Effect of gut flora mediated-bile acid metabolism on intestinal immune microenvironment

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Abstract

According to reports, gut microbiota and metabolites regulate intestinal immune microenvironment. In recent years, an increasing number of studies reported that bile acids (BAs) of intestinal flora origin affects T helper cells and Treg cells. Th17 cells play a pro-inflammatory role and Treg cells usually act an immunosuppressive role. In this review, we emphatically summarized the influence and corresponding mechanism of different configurations of the LCA and DCA on intestinal Th17 cells, Treg cells and intestinal immune microenvironment. The regulation of BAs receptors G protein-coupled bile acid receptor 1 (GPBAR1/TGR5) and farnesoid X receptor (FXR) on immune cells and intestinal environment are elaborated. Furthermore, the potential clinical applications above were also concluded in three aspects. These above will help researchers better understand the effects of gut flora on the intestinal immune microenvironment via BAs and contribute to the development of new targeted drugs.

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Running title: Bile acids regulate immunocytes

Highlights:

1. Intestinal flora enzymes metabolize small molecules of bile acid.

2. Multiple configurations of bile acids regulate Th17 and Treg cells and affect the intestinal immunity.

3. Bile acid molecules regulate the intestinal immune microenvironment by activating or inhibiting FXR and TGR5 in immune and intestinal epithelial cells.

4. Agonists and antagonists targeting FXR and TGR5 show great promise for alleviating intestinal inflammation and treating tumors.

Abstract:

According to previous reports, the gut microbiota and metabolites regulate the intestinal immune microenvironment. In recent years, an increasing number of studies have reported that bile acids (BAs) of intestinal flora origin affect T helper and Treg cells. Th17 cells play a pro-inflammatory role and Treg cells usually play an immunosuppressive role. In this review, we summarize the influence and corresponding mechanism of different configurations of LCA and DCA on intestinal Th17 cells, Treg cells, and the intestinal immune microenvironment. The regulation of BAs receptors G protein-coupled bile acid receptor 1 (GPBAR1/TGR5) and farnesoid X receptor (FXR) in immune cells and the intestinal environment is elaborated. The potential clinical applications described above were also concluded in three aspects. These findings will help researchers to better understand the effects of gut flora on the intestinal immune microenvironment via BAs and contribute to the development of new targeted drugs.

Keywords: Metabolism, G protein-coupled bile acid receptor 1 (GPBAR1/TGR5), Farnesoid X receptor (FXR), Th17 cells, Treg cells.

Introduction

The gastrointestinal tract is an important immune organ containing numerous immunocytes. In recent years, research on the intestinal immune microenvironment has become increasingly extensive and in-depth, and the imbalance of this environment is closely related to many diseases, such as cancer [1], digestive system diseases[2], metabolic diseases [3], nervous system diseases [4], respiratory system diseases[5], endocrine system diseases [6], etc.

Intestinal flora metabolism and gut immune microenvironment are closely related. The intestinal flora transforms or modifies dietary components into small-molecule metabolites, which influence the phenotype and function of immunocytes [7]. Recently, researchers have explored how BAs and their derivatives regulate the development and function of Th17 and Treg cells in the gut[8] . The BA receptors TGR5 and FXR are widely expressed in various immune and gastrointestinal epithelial cells. Researchers have identified natural agonists for both receptors and developed artificial agonists. Progress has been made in studying their regulatory effects in diseases, such as liver ischemia-reperfusion(I/R) and bowel cancer[9,10].

The intestinal mucosal immune microenvironment

The human intestinal immune barrier contains several lines of defense, including the intestinal mucosal barrier, gut-associated lymphoid tissue (GALT), and intestinal commensal microbiota[11,12]. The intestinal mucosal lamina propria contains a wide variety of immunocytes, such as B cells[13], T cells[14], dendritic cells (DC) [15]and macrophages[16]. In the gut, GALT and local lymph nodes provide sites to initiate adaptive immune responses. Effector immunocytes disperse throughout the lamina propria and epithelium[17]. Intestinal flora exist widely in the human gut and can directly resist exogenous pathogens or regulate the immune system, thereby maintaining the health of the intestine[18].

Metabolism of BAs by intestinal flora

The intestinal microecosystem functions as a barrier for protection, nutrition, and metabolism. Not only do metabolites provide energy and nutrition for gut microbiota growth and reproduction, but they also influence the physiology of the host[19,20]. Intestinal flora metabolites include SCFAs (butyrate, propionate, and acetate)[21-23], amino acids[24], vitamin[25,26] and BAs[27]. Primary BAs (PBA) are synthesized in the liver and conjugated to taurine or glycine before secretion into bile. A small portion of BAs is transformed into secondary BAs (SBAs) by microbiome[28]. Some of these modified BAs are reabsorbed and exert signaling functions in the host[29]. Gut microbiota generates cholic acid(CA) and chenodeoxycholic acid(CDCA) through deconjugation[30]. Gut microbiota encodes enzymes that exert a 7α-dehydroxylation reaction. After dehydroxylation, CA becomes DCA, whereas CDCA is converted to LCA[31]. CDCA can be converted to ursodeoxycholic acid (UDCA) by HSDH[32]. DCA, LCA, UDCA, and their derivatives have different effects on Treg or Th17 cells, which will be elaborated in the following essay.

Microbiota influence intestinal immune

Many intestinal flora species exist in the human gastrointestinal tract[33], and the intestinal mucosal immune system responds reasonably well to food antigens and commensal bacteria[34]. Local immunocytes must resist pathogenic pathogens and maintain their immune tolerance to beneficial microorganisms[35] . Studies have shown that metabolites mediate communication between the commensal microbiota and host immune system by shaping the composition and function of colonic immunocytes[8,27].

First, gut microbes promote the maturation of the host immune system. Among these, B. thetaiotaomicron has the most important impact on the immune system[36]. It induced immune system maturation similar to that induced by the conventional microbiota. It increased Foxp3 expression in the mouse colon, and genes such as IL-10, TGFβ, and PDCD1, and functions in Treg pathways were also upregulated. Second, the gut microbes regulate the immune system. The lack of bifidobacteria is associated with systemic inflammation and dysfunctional immunity in early life [37]. The transplantation of special microbiota restores the balance between retinoic acid receptor-related orphan nuclear receptor-γt (RORγt+) Treg cells and Th17 cells in mice[38]. Some studies have proposed that microorganisms affect immunity through specific molecules such as PSA[39]. Mager et al. found that intestinal B. pseudolongum enhances the immunotherapy response by inosine, which requires T cells to express adenosine A2A receptors and requires costimulation[40]. The influence of commensal bacteria on the host and the direct or indirect regulation of intestinal immunocytes are indispensable to stabilize the intestinal immune microenvironment.

Gut bacteria regulates Treg and Th17 cells—mediated by BAs metabolism

Resident microbiota exert direct or indirect effects on Treg and Th17 cells at the cellular and molecular level [41](Fig. 1). BAs are important bacterial metabolites that function as T cell modulators[42]. Some BAs are implicated as endogenous etiologic agents, whereas other BAs confer resistance to pathogens, such as Clostridium difficile [43,44]. The role of BAs in immunity has been increasingly studied, and more intrinsic mechanisms are being discovered. BAs exert their influence mainly through activation of TGR5, FXR, and vitamin D receptor (VDR)[45].

5.1 Treg cells

Intestinal health requires Treg cells to exert an immunosuppressive function[46]. Forkhead box P3 (Foxp3+) is a transcription factor of Treg cells[27]. Induced extrathymically by dietary or antigens from commensals[47], Foxp3 is involved in the differentiation and function of Treg cells [27]. Conserved non-coding sequences (CNS1-CNS3) regulate Foxp3 gene expression by interacting with different transcription factors[48]. Foxp3-expressing Treg cells are vital in the prevention of autoimmunity and maintenance of immune homeostasis, and dysregulation of Treg cells is also a potential oncogenic factor[49]. Gut-resident Foxp3+CD4+ Treg cells exhibit gut-specific phenotypes and functions[50].

Hang et al. found that BAs metabolites directly modulate the Th17/Treg balance in the intestinal lamina propria [8]. The energy resources of Treg cells mainly originate from oxidative phosphorylation[51]. The results showed that as a derivative of LCA, isoalloLCA increases mitochondrial reactive oxygen species (mitoROS),

increases the formation of an open chromatin structure, and promotes H3K27ac at the Foxp3 promoter region to increase Foxp3 expression in Treg cells[8]. This process also requires TGF-β-induced signaling (Fig. 1). Bacterial-derived small molecules such as butyrate and vitamin A derivatives increase Foxp3 expression in Treg cells depending on CNS1, and isoalloLCA enhances Foxp3 expression requires CNS3 [8]. The differentiation of Th17 cells can be initiated by IL-6 and TGF-β, and RORγt expression requires CNS6 and CNS9[48]. Studies of Foxp3 and RORγt expression and related regulatory molecules have provided us with a deeper understanding of the activities of Treg and Th17 cells. Transcription factor NR4A1, a key regulator of T cell dysfunction, is stably expressed at high levels in tolerant T cells. Its overexpression inhibits the differentiation of effector T cells, and NR4A1 deletion enhances anti-tumor immunity[52]. Li et al. showed that NR4A1 is required for isoalloLCA-mediated differentiation of Treg cells[42]. IsoalloLCA treatment increased the binding of NR4A1 to the Foxp3 locus and promote Foxp3 gene transcription in a CNS3-dependent manner. These results indicate that isoalloLCA can exert immunosuppressive effects through NR4A1 in the intestinal tract, which may affect local intestinal immunity and lead to tumors and other diseases.

RORγt belongs to the family of nuclear receptors and is an intracellular transcription factor [53]. Many colonic CD4+FoxP3+ Tregs express Rorγ [54]. Helios and Nrp1 are markers of thymus-derived Tregs, and are absent in colonic RORγ+ Tregs. Colonic Treg cells express higher levels of Vdr than splenic Treg cells, especially RORγ+ Treg cells[29]. VDR is a ligand-dependent nuclear transcription factor that regulates cell proliferation and differentiation [55]. The removal of VDR in Treg cells induces severe enteritis via DSS[29]. Song et al. showed that some intestinal PBAs, such as CA, CDCA, and UDCA, as well as some SBAs species, such as LCA and 3-oxo-LCA, modulate RORγ+ Treg cells through the BAs receptor VDR [29](Fig. 1). The regulation of RORγ+ Treg cells by VDR in colon tissue cells is not mediated by DC or epithelial cells that have high VDR expression but is inherently regulated by RORγ+ Treg cells[29]. It can be speculated that changes in VDR genes or intestinal metabolites lead to heterogeneity in intestinal Treg cells and cause diseases, such as inflammation or tumors. Song et al. found that a combination of LCA/3-oxo-LCA restored colonic RORγ+ Treg cell counts; however, a similar effect was not found in colonic Th17 cells[29]. The modulatory function of BAs on Treg cells is limited to specific cells and tissue types. Interestingly, at the onset of colitis, BAs supplementation increased RORγ+ Treg cell counts. After the onset of colitis, BAs supplementation barely alleviated the colitis. This phenomenon indicates that maintaining the RORγ+ Treg cell pool by BAs during homeostasis affects the treatment effect in host DSS colitis.

DC is antigen presenting cells[56]. They process antigens, secrete cytokines and chemokines, and induce and maintain an immune tolerance[57]. Campbell et al. found that SBAs isoDCA induced Foxp3 by influencing FXR and reducing immunostimulatory functions of DCs [27], ablating FXR in DCs increased the number of Treg cells, and the transcriptional profile in DCs resembled that induced by isoDCA [27](Fig. 1). Furthermore, consortia that produce isoDCA increase colonic RORγt+ Treg cells, and this effect relies on CNS1. However, isoDCA did d not affect Th17 cell generation. This study found that the FXR of myeloid cells influences the induction of pTreg cells; however, more information concerning immunocytes and BA-sensing receptors that mediate the effects of BAs on the mucosal immune environment deserves further study.

5.2 Th17 cells

Th17 cells are CD4+T cells that secrete cytokines, such as IL-17, IL-21, and IL-22 [58]. On the one hand, Th17 cells resist pathogens such as fungi, maintain the immune barrier integrity of digestive tract[59]. However, excessive inflammatory induction by Th17 cells leads to various disease [60], such as experimental autoimmune diseases and human inflammatory conditions [59].

After culturing with the LCA + E. lenta DSM2243 (3α HSDH+) supernatant, the differentiation of naive CD4+ T cells into Th17 cells was inhibited. After Citrobacter rodentium significantly induced Th1 and Th17 cells, 3-oxoLCA treatment resulted in decreased Th17 and IFN-γ +Th17 cell levels in the colon, while Th1 and Treg cells were unaffected[61]. LCA processing showed the opposite of the above results. 3-oxoLCA and isoLCA reduced the differentiation of Th17 cells by interacting with RORγt and inhibiting its transcriptional activity[8,61](Fig. 1). Notably, isoalloLCA reduced the differentiation of Th17 cells without affecting RORγt

expression and did d not impair cell viability[8]. The regulatory effects of 3-oxoLCA and isoalloLCA on Th17 and Treg cells did not affect intestinal commensal bacteria; they directly regulated Th17 and Treg cells in mice. However, these metabolites are not present in germ-free mice, implying that the production of these metabolites needs commensals[8]. More studies are needed to determine the identity of gut-residing bacteria and the corresponding enzymes that convert LCA into 3-oxoLCA and isoLCA [61]. It has been shown that 3β-HSDH encoded by BF3538 in B. fragilis enables the production of isoLCA; 3α-HSDHs encoded by Elen_0690 and its homologues in E. lenta strains are required for 3-oxoLCA. The researchers used 3α-HSDH and 3β-HSDH positive and negative bacteria as tools to study the effects of the two LCA derivatives on TH17 cells. The study of the genes encoding various metabolism-related enzymes in the strain will help clarify the link between the intestinal flora and immune cells. It provides a reference for the development of engineered bacteria, which benefits scientific research and treatment of diseases.

Studies have shown that UDCA decreases Th17 cells and IL-17 via the pAMPK-SMILE pathway[62](Fig. 1). This revealed the role of UDCA in regulating the balance between Th17 and Treg cells. BAs were cytotoxic to cells at high concentrations ([63]. CD4+ T effector cells (Teff cells) include Th1 cells that produce interferon-gamma (IFNγ) and Th17 cells, and studies have shown that the relationship between BAs and Teff cells, conjugated bile acids (CBA), drives oxidative stress in Teff cells and kills transformed epithelial cells. The xenobiotic transporter Mdr1, which is induced by CD103+ DCs, enforces T cell homeostasis in the presence of CBA[64](Fig. 1). Abnormal concentrations of BAs affect the activity of T cells, and the interaction between DC and T cells can resist adverse effects, while changes in related genes are not conducive to the maintenance of normal homeostasis.

Gut flora need special enzymes and BAs conformations to regulate immunocytes

Diet directly controls the liver synthesis of BAs, whereas the gut flora and host mainly control the modification process of BAs in the gut. The appearance of SBAs in stool is the major difference between conventionalized and germ-free mice [36]. The overall concentration of BAs in mice mono-colonized with gut microflora (E. coli and B. thetaiotaomicron) was higher, and SBAs were not detected. This indicates that the metabolism of PBAs requires special bacteria, and different gut microflora have their respective metabolic activities. Ridlon et al. also concluded that bile salt hydrolysis and hydroxy group dehydrogenation reactions are induced by extensive intestinal anaerobes[65]. However, BAs 7-dehydroxylation is restricted to a small part of intestinal anaerobes[66].

Clostridium scindens has been widely used to convert PBAs into both LCA and DCA in previous studies. However, an established multi-strain also produces SBAs without this strain because Extibacter sp. GGCC_0201 provides a 7-dehydratase that converts CA and CDCA into DCA and LCA respectively [67]. This suggests that specific enzymes are indispensable for bacterial metabolic activity. Human gut bacteria that convert LCA into 3-oxoLCA and related genes that encode 3α-/3β-HSDHs are negatively associated with Crohn's Disease (CD) in humans[61]. The generation of isoDCA requires some key enzymes; researchers constructed several bacterial strains with key enzymes and produced a large amount of isoDCA, which also excluded bacterial strain backgrounds[27]. Building strains that metabolize specific molecules is a strong indication of the centrality of enzymes and proves the operability of developing therapeutic approaches.

IsoalloLCA enhanced FOXP3 expression, while other LCA isomers did not show the same effect, indicating that both the 3β-hydroxyl group and trans (5α-hydrogen) A–B ring configuration of isoalloLCA are required to regulate Treg cells [8]. Paik et al. observed that isoLCA inhibited naive CD4+ T cells to differentiate into Th17 cells as efficiently as 3-oxoLCA, whereas isoDCA, which is abundant in 3β-OH, did not inhibit differentiation[61]. Campbell et al. reported that the spatial orientation of specific hydroxyl (-OH) groups is vital for isoDCA and ω-MCA to exert effects[27]. Therefore, microbial epimerization and specific spatial conformations bring about the unique properties of BAs to regulate immunity.

Roles of TGR5 and FXR in immune cells and intestinal epithelial cells

TGR5/GPBAR1 is a receptor located on the cell membranes of cells in the gallbladder, ileum, colon, and liver. FXR is a nuclear receptor involved in the regulation of BAs and lipid homeostasis. There are many

studies on the influence of receptor activation on the immunocytes of the body.

7.1 Macrophage

7.1.1 TGR5

As important anti-tumor immune cells, macrophages have the ability to chemotaxis, phagocytosis, antigen presentation, and secretion of cytokines. The effect of TGR5 on macrophages has been extensively studied in organ (I/R) injury, IBD, and liver disease; however, it has been less studied in tumors.

BAR501 is an agonist of GPBAR1, and LPS-induced elevation of M1 markers (CD38, Fpr2, and Gpr18) was reversed after treatment with BAR501(Fig. 2). Moreover, BAR501 up-regulates the markers of M2 (Egr2 and c-myc)[68]. TGR5-deficient BMDMs showed higher levels of the M1 markers iNOS and IL-6 and lower levels of the M2 markers PPARγ and Arg-1[69]. UDCA enhancement of TGR5 activation is beneficial for its anti-inflammatory effects and promotes M2 polarization. In vitro experiments showed that TGR5 inhibits macrophage migration by inhibiting Cat E[69]. Another study showed that TGR5 inhibits macrophage migration by inducing the differential expression of C/EBp-β via the mTOR complex[70]. The above studies demonstrated the effect of TGR5 activation on the macrophage phenotype and migration.

In non-small cell lung cancer(NSCLC), TGR5 promotes the formation of tumor-associated macrophages (TAMs) by activating the cAMP-STAT3/STAT6 signaling pathway. This inhibits CD8+ T cells and decreases the production of granzyme B, IFN-γ, and TNF-α, thus inhibiting anti-tumor immunity [71]. The phagocytosis of tumor cells by TGR5 deficient macrophages is enhanced; therefore, we can reasonably speculate that TGR5 reduces the phagocytosis of macrophages. We can think that in intestinal tumors, the changes in microbiota metabolites, especially the BA molecules regulating TGR5, may affect the formation of TAMs, thus unfavorable to anti-tumor effects. In human patients with NSCLC tissue, TGR5 expression correlates with infiltration of TAMs, and their high expression is associated with poorer prognosis and shorter overall survival.[71] Taurolithocholic acid (TLCA) inhibits the expression of LPS-induced IL-6, IL-12, TNF-α, and TNF-β[72]. The inhibitory effect of TGR5 on IFN-β expression by cAMPPKA is also reflected by the downregulation of the IFN-stimulated genes MxA and PKR in human macrophages[72]. IFN and T cells have intricate relationships and studies have shown that IFN-β increases the induction of Treg cells[73]. This suggested that the activation of TGR5 regulates the expression of interferon in macrophages. This information helps us study the coordination between macrophages and T cells to exert antitumor effects in the intestinal tumor immune microenvironment. In microglia, BAs, such as tauroursodeoxycholic acid (TUDCA) or taurolithocholic acid (TLCA), reduce PKM2 expression and regulate the glycolytic pathway[74]. This deepens our understanding of the energy regulation of BAs.

TCDCA acts on the TGR5 receptor and modulates inflammation through the cAMP-PKA-CREB signaling pathway. TCDCA reduces inflammatory cytokines, such as IL-1β, IL-6, IL-8, IL-12, and TNF-α by affecting NF-ϰB activity[75]. IBD patients have higher levels of TGR5 expression in intestinal mucosal lamina mononucleus cells (LPMCs), and TGR5 agonists and BAs (DCA and LCA) inhibit TNF-α production in macrophages through the TGR5- cAMP pathway. In this pathway, c-Fos phosphorylation is induced to regulate NF-ϰB p65[76]. TGR5 inhibited the upregulation of the TLR4-NF-ϰB pathway and activation of Caspase-8 in vivo[77]. In in vitro hypoxia/reoxygenation macrophage models, activation of TGR5 downregulates the expression of TNF-α and IL-6, and upregulates the expression of IL-10[77]. Another study showed that the activation of TGR5 alleviates inflammation through the Keap1- Nrf2 pathway. Specifically, it increased the expression of Nrf2 and Ho-1 in the nucleus, but decreased the expression of Keap1[9]. Previous studies have shown that TGR5 inhibits NLRP3 inflammasome activation and caspase-1 cleavage[78]. A recent study found that BA supplementation activated the NLRP3 inflammasome in macrophages and promoted inflammation under noninflammatory conditions. However, BA inhibits NLRP3 inflammasomes and reduces inflammation in LPS-induced inflammatory macrophages[79].

7.1.2 FXR

FXR regulates macrophage activation and oxidative stress and contributes to the anti-inflammatory pheno-

type and function of macrophages[80]. The relationship between the gut microbiome, BAs, FXR, and NLRP3 inflammasome remains uncertain. Gut microbiome metabolites act as natural FXR regulatory molecules and BAs are important components. In turn, FXR alters the BAs and gut microbiome composition[81]. BAs activate the NLRP3 inflammasome by promoting calcium influx, but FXR inhibits the NLRP3 inflammasome[82].

Osteoclasts originate in the mononuclear macrophage system, which ich is a special type of terminally differentiated cell. FXR agonists inhibit the c-Jun N-terminal kinase (JNK) 1/2/nuclear factor of activated T-cells 1 (NFATc1) pathway JNK1/2/NFATc1 and alleviate subchondral osteoclast fusion[83]. Kupffer cells, which are liver macrophages, showed decreased TNF-α and increased IL-10 expression with the activation of FXR by GW4064[84]. GW4064 increased FXR binding to the Abcb11 promoter and decreased the expression of genes related to recruitment and activation of macrophages in the liver. This is not conducive to the accumulation, activation, and infiltration of liver macrophages[85,86]. Loss of nuclear receptors FXR and SHP leads to YAP activation in mice with unbalanced bile acid homeostasis and spontaneous liver tumor[87].

7.2 DC

The expression of TGR5 is down-regulated during the differentiation of monocytes into DC. BA-cultured DC produce lower levels of IL-12 and TNF-α under the stimulation of symbiotic bacterial antigens, which is mediated by the TGR5-cAMP pathway[88]. DCA regulated the function of DC through the TGR5-cAMP-PKA pathway and inhibited the activation of NF-kB (Fig. 3). DCA decreased the secretion of IL-1β, IL-6, IL-12, and TNF-α from LPS-induced bone marrow-derived DCs. It is noteworthy that the expression of the DC co-stimulatory molecules CD40, CD80, CD86, and MHC II was also inhibited. It is not conducive to T cell differentiation and Th1 and Th17 cell development, and the secretion of IL-17 and IFN-γ is reduced [89]. The discovery that bile acids regulate T cell differentiation and function through DC suggests the potential research value of bile acid signaling molecules in the local immune microenvironment, which is conducive to promoting related research on inflammatory and tumor diseases, especially intestinal cancer.

7.3 NKT

Natural killer T (NKT) cells are a special T cell subgroup with both TCR and NK cell receptors on the cell surface. According to the constancy of the TCR, NKT cells are divided into types I and II. Type I NKT cells mainly play an antitumor role, while type II NKT cells can promote the development of tumors [90]. Type I NKT cells include pro-inflammatory NKT1 subsets that produce IFN-γ, and regulatory NKT10 subsets that secrete IL-10. In a mouse model of hepatitis, ablation of GPBAR1 exacerbated liver damage and resulted in a phenotype of type I NKT cells biased towards NKT1. While activation of GPBAR1 rescues liver damage, NKT cells are polarized into NKT10. In addition, GPBAR1 excitation significantly expanded the IL-10-secreting type II NKT cell subsets[91]. LCA inhibits hematopoietic stem cell activation via the Smad pathway (reduces TGF-β) or MAPK-ERK pathway. LCA increases recruitment of NK cells and reduces activation of NKT cells. However, the effect of LCA weakened when antibiotics reduced the diversity and abundance of gut microbes[92].

7.4 MDSC

Intravenous infusion of TDCA decreased serum proinflammatory cytokines, increased the number of granulocyte myeloid suppressor cells (MDSCLTS) in the spleen of septic mice, and inhibited T cell proliferation[93]. Activation of FXR enhances the immunosuppressive activity of MDSCs on T-cell proliferation by binding to and upregulating the PIR-B promoter. FXR activation drives the accumulation of MDSCs in the liver through upregulation of S100A8 mRNA expression[94].

7.5 B cell

Immunoglobulin A (IgA) is present in mucosal tissue and resists the invasion of pathogens, and its absence leads to intestinal inflammation[95]. In PBA-fed rats, IgA levels in the ileum mucosa were increased[96]. UDCA belongs to SBAs, and in in vitro experiments, UDCA inhibits the production of IgM, IgG, and IgA in peripheral blood monocytes. UDCA also acts on B cells by suppressing Ig production in human B cells[97]. The effects of various BAs on local B cells and mucosal immunity in vivo warrant further investigation.

7.6 Intestinal epithelial cells

In an oxazolone-induced colitis model, the GPBAR1 agonist BAR501 alleviated the symptoms of enteritis, inhibited inflammatory markers such as IL-1β, IL-6, and IFN-γ, and increased the expression of TGF-β, IL-10, and Foxp3[68]. Gut microbiota-BAs-TGR5 Axis is beneficial for restoring the integrity of the damaged colonic epithelium[98]. During organoid growth, TGR5 activation increases the activation of Yes-associated protein 1 (YAP1) and its upstream regulator SRC from intestinal stem cells (ISCs). TGR5 activates ISCs and promotes epithelial cell regeneration, causing them to renew and proliferate in response to injury[99]. Another study indicated that DCA retards wound healing in colon epithelial cells by activating the AKT pathway via GPCR5[100].

Fibroblast growth factor 15/19 (FGF15/19) is a hormone released by ileal gut cells in response to stimulation by FXR (usually via absorbed BAs) that provides negative feedback for BAs synthesis in hepatocytes[101]. In intestinal epithelial cells, FXR activates the transcription of intestinal bile acid-binding protein (I-BABP) and FGF15, both of which regulate key aspects of the liver and intestinal homeostasis. SHP is a regulatory gene of FXR and the synthetic ligand of FXR can reduce organ damage and immune cell activation in vivo. Activation of FXR increased the expression of I-BABP, FXR, and SHP in the colon and decreased the expression of IL-1β, IL-6, TNF-α, iNOS, cyclooxygenase (COX)-1, and COX-2 in THP1 cells, reducing the severity of the disease[102].

In mouse models of intestinal tumors and chronic colitis, loss of FXR promotes Wnt signaling in the intestinal mucosa through neutrophil and macrophage infiltration and TNF-α production, leading to early death and increased tumor progression. When activated, FXR induces apoptosis and clearance of genetically altered cells[103]. This suggests that strategies to reactivate FXR expression in colon tumors may be useful for the treatment of colon cancer. BA-activated FXR not only increases GLUT2 expression and controls glucose uptake through the FXR-S1PR2-ERk1/2 signaling cascade but also reduces cell energy production by inhibiting oxidative phosphorylation[104]. In the case of bowel cancer, how FXR regulates tumor growth by affecting energy is worthy of further investigation. DCA activates the STAT3 signaling pathway, interferes with the gastric microbiome and BA metabolism, and induces gastrointestinal metaplasia[105]. DCA reduces the expression of FXR, activates the Wnt signaling pathway, increases the levels of β-catenin and c-Myc, and promotes the proliferation and migration of colon cancer cells. The FXR agonist GW4064 reduces the proliferation of colon cancer cells by inhibiting the Wnt signaling pathway[106]. These studies suggest a relationship between DCA, FXR, and the Wnt signaling pathway. The authors highlighted the value of FXR agonists in intestinal cancers.

BAs, immune and disease

BAs promote the absorption of lipid nutrients in the intestine and act as signaling molecules. BAs also influence immune homeostasis and energy utilization. Disorder of intestinal flora and an imbalanced BAs pool lead to various diseases (Fig. 5).

Intestinal microbiota regulate enteric virus[107,108] , norovirus infections are major causes of gastroenteritis [109] . FXR is expressed differently in the gut, and the proximal bacterial biotransformed BAs initiate a type III interferon response and resist viral infection. Therefore, commensal bacteria inhibit viral infection of the proximal gut, while promoting viral infection of the distal gut[110] . The cause of enteritis is complex**.** Studies have shown that dietary astragalus polysaccharide influences the gut microbiota, metabolites, and Th17/Treg balance in necrotic enteritis (NE) chickens[111] . Primary sclerosing cholangitis (PSC)-IBD is also a result of a dysregulated Th17/Treg balance[112]. IBD is often accompanied by dysregulated bacterial flora, BAs, and pro-inflammatory factors[113]. Genes encoding various metabolism-related enzymes in the gut flora regulate anti-inflammatory BAs small molecules and their derivatives, and are negatively correlated with intestinal IBD[27,61].

The intestinal flora and BAs are also closely associated with endocrine and metabolic diseases. Glycodeoxycholic acid induces ILC3 to secrete IL-22, which improves the phenotype of Polycystic ovary syndrome[114]. Pigs hyocholic acid (HCA) acts on enteroendocrine cells, activates TGR5, and inhibits FXR to promote the

production and secretion of glucagon-like peptide-1 (GLP-1), consequently improving glucose homeostasis and avoiding diabetes [115]. In mice, feces from patients with coronary artery disease (CAD) promote intestinal inflammation by disturbing the lamina propria Th17/Treg cell balance and worsening gut barrier permeability [116]. These studies offer a new perspective on the treatment of metabolic and endocrine system diseases.

Hydrophobic BAs damage intestinal cells and are risk factors for colorectal cancer (CRC)[117]. High-fat diet and APC mutation of WNT signaling change BAs profiles and promote Lgr5+ cancer stem cell cells (CSC) proliferation and DNA damage[10]. However, activation of intestinal FXR limits its growth and suppresses CRC progression. The role of FXR implicates it as a potential therapeutic target for CRC. Moreover, DCA and LCA derivatives that promote Treg cell differentiation and inhibit Th17 cell differentiation may also cause CRC. Studies on TGR5, FXR, and their activation in macrophages, DC, NKT cells, MDSC, B cells, and intestinal epithelial cells also provide references for the exploration of the etiology of CRC and for better cancer treatment.

Clinical applications

9.1 Agonists of TGR5 and FXR

Progress has been made in the study of the efficacy of natural or synthetic TGR5 and FXR agonists in the treatment of liver and intestinal diseases. In an oxazolone-induced colitis model, the GPBAR1 agonist BAR501 alleviated the symptoms of enteritis and inhibited inflammatory markers[68]. GW4064 activates FXR and improves LPS-induced ileocolitis by inhibiting mitochondrial dysfunction in mice[118]. FXR activation also inhibits endoplasmic reticulum stress and inflammation [119]. In tumor-bearing models, the FXR agonist synergistically inhibited the growth of hepatocellular carcinoma with the anti-PD-1 antibody[120]. Obeticholic acid (OCA) is a clinically approved selective FXR agonist and Nanoemulsion-loaded OCA (OCA-NE) results in increased secretion of CXCL16, IFN-γ. The number of NKT cells in the tumor increases, resulting in a better liver tumor inhibition effect. The development of BA receptors, such as TGR5 and FXR agonists, and the targeted delivery of these drugs have greatly facilitated precision cancer therapy[121]. OCA is used to treat non-alcoholic steatohepatitis (NASH) by inhibiting activation of the NLRP3 inflammasome[122]. OCA accelerates the maturation of mouse intestinal epithelial cells in a constitutive androstane receptor (CAR)-dependent manner[123]. Further research on OCA is necessary to expand its application range. Salvia-Nelumbinis naturalis (SNN), a traditional Chinese medicine, is effective in the treatment of NASH. It activates the FXR-FGF15 signaling pathway in the colon by increasing BA-associated microbiome[124]. Research on the regulatory mechanism of traditional Chinese medicine on hepato-intestinal disease has important implications for better application of traditional Chinese medicine and the development of new targeted drugs.

9.2 Microbia-based therapy

For diseases whose pathogenesis involves dysregulation of the intestinal flora and disruption of the intestinal mucosal barrier, promising novel therapies are being developed. FMT is a good therapeutic strategy for treating Clostridioides difficile infection [125]. However, its efficacy is limited by the host inflammatory immune status[126]. Side effects such as fever and a temporary increase in C-reactive protein levels after FMT deserves attention[67]. Defined bacterial consortia were selected based on their desired biological functions. Atarashi et al. isolated Treg cell-inducing bacterial strains [67]. This strain alleviates colitis and allergic diarrhea in mice. Using defined bacterial consortia brings hope for tailoring therapeutic products for human immune disorders. The appointed combinations of microbes have more predictable responses, more targeted efficacy, and fewer adverse responses, such as infection by pathogens.

9.3 BAs-based therapy

Researchers have synthesized LCA 3-sulfate (LCA-3-S) that binds to RORγt and selectively suppresses Th17 cell differentiation[127]. UDCA has been used clinically for many years and has a good curative effect on PSC[128].It also degrade TGF-β and inhibits the differentiation and activation of Treg cells[129], and UDCA

enhances the anti-tumor efficacy of anti-pd-1. Researchers have established a set of steps that contain the necessary enzymes and engineer them into Clostridium sporogenes, successfully producing DCA and LCA[130]. This also provides us with hope to take advantage of gut flora. Natural extraction or artificial synthesis of BAs and reasonable combinations of several kinds to achieve smooth regulation of Th17 and Treg cells is a promising method for the treatment of IBD and other diseases. However, drug therapy also needs to consider the condition of the patient's gut so that it can be tailored to each individual.

Conclusion

Gut microbes are indispensable in the gut, and their metabolic roles have been widely studied using metabolomics and bacterial profiling. BAs are metabolized into various configurations by bacteria in the gut and serve as signaling molecules to regulate immunocytes such as Th17 cells and Treg cells in the intestine, thereby regulating intestinal immune balance. The intricate network of relationships among the gut flora, BAs, immunocytes, and cytokines is closely related to multiple diseases throughout the body. Therefore, related research will be conducive to the development of drugs for treating multiple diseases. Research on the mechanism of the activation effect of TGR5 and FXR in macrophages, DC, NKT cells, MDSC, B cells, and intestinal epithelial cells contributes to the development of molecular-targeted drugs. At present, these studies have mainly focused on liver diseases and ischemia-reperfusion injury. These results support the possibility of using intestinal microbial community analysis techniques, metabolomics analysis, and single-cell sequencing techniques to further explore the immunocyte subgroup regulated by the intestinal flora in the tumor immune microenvironment.

Abbreviations

Treg cells: regulatory T cells; BAs: bile acids; LCA: Lithocholic acid; IsoLCA: isolithocholic acid; 3-oxoLCA:3-oxolithocholic acid; DCA: deoxycholic acid; IsoDCA:3β-hydroxydeoxycholic acid; PSA: polysaccharide A; GALT: gut-associated lymphoid tissue; DC: Dendritic cell; SCFAs: short-chain fatty acids; pTreg cells: peripherally induced Treg cells; IBD: inflammatory bowel disease; Foxp3+: forkhead box P3; MitoROS: mitochondrial reactive oxygen species; IL-17: interleukin 17; GPBAR1/TGR5: G protein-coupled BA receptor 1; FXR: farnesoid X receptor; VDR: vitamin D receptor; Teff cells: T effector cells; CBA: conjugated bile acids; RORγt: RAR-related orphan receptor-γ· IFNγ: interferon-gamma; CNS: conserved non-coding sequence; UDCA: Ursodeoxycholic acid; NE: Necrotic enteritis; PCOS: Polycystic ovary syndrome; ILC3: intestinal group 3 innate lymphoid cell; HCA: hyocholic acid; GLP-1: glucagon-like peptide-1; CAD: coronary artery disease; CRC: colorectal cancer; Lgr5+: Lgr5-expressing; PSC: Primary sclerosing cholangitis; FMT: Fecal microbiota transplantation

Additional Information

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Authors' contributions

Y.Z., L.L., and C.W. provided direction and guidance throughout the preparation of this manuscript. X.G., Y.L., and Z.S. drafted the manuscript and prepared the figures. S.G., L.P., and Y.F. collected related references and participated in the discussion. W. W. revised the manuscript. All authors contributed to the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Data availability

Not applicable.

Competing interests

The authors declare no conflict of interest.

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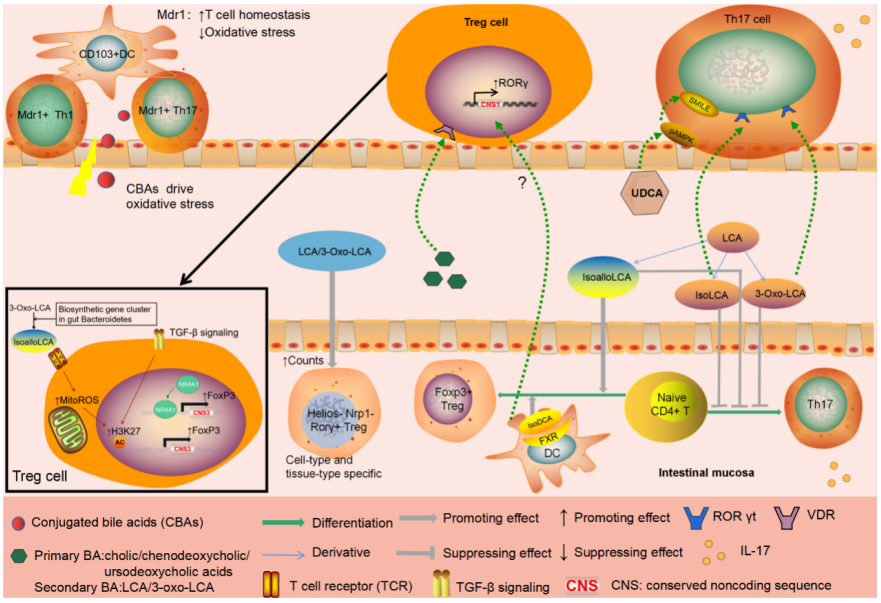

Fig. 1 The derivatives of DCA and LCA regulate Treg cells and Th17 cells.

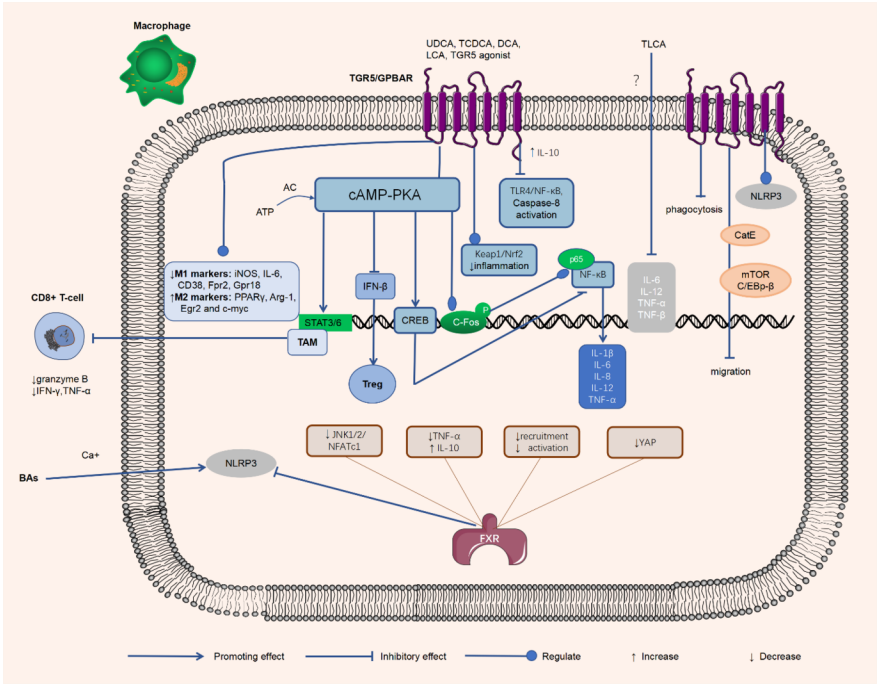

Fig. 2 Activated TGR5 and FXR regulate macrophage and macrophage regulate T cell differentiation and fuction.

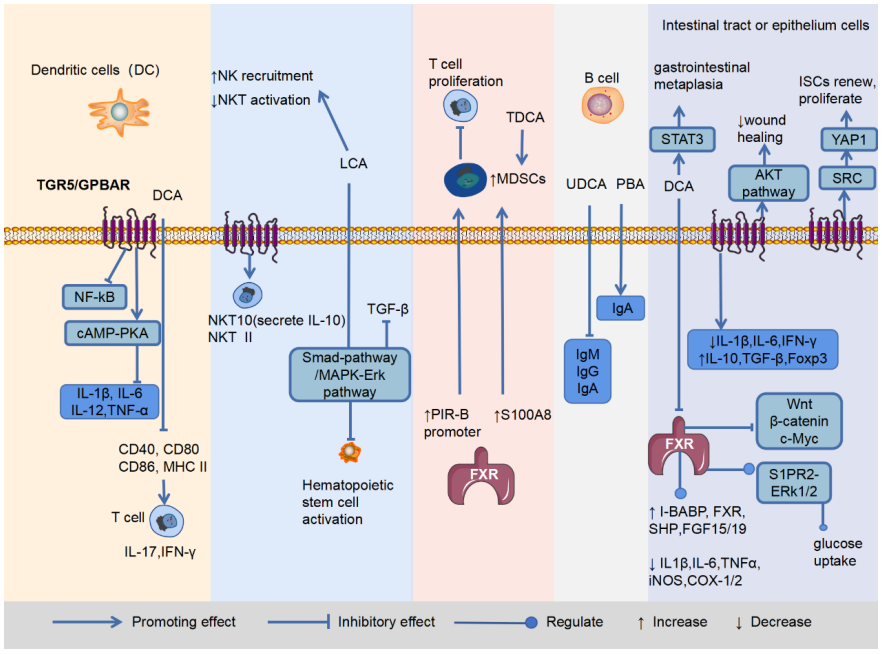

Fig. 3 Activated TGR5 and FXR regulate DC, NKT cells, MDSC, B cells and intestinal tract/epithelium cells.