believe that RORY T can be used as an important target for the treatment of autoimmune and inflammatory diseases. Treg cells are newly discovered T cell subsets that negatively regulate the body's immune response, and their immune regulatory function is closely related to the continuous expression of Foxp3[97]. Foxp3 is considered to be a key transcription factor and specific marker of Treg cells, which can regulate the expression and function of multiple genes after binding to chromosomes, thus controlling the development and function of Treg cells[98]. In vitro studies have shown that TGF- β can inhibit RORyt function and promote Treg differentiation by inducing Foxp3 expression, and the full-length Foxp3 subtype can bind to RORY T to inhibit RORY T function[99]. In the presence of proinflammatory cytokines, Foxp3 levels decreased and RORy T levels increased, ultimately promoting Th17 cell differentiation. In a mouse model of colitis, RORY T binding reduced IL-17 production and Th17 cell count and reduced intestinal inflammation[100]. Studies have shown that Th17 lymphocytes are involved in the pathogenesis of CD and UC. Increased IL-17 expression in mucosa and serum of IBD patients was associated with increased RORy T expression and Th17 cell number[101]. Therefore, Th17 and Treg cells antagonize each other functionally and are closely related in differentiation. Under normal circumstances, they maintain a relative balance, which is beneficial to maintain the immune stability of the body[102]. At present, the relationship between Th17/Treg cell imbalance and disease occurrence and development has become the focus of people's attention.

INTERACTION BETWEEN INTESTINAL FLORA AND BAS

Intestinal flora and BA synthesis

Intestinal flora can further modify the synthetic BAs to form a series of intestinal BA metabolites. These metabolites can act as important signaling molecules to regulate cholesterol metabolism and energy balance of the host through BA receptors[103]. The involvement of intestinal flora in the synthesis of BAs increases the diversity of BAs and the hydrophobicity of BA pools, which is conducive to BA excretion[104]. The modification of BAs by intestinal flora mainly includes early uncoupling, dehydrogenation, dehydroxylation and differential isomerization of BAs. Bile salt-hydrolases (BSHs) produced by intestinal bacteria catalyze BSHs, and then uncouple bile c-24 with n-acetyl amino bonds bound to amino acids to form free BAs^[105]. Studies have found that there are many bacteria in the intestinal tract of the organism that can produce BA salinase, such as bifidobacterium, Lactobacillus, Bacteroides, Listeria and Clostridium have BA salinase activity[106]. 7α-hydroxyl dehydrogenation occurs in free BAs under the catalytic action of Clostridium and Clostridium, and hydroxyl steroid dehydrogenase (HSDH) produced by intestinal microflora such as Clostridium, Eubacter, Ruminococcus, Bacteroidetes and Digestive streptococcus dehydrogenases at the positions of C-3, C-7 and C-12. Secondary BAs DCA and shicholic acid (LCA) were then produced, as shown in Figure 1. Increased LEVELS of DCA have been associated with obesity and cancer in mice, further supporting the important role of BA conversion in the intestinal flora in host metabolism[107].

Metabolome study found that in C57BL/6 mice, under the action of intestinal microflora on BA dehydroxylation and decoupling, the primary BA gradually decreased and the secondary BA gradually increased during the continuation process from small intestine to large intestine[108]. Compared with specific pathogen-free (SPF) mice fed a normal rich-diet diet, the changes of BA components in feces of SPF mice fed with minimal chemical diet and germ free (GF) mice fed with normal diet were detected by mass spectrometry. Levels of liver-derived taurine conjugated primary BAs in the intestinal tract of the minimal pathogen-free mice were significantly decreased compared with those in the RICH-diet SPF mice, while they were increased in the RICH-diet GF mice[109]. The results indicate that diet can directly control the hepatic synthesis of BAs, and the intestinal flora mainly controls the modification process of BAs in the intestine.

As a potential regulator of gut microbiota composition and host metabolism, microbial HSDH may open up new pathways for how the microbiota regulates signaling pathways in the host.

THE EFFECT INTESTINAL FLORA ON BAS VIA FXR

Study method of alcohol receptor in closely related to the metabolism of BA synthesis of highly expressed in the organs, such as the liver, small intestine, BA synthesis of organisms play a regulatory role of BA in the BA, goose DCA and LCA and DCA is liver alcohol receptor agonist, CYP7A1 is the



Zheng L. Interplay between intestinal flora and bile acids in IBD



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Figure 1 Synthesis and metabolism of bile acids. DCA: Deoxycholic acid; LCA: Lithocholic acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid.

promoter of BA synthesis[110]. In the liver, BA-activated FXR induces the expression of a small heterodimer partner (SHP) that binds to liver receptor homologous protein-1, thereby inhibiting *Cyp7a1* gene expression. In addition to local effects in the liver, FXR is also activated by BAs in the distal ileum. FXR induces expression of FGF15 (FGF19 in humans) in the ileum. So farnesol receptor-FGF15/19 signaling pathway plays an important role in BA synthesis. In the study of lactobacillus rhamnosus GG (LGG) on BDL mice, it was found that compared with the sham operation group, In BDL mice, the content of DCA (deoxycholic acid is a strong agonist of FXR) and the concentration of T- α MCA and T- β MCA (MCA is an antagonist of FXR) were decreased, and the mRNA expression of CYP7A1 and FGF15 in BDL mice were increased[111]. The BA content and the size of total BA pool in liver were significantly increased, and the BA content and total BA pool size were significantly decreased after LGG treatment. At the same time, it was found that the mRNA expression level of FXR target gene SHP and FGF15 were significantly decreased in the ileum of BDL mice, while LGG could inhibit the decrease of FGF15 protein level[112].

This confirms that in BDL mice, LGG treatment-mediated reduction in BA synthesis is achieved through upregulation of the intestinal FXR-FGF15 signaling pathway[113]. Other studies confirm the BA levels of traditional breeding mice, and the germ-free mice raised in BA levels, may be due to the traditional breeding mice intestinal microbial flora make mice reduced levels of MCA, activation of FXR, make FGF15 higher expression, thus inhibiting the activity of CYP7A1 to inhibit the synthesis of BA [114].

It was found that after fecal microbiota transplanta-tion (FMT) of sterile mice received FMT, the expression of FXR in intestinal epithelium was up-regulated, and FXR further induced the expression of FGF15, thereby inhibiting the activities of CYP7A1, CYP8B1 and other enzymes. Thus inhibiting the synthesis of BAs[115]. The expression of FGF15 in ileum was inhibited by antibiotics, and the expression level and activity of CYP7A1 in liver increased significantly, resulting in BA synthesis. *Parabacteroides distasonis* was used to treat obese mice. It was found that *Parabacteroides distasonis* can hydrolyse a variety of conjugated BAs, convert primary BAs into secondary BAs (LCA, UDCA, *etc.*), and produce a large amount of succinic acid[116]. LCA and other secondary CAs increased the level of FGF15 in serum and colon, and decreased the level of CYP7A1 in liver by activating the intestinal FXR signaling pathway. UDCA can repair intestinal wall integrity and succinic acid can improve host sugar metabolism disorder[117].

TGR5 can also be activated by intestinal flora to inhibit BA synthesis. TGR5 is a GPCR, and it has been found that compared with WT mice, the BA pool size of mice lacking the *TGR5* gene in a high-fat diet decreased by 21% to 25%, and body fat accumulation increased, and body mass increased[118]. Intestinal bacteria can also induce the expression of cardiac transcription factor 4 in intestinal epithelial cells by stimulating them continuously, and inhibit the expression of ABST, resulting in reduced BA reabsorption in the terminal ileum[119].

In conclusion, intestinal flora not only participates in the processes of BA decoupling, dehydrogenation and dehydroxylation, but also negatively regulates BA synthesis through the FXR-FGF15/19 pathway.

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INTESTINAL FLORA PARTICIPATES IN THE REGULATION OF NORMAL METABOLISM OF BAS

The metabolism of BAs in the body is mediated by intestinal flora. The whole metabolic process of BAs synthesized in liver cells is regulated by intestinal flora. The intestinal flora in patients with gallstones is unbalanced and the metabolism of BAs is also in disorder, which may be because the imbalance of intestinal flora in the body affects the hepatoenteric circulation of BAs in the body and causes the metabolic disorder of BAs and cholesterol. BSHs produced by bifidobacterium, Clostridium, Lactobacillus, Listeria, enterococcus, bacteroidetes and other bacteria in the intestinal tract of the body can reduce the production of cholesterol in serum[120]. BSHs is mainly involved in the uncoupling of conjugated BAs to form free BAs in the body. When intestinal flora in the body is unbalanced, BSH activity increases and free BA content increases, which then activates the NEGATIVE feedback regulation system of FXR-FGF15/19 BA, resulting in reduced BA synthesis content and over-saturated cholesterol[121]. If it is not dissolved effectively by BAs, it will remain as a deposit, slowly turning into a stone state. In addition, lactobacillus and bifidobacterium in intestinal flora also has the ability of removing cholesterol, mainly through the intake to the cholesterol assimilation or binding to the cell or and BA form coprecipitation [122], some intestinal bacteria also can produce cholesterol reductase, catalytic cholesterol into insoluble prostaglandins, and turn it into the feces. Other studies have confirmed that intestinal flora mediates normal metabolism of BAs. In the study of liver cancer, antibiotics can increase the Natural kilkR T cell (NKT) in mouse liver, and CXCL16, a chemokine expressed by hepatic sinusoid endothelial cells, can inhibit the growth of liver tumors by regulating hepatic NKT cells[123]. The primary BAs in liver can promote the expression of CXCL16, while the secondary BAs can inhibit the expression of CXCL16. When mice were treated with vancomycin (an antibiotic), vancomycin eliminated gram-positive bacteria (including those involved in primary BA conversion) from their intestines and induced the accumulation of hepatic NKT cells, thereby inhibiting the development of liver cancer[124]. At the same time, vancomycin-treated mice were fed with secondary BAs or clostridium bacteria that colonized and transformed primary BAs, and the accumulation of NKT cells in the liver was reduced and the antitumor effect was reduced[125].

Studies have shown that in patients with UC, the levels of secondary BAs (deoxycholic acid and stone CA) in the intestinal tract are reduced, and rumen bacteria and other bacteria that convert primary BAs into secondary BAs are also reduced [126]. Supplementation of secondary BAs with G-protein-coupled receptor for BAs (TGR5) improved intestinal inflammation in mice with colitis. In the enterohepatic circulation with normal enteral nutrition, BAs activate the enterofarnicol receptor (FXR), triggering the release of FGF19 into the portal vein circulation [127]. FGF19 regulates the synthesis of intrahepatic BAs through enteral nutrition. This signaling pathway is impaired in patients with total venous nutrition (TPN), and studies have shown a decrease in serum FGF19 levels in subjects receiving TPN. Due to intestinal dysfunction, the intestinal microbiota in TPN patients is severely altered. Changes in intestinal flora can affect patients' immune response and promote endotoxin secretion, thus negatively affecting liver function, suggesting that intestinal flora affects the related BA signaling pathway in the treatment of TPN[128].

BAS AFFECT THE COMPOSITION OF INTESTINAL FLORA

The regulation between intestinal flora and BA metabolism is bidirectional, intestinal flora can participate in the synthesis and normal metabolism of BA, and BA can in turn regulate the composition of intestinal flora. The effects of BAs on intestinal flora include damage to bacterial cell membrane, destruction of bacterial amino acids, nucleotides and carbohydrate metabolism, activation of innate immune genes in the small intestine to change the composition of intestinal flora and affect body metabolism[129]. The size and diversity of BA pools can affect the intestinal flora of the body. Studies on colorectal cancer (CRC) patients found higher concentrations of Clostridium 7α-dehydroxy in feces, which can promote the production of secondary BAs. High levels of clostridium 7α -dehydroxy increase the content of secondary BAs in the intestinal tract, leading to an imbalance of intestinal microflora that promotes the development of CRC[130]. High-fat diet can cause the imbalance of intestinal flora in mice. When adding ursodeoxycholic acid into the diet of high-fat diet mice, it was found that the intestinal flora in mice restored to the similar level as normal mice (for example, the contents of Faecalis and Ackmanniella increased, while the contents of Spironella and ruminococcus decreased)[131]. The effects of BAs on the composition of intestinal flora can also be mediated by FXR. When mice were fed a high-fat diet, the levels of T-BMCA in FXR deficient mice increased and the abundance of *Firmicutes* increased while the abundance of *Bacteroidetes* decreased compared with the control mice. It is possible that the FXR-mediated high-fat diet altered the BA pool in mice, leading to changes in gut microbiota[132].

BAs can also change the composition of intestinal flora by inhibiting the growth of intestinal bacteria, and the antimicrobial activity of non-conjugated BAs is stronger than conjugated BAs, and the sensitivity of gram-positive bacteria to BAs is stronger than gram-negative bacteria[133]. It was found that the synthesis of BA in rats with liver cirrhosis was lower than that in healthy rats, and the total



bacterial content in ileum and bacterial translocation rate were increased[134]. After BA injection, the bacterial quantity in ileum of cirrhotic rats returned to healthy level and the bacterial translocation rate decreased. Obeccholic acid (OCA) is a BA derivative that activates FXR to inhibit endogenous BA synthesis. When healthy subjects were given doses of OCA, they found increased levels of grampositive bacteria in their small intestines, such as Lactococcus lactis, Lactobacillus casei and Streptococcus thermophilus, while normal levels of BA inhibited the growth of these bacteria. When healthy mice were fed OCA, the BA content in their small intestine decreased, while the content of firmicide bacteria, mainly gram-positive bacteria, increased, suggesting that OCA can inhibit BA synthesis through activation of FXR and thus alter the intestinal microflora [135-137].

INTESTINAL FLORA, BA METABOLISM AND IBD

Probiotics and prebiotics

Exogenous supplementation of probiotics to regulate BAs to prevent or treat diseases has been demonstrated in metabolic diseases, such as hypercholesterolemia or obesity [138]. Probiotics can relieve the clinical symptoms of IBD patients to different degrees. Probiotic mixture VSL#3 can significantly reduce cryptitis, and Clostridium butyricum MIYAIRI is also better than placebo in clinical efficacy, but its exact efficacy needs to be further studied [139]. BAs levels are reduced in IBD patients and experimental enteritis animals[130]. However, the improvement of enteritis symptoms by exogenous *Clostridium* scindens supplementation has only been demonstrated in animals, and clinical studies on strains that regulate BSH or 7α dehydroxylase in a targeted way are lacking[140].

Fecal microbiota transplantion

FMT is a process in which feces from healthy people are transferred to patients, and it was first used to treat patients with recurrent Clostridium difficile infection. Recent studies have shown that FMT can significantly improve the composition of BAs in the gut of patients with C. difficile, increase the content of secondary BAs and prevent C. difficile colonization[141]. Because of its apparent efficacy in treating recurrent C. difficile infection, it has been applied to other intestinal diseases, such as IBD, IBS, and pancreatitis. In IBD studies, FMT has shown significant efficacy in inducing remission of UC. A study of UC in children showed that the gut microbiota and metabolome of FMT responders were significantly more similar to those of healthy people[141].

Antibiotics

Studies have found that antibiotics on DCA induced inflammation of the intestinal protective, may significantly reduced intestinal flora diversity and broad-spectrum antibiotics, reduced intestinal tract has 7 alpha to hydroxylation enzyme bacteria, lead to waste source of primary BA dominate in the host, and the source of intestinal flora secondary BA decreased [140]. However, the choice of antibiotics is also important. In a 12-wk clinical study, the nonabsorbable antibiotic rifaximin showed higher remission rates in patients with active CD. Given that different antibiotics have different effects on BA concentration and composition as well as IBD, antibiotic and patient selection will be important in evaluating antibiotic efficacy against IBD in the future[141].

CONCLUSION

Changes in lifestyle and diet have contributed to the increasing incidence of IBD. High fat diet not only changes the characteristics of intestinal flora, but also affects the metabolism of BAs in intestinal lumen. Therefore, studies focusing on BAs and gut microbiota have attracted much attention in digestive diseases. Characteristic changes in the gut microbiota in IBD patients affect the composition of the BA pool. Secondary BAs, as anti-inflammatory factors, may be non-invasive biomarkers in mucosal healing. The emergence of novel metabolomics has revealed the bacterial species that transform BAs and the mechanism of signaling pathways that regulate the development of IBD disease. The interaction between gut microbiota and BAs represents a promising new therapeutic approach for IBD. Some animal studies have shown the important value of the gut microbial-BA axis. However, there is no clear evidence of a similar effect in clinical practice, and further clinical studies are needed to verify it.

FOOTNOTES

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