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Bile acid receptors regulate the role of intestinal macrophages in inflammatory bowel disease

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Many factors, including genetic vulnerability, barrier function, intestinal immune cells, and intestinal microbiota, may combine to affect the occurrence and progression of inflammatory bowel disease (IBD). Through targeting bile acid receptors (BARs), bile acids have been demonstrated to have a range of regulatory effects on intestinal immune responses in recent decades. As the basis of intestinal immunity, macrophages play an indispensable role in intestinal homeostasis. BARs connect the intestinal microbiota with immune cells, significantly impacting IBD. This review focuses on the role of bile acids in regulating the differentiation and function of intestinal macrophages in IBD.

KEYWORDS

bile acids receptors, bile acid synthesis, bile acid metabolism, macrophage polarization, IBD

1 Introduction

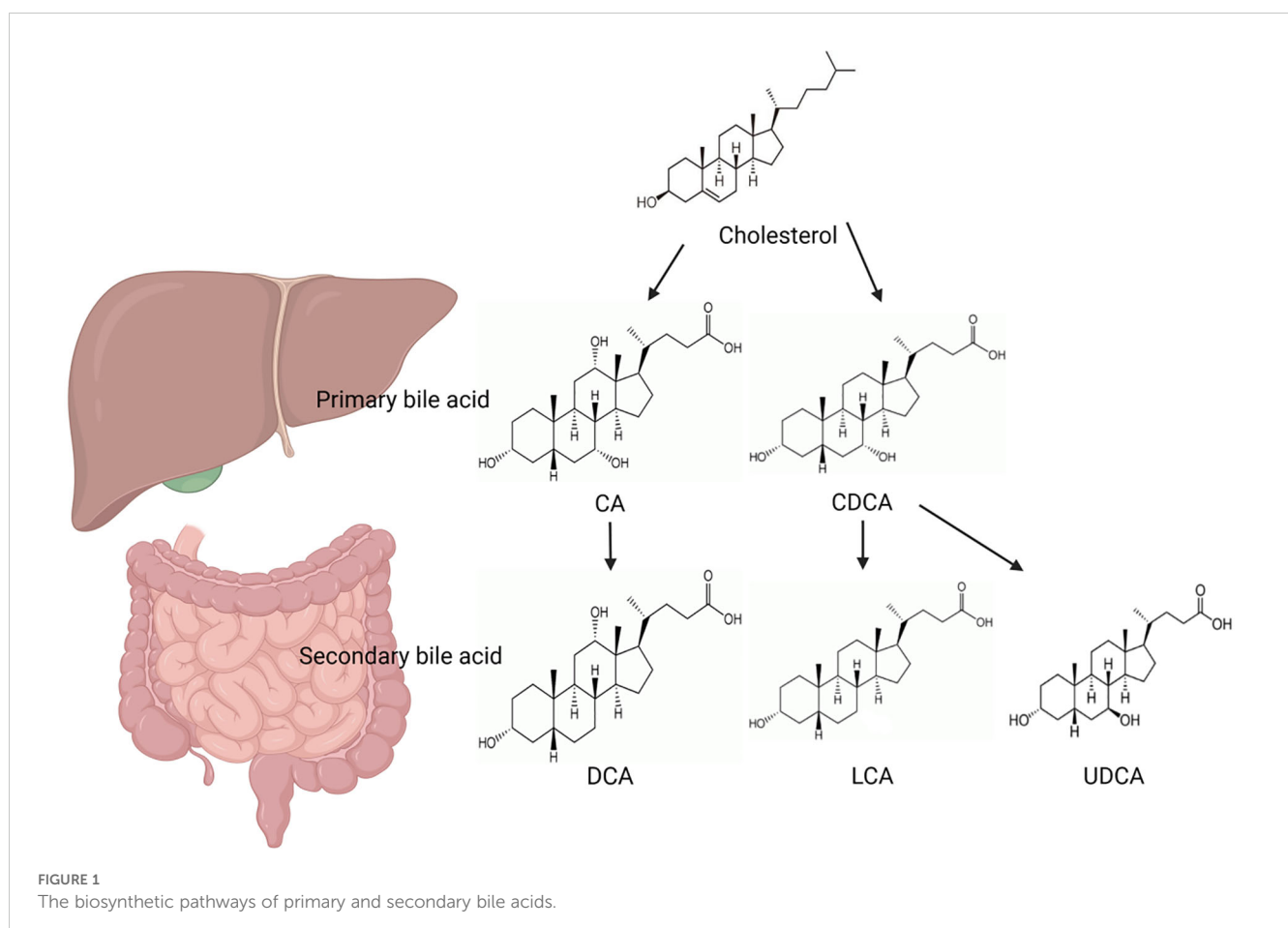
Although it has long been thought that intestinal microecological abnormalities are connected to several intestinal diseases, including IBD, it is still unclear how the host and intestinal microbiome interact. One significant mechanism of interaction between the microbiome and the host is the production of small molecules by the intermediate or final products of microbial metabolism. As an important component of the metabolism of the intestinal microbiota, bile acids are also signaling molecules that participate in regulating various physiological processes through bile acid receptors (BARs) (1). They have been found to have functions of regulating energy metabolism, inflammatory responses, and immune regulation in metabolic diseases, inflammatory diseases, and tumors (2). Bile acids can be involved in the progression of IBD by participating in the regulation of macrophage recruitment, maturation, polarization and function (3–6). As an important factor connecting the intestinal microbiota and intestinal immune cells, it has become a therapeutic target for exploring new therapies for IBD (7–9). Therefore, we reviewed the metabolic process of bile acids and their role in nutrient absorption, analyzed their regulatory mechanism on macrophages and their role in IBD, and summarized some drug treatment methods for IBD.

2 Bile acid metabolism

Bile acids, the primary metabolites of cholesterol, are synthesized at a rate of approximately 1–1.5g per day in healthy individuals. The liver transforms 0.4–0.6g of this into bile acids, which are then expelled with bile (10, 11). Considering their origin, bile acids can be classified as primary and secondary varieties (10). Primary bile acids, such as cholic acid (CA) and chenodeoxycholic acid (CDCA), are synthesized from cholesterol in liver cells and may bind with glycine or taurine. The secondary bile acids, including lithocholic acid (LCA) and deoxycholic acid (DCA), are formed through the deoxygenation of the 7th α hydroxyl group by intestinal bacteria. These acids, along with their conjugates, are combined with glycine or taurine in the liver (12–14). Bile acids are categorized into free and conjugated forms based on their structure. Free bile acid includes CA, CDCA, DCA and a small amount of LCA. These free bile acids combine with glycine or taurine respectively to form various conjugated bile acids including glycocholic acid (GC), taurocholic acid (TCA), glycochenodeoxycholic acid (GCDCA) and taurochenodeoxycholic acid (TCDCA). Conjugated bile acids are more water-soluble and generally exist in the body as sodium salts, which is more stable than free bile acids.

There are two types of bile acid synthesis: the classical pathway and the alternative pathway (Figure 1) (10, 15, 16). About 90% of

primary bile acids are synthesized through classical pathways (10, 13), cholesterol is first catalyzed by cholesterol 7 α -hydroxylase (CYP7A1) to form 7 α -hydroxycholesterol (10). The conversion of the latter to bile acid includes the 3- α and 12- α hydroxylation, hydroreduction, side chain oxidative cleavage, water addition and other multi-step complex enzymatic reactions, which first produce 24-carbon cholanyl CoA. The latter can be hydrolyzed to produce primary free bile acids, namely cholic acid and deoxycholic acid, or can be directly combined with glycine or taurine to produce corresponding primary bound bile acids, which are carried into the intestine by bile in the form of sodium or potassium bile acids. Cholesterol 7 α -hydroxylase is a key enzyme in the bile acid synthesis pathway and is regulated by the negative feedback of the end product bile acid. After the primary bile acids enter the intestine to promote the digestion and absorption of lipids, secondary bile acids are formed in the ileum and upper colon by the intestinal bacteria to catalyze the unbinding reaction of bile acids and the dehydroxy effect of 7 α (17). Cholic acid removes 7 α -hydroxyl to form deoxycholic acid. Chenodeoxycholic removes 7- α hydroxyl to form Lithocholic acid (18). These two free secondary bile acids can also be reabsorbed into the liver through enterohepatic circulation and combined with glycine or taurine to form binding secondary bile acids. In addition, enterobacteria can also convert chenodeoxycholic acid into ursodeoxycholic acid, that is, 7 α -hydroxyl of cholic acid into 7 β -hydroxyl, which is also



classified as secondary bile acid (19). Ursodeoxycholic acid content is very small, although not important for metabolism, but has a certain pharmacological effect. Ursodeoxycholic acid has anti-oxidative stress effect in the treatment of chronic liver disease, can reduce liver damage caused by bile acid retention in the liver, improve liver function and slow down the disease process. The alternative pathway first converts cholesterol to 27-hydroxycholesterol by cholesterol 27-hydroxylase (CYP27A1), then hydroxylated by oxysterol 7- α -hydroxylase (CYP7B1), and then side chain modification to produce CDCA. Bile acids are primarily reabsorbed in the ileum and returned to the liver via portal circulation, where they are released back into the bile, after the promotion of emulsification, digestion, and absorption of lipids and fat-soluble vitamins. Enterohepatic circulation of bile acids is the term for this process (10, 20). About 5% (0.4-0.6g) of bile acids are excreted in the stool, which is in balance with the amount of bile acids synthesized by liver cells.

3 The function of bile acids

After being converted into bile by liver cells, bile acids are retained in the gallbladder and released into the intestinal lumen when the gallbladder contracts. Bile acids are crucial for preserving the dissolved state of cholesterol and can aid in the digestion and absorption of lipids. The structure of bile acid is characterized by the three-dimensional configuration of two sides of hydrophilic and hydrophobic structures. This structure makes bile acid have strong interfacial activity and is a strong emulsifier, which can effectively reduce the interfacial tension of oil/water two phases, make the lipid emulsification into 3-10 μ m fine micro-groups, increase the contact area of lipase and lipase, and facilitate the digestion of fat. Bile acids and the digested lipids will combine to produce phospholipids, which will then form mixed microclusters with a diameter of just around 20 μ m., which is conducive to the absorption of lipids through the intestinal epithelial mucosa. 99% of the cholesterol in the human body is excreted through the intestines with bile, of which about two-thirds is excreted in direct form. Cholesterol is difficult to dissolve in water, but cholesterol can form soluble microclusters under the synergic action of bile acid and lecithin, and be transported to the intestine through the biliary tract. The relative concentration of bile acids is an important factor in maintaining the solubility of cholesterol in bile (21),once the balance is broken, cholesterol is easy to precipitate from the bile, forming gallstones, and according to the cholesterol content of gallstones, gallstones can be divided into three categories: cholesterol stones, melanin stones and brown stone (22, 23).

By connecting to bile acid receptors, bile acids can play a variety of roles in controlling immune cell function in addition to their crucial involvement in nutrition absorption and cholesterol dissolution (24). Before the discovery of bile acid receptors, bile acid metabolites CDCA and UDCA had been used as drugs for the treatment of gallstones, which could effectively promote the dissolution of gallstones, and were the first choice for the treatment of gallstones. Today, UDCA remains the primary drug

used to alleviate disease progression in primary cholangitis (PBC). In 1999, bile acid receptors were reported (1, 25), the study of bile acids has gained renewed interest. Bile acids are currently believed to primarily function through bile acid receptors, which is a crucial mechanism of action between intestinal immune cells and intestinal microbiota. Investigating intestinal disorders and their processes greatly benefits from the presence of bile acids in conjunction with intestinal microbiota and intestinal immune cells (18).

The two primary categories of bile acid receptors now exist are membrane receptors and nuclear receptors (1, 11, 26). By controlling immune cell activity and bile acid metabolism, it contributes significantly to human health. With the discovery of specific receptors activated by bile acids in intestinal flora, more focus has been placed on how bile acids affect intestinal immune cells. As the first line of defense against bacteria and antigens, intestinal macrophages mediate inflammatory reactions to food, bacteria, and metabolites. Macrophages are regarded as therapeutic targets for a number of illnesses, including IBD, due to their ability to coordinate tissue repair and inflammation resolution (27). According to pertinent research, bile acids can control macrophage polarization via bile acid receptors and are crucial in intestinal disorders (Table 1). The development and course of intestinal illnesses are also significantly influenced by their interaction with macrophages. According to recent research, bile acids have two roles in intestinal disorders: they can prevent cancer and reduce inflammation by blocking bile acid receptors, but they can also cause damage that is both carcinogenic and pro-inflammatory. The polarization and function of macrophages may be connected to the various roles.

4 Intestinal macrophages

With the development of the technology, studies have confirmed that most tissue-resident macrophages originate from erythrocyte - myeloid progenitor cells in the yolk sac during embryonic development, which can regulate function and differentiation according to niche signals, and have the ability to self-renew (28, 29). Macrophages are highly plastic, and the process of producing

TABLE 1 BARs and their endogenous bile acid ligands and synthetic ligands.

Cell membrane receptors	Natural bile acid agonists rank of potency	Synthetic ligands
GPBAR1(TGR5)	LCA>DCA>CDCA>UDCA>CA	BAR501,BAR502, INT-767,INT-777
S1PR2	Conjugated bile acid	JTE-013
Nuclear receptors		
FXR	CDCA>DCA>LCA>CA	BAR502; Fexaramine D,GW4064
VDR	LCA and its derivatives	

specific phenotypic and functional responses to microenvironmental stimuli and signals in tissues is called polarization of macrophages. Based on their phenotype and function, macrophages have historically been divided into two types: classically activated macrophages (M1) and alternatively activated macrophages (M2) (30–32) (Figure 2).

M1 macrophages are pro-inflammatory cells that, in response to infection or inflammation, release cytokines like interleukins (IL-1 β , IL-6, IL-12, and IL-23) and tumor necrosis factor α (TNF- α). It mainly plays the role of promoting inflammation and causing tissue damage (33, 34).

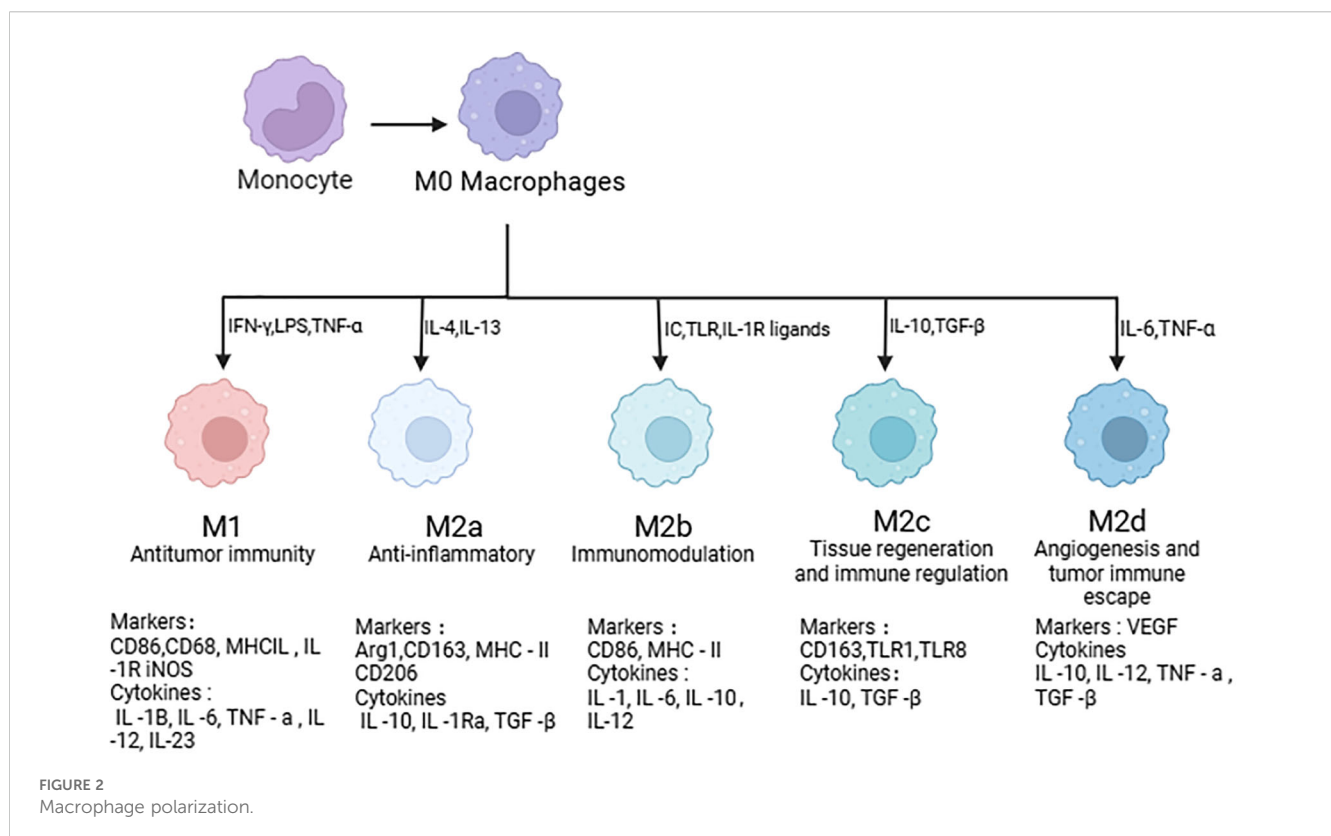
M2 macrophages can be induced into distinct subclasses (M2a, M2b, M2c, and M2d) by various stimulus signals, and they can also have distinct functions in inflammation (35, 36). In addition to expressing elevated amounts of CD206, IL-1 receptor, and CCL17, M2a macrophages can be activated by IL-4 and IL-13. They also release profibrotic substances, encourage Th cell activation, suppress inflammation, support tissue repair, and stimulate angiogenesis (35, 37). M2b macrophages secrete significant amounts of IL-10 and little levels of IL-12, as well as pro-inflammatory cytokines including IL-1 β and TNF, when they are triggered by lipopolysaccharide, immune complexes, TLR agonists, or IL-1 receptor ligands (35, 38). Immune complexes, glucocorticoids, prostaglandins, and IL-10 activate M2c macrophages, which then use exudation, extracellular matrix (ECM) remodeling, and angiogenesis to aid in tissue repair (35, 39). Numerous factors, such as co-cultivation with cancer cell ascites or exposure to IL-6, leukemia inhibitors, or purine adenosine, can polarize M2d macrophages (tumor-associated macrophages), which in turn promotes angiogenesis and cancer dissemination (40, 41).

The cause of IBD remains unidentified, but macrophage polarization is pivotal in its immune mechanism. During the active phase of IBD, macrophages polarize towards M1 macrophages and release a large number of inflammatory factors, leading to the continuous progression of intestinal inflammatory response. In the remission period of IBD, M1 macrophages decreased, and their ability to release inflammatory factors was also significantly decreased, and the related markers of M2 macrophages were up-regulated, thus alleviating intestinal inflammatory response. Thus, controlling the polarization and activity of macrophages may aid in alleviating IBD symptoms.

5 Bile acid receptors and their functions in macrophages

5.1 FXR

Farnesoid X receptor (FXR) is a ligand-dependent bile acid nuclear receptor (BAR), first discovered by Forman in 1995 and named for its transcriptional activity that can be enhanced by physiological concentrations of farnesol (42). In 1999, it was discovered that bile at the physiological level is an endogenous ligand of FXR, hence FXR is known as the BA receptor. It is found throughout the body in many organs, mostly existed in the intestines and liver, and primarily triggered by primary bile acids (42, 43). It is one of the two bile acid-related receptors that have received the most attention. Apart from playing a crucial role in maintaining the balance of bile acids (44, 45),



FXR influences the course of numerous illnesses, such as liver cancer, metabolic diseases, gastrointestinal problems, and non-alcoholic steatohepatitis (46–48). Some studies believe that FXR can participate in the maintenance of intestinal homeostasis through various mechanisms, and it can improve intestinal inflammation and inhibit the growth of colitis-related tumors by regulating the recruitment and polarization of intestinal macrophages and crosstalk with Th17 cells. Patients with colitis-associated colorectal cancer (CAC) and IBD had significantly reduced FXR.

FXR is a major regulator of BAs homeostasis, a key gene that regulates bile acid synthesis, transport and reabsorption metabolism (10, 49). FXR mainly regulates bile acid metabolic homeostasis through the liver FXR/SHP axis and ileal FGF 15/19 (FGF19 in humans and FGF15 in mice)/liver FGF receptor 4 (FGFR4) axis, and inhibits the activity of rate limiting enzyme CYP7A1, thus inhibiting bile acid synthesis (50–55). After the ileal cells release it, FGF15/19 reaches the liver via portal circulation. In hepatocytes, FGF15/19 binds to FGF-R4, inhibiting CYP7A1 activity and thereby decreasing BAs synthesis in liver tissue (50, 53–55). Bile acids can also up-regulate the expression of SHP protein by activating the FXR-SHP axis, and the up-regulated SHP binds to liver receptor homologous 1 (LRH-1) into heterodimer and inactivates LRH-1, which can positively regulate the expression of CYP7A1 (10). Consequently, the FXR-SHP axis activation suppresses the synthesis of bile acid rate-limiting enzymes, thereby inhibiting bile acid production and maintaining metabolic homeostasis (44, 51, 52). By controlling gene expression to stop bile acid accumulation, FXR protects the liver from bile acids' damaging effects.

IBD causes intestinal damage and exposes macrophages to more bile acids. FXR stabilizes the nuclear receptor corepressor protein 1 (NCoR1) complex by directly targeting the promoters of pro-inflammatory genes, including iNOS, TNF- α , and IL-1 β , when it is activated by ligands such as primary bile acids. The NCoR1

complex attaches to gene promoters, blocking NF- κ B binding and thus inhibiting inflammatory factor secretion to exert an anti-inflammatory effect. NCoR1 is eliminated from these promoters upon TLR-4 activation. One of the mechanisms by which FXR exerts anti-inflammatory effects in macrophages is through SHP, where FXR regulates SHP in a promoter-dependent manner and blocks the AP-1 pathway by inducing up-regulation of SHP, thereby preventing its binding to inflammatory genes. FXR exerts anti-inflammatory effects by regulating the NLRP3 inflammasome, whose overactivation is linked to various inflammatory diseases. FXR prevents NLRP3 and caspase 1 from physically interacting to activate the NLRP3 inflammasome, which stops them from assembling into an inflammasome (Figure 3) (56–58). Many studies have demonstrated that in wild mice with drug-induced colitis, the injection of FXR agonists may considerably reduce intestinal inflammation, block the reduction of cup cells, repair the damaged intestinal mucosal barrier, reduce intestinal permeability, and therefore ameliorate colitis. However, the application of FXR agonists in whole-body FXR knockout mice did not improve colitis. FXR signals are damaged in both IBD and CAC mouse models as well as in IBD and CAC patients. The absence of FXR will increase the susceptibility to inflammation and cancer. Moreover, FXR contributes to the metabolism of carbohydrates and lipids. By encouraging the expression of genes linked to fatty acid oxidation, thermogenesis and mitochondrial biogenesis, FXR activation can help reduce obesity and stop diet-induced weight gain. It is also associated with Browning of adipose tissue and can reduce inflammatory cytokine levels while upregulating beta-adrenergic signaling. FGF15/19 efficiently increases insulin sensitivity and is currently utilized to treat major metabolic illnesses such as diabetes, obesity, and non-alcoholic steatohepatitis (NASH). Activation of FXR can also result in liver insulin sensitization and ameliorate insulin resistance (59). The therapeutic role of Obeticholic acid (OCA), an FXR receptor agonist

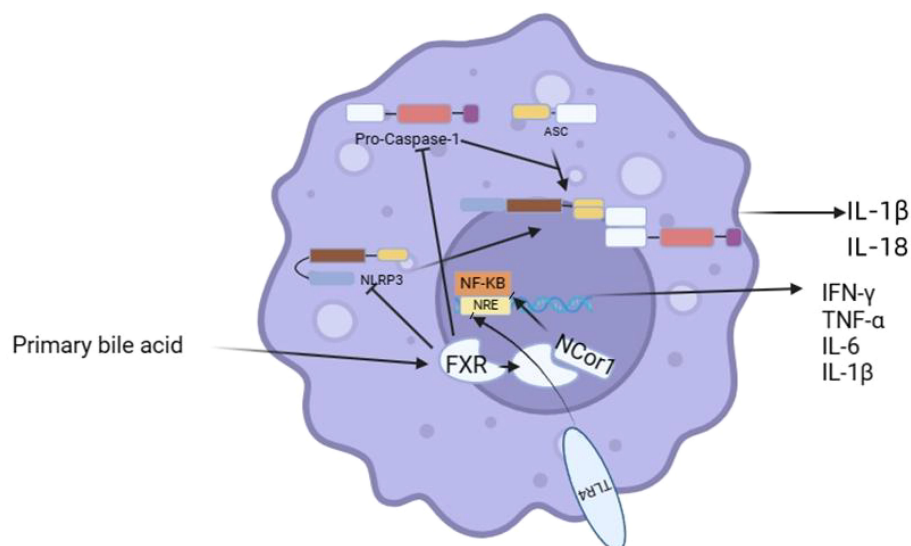


FIGURE 3
FXR regulates macrophages.

used to treat primary biliary cholangitis (PBC), in hepatic steatosis and cirrhosis has been extensively studied.

Therefore, activating FXR can not only directly affect the differentiation and function of intestinal macrophages and reduce inflammatory factors, but also regulate the recruitment of intestinal macrophages, inhibit the activation and recruitment of intestinal macrophages, and thereby suppress the progression of inflammatory bowel disease (5). In addition to improving intestinal inflammation through intestinal macrophages, it can also regulate bile acid metabolism to restore intestinal homeostasis, and plays an important role in regulating lipopolysaccharide metabolism and energy metabolism. FXR may become an important target for the treatment of IBD and maintaining human health.

5.2 GPBAR1

Initially identified by Maruyama et al. in 2002, GPBAR1 is a seven-transmembrane G-protein-coupled receptor that is also referred to as M-BAR or TGR5 (60, 61). GPBAR1 is broadly distributed throughout the body. High levels of GPBAR1 mRNA have been detected in the small intestine, stomach, liver, lung, placenta, spleen, and other organs (62). Secondary bile acids are primarily responsible for its activation, and different types of BAs have different levels of activation on GPBAR1: LCA > DCA > CDCA > UDCA > CA. The physiological ligands of GPBAR1 are the secondary bile acids DCA and LCA (61).

GPBAR1 is thought to be essential for the preservation of intestine and hepatic immunological homeostasis and is expressed in innate immune cells, macrophages, and NKT cells (62–67). GPBAR1 plays an important role in cell signal transduction. In macrophages, by being activated by DCA and LCA, GPBAR1 increases the amount of cAMP by enhancing the recruitment of

cAMP response element binding protein (CREB) to the target gene CRE (cAMP response element), thereby controlling the expression of numerous genes in the target cells. Studies by Michele Biagioli found that under physiological conditions, GPBAR1 activation inhibits the development of inflammatory immune responses and promotes the formation of anti-inflammatory phenotypes in macrophages. This effect may be mediated by the cAMP-response element binding protein (CREB) binding to the IL-10 gene promoter (68, 69). The CAMP-KA-CREb pathway reduces NF- κ B activity and inhibits IL-10 secretion, and the use of BAR501, a selective GPBAR1 agonist, promotes IL-10 production by increasing CREB binding to IL-10 promoters, which exerts anti-inflammatory effects (64). By stimulating GPBAR1, the secondary bile acids DCA and LCA can prevent the NLRP3 inflammasome from activating (56, 70). DCA and LCA can lead to the ubiquitination of NLRP3 inflammasome-dependent GPBAR1/cyclic adenosine phosphate (cAMP)/protein kinase A (PKA) pathway, thereby inhibiting its activation and effectively inhibiting the production of IL-1 β , and significantly damaging the phagocytosis and secretion functions of macrophages, thus playing a role in inhibiting inflammation (Figure 4) (71). Apart from its pro-inflammatory function, IL-1 β also encourages the drying of epithelial villi cells, which leads to the development of inflammation-related colon cancers. Furthermore, the activation of GPBAR1 increases the levels of camp-dependent thyroid hormone-activating enzyme (D2-type thyroginine deiodinase) in brown adipose tissue and skeletal muscle cells, promotes the release of glucagon-like peptide-1 (GLP-1), and participates in regulating intestinal motility. These findings collectively indicate that this receptor can be used to treat a variety of metabolic disorders, such as obesity, metabolic syndrome and type 2 diabetes (72–75).

In summary, GPBAR1 promotes anti-inflammatory effects by regulating the polarization of macrophages towards the anti-

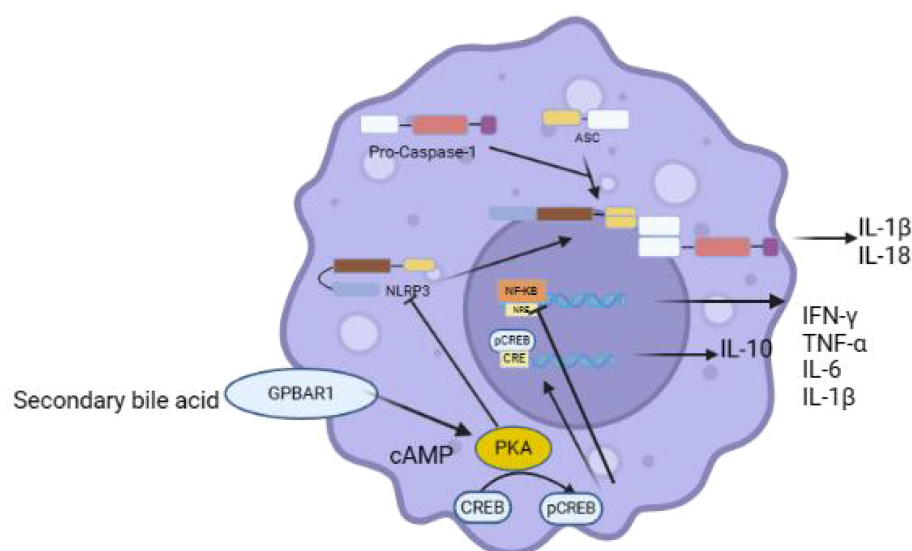


FIGURE 4
GPBAR1 regulates macrophages.

inflammatory M2 phenotype and inhibiting the production of pro-inflammatory cytokines, thereby maintaining intestinal homeostasis. The activation of GPR41 can also enhance the intestinal barrier function and promote the secretion of glucagon-like peptide-1 (GLP-1), which is beneficial to intestinal integrity and metabolic health (76).

5.3 VDR

VDR mediates the biological activity of 1,25(OH)₂D₃ and belongs to the nuclear receptor superfamily (77, 78). The vitamin D-VDR endocrine system is present in almost all nucleated cells. The active form of vitamin D, calcitriol, activates the nuclear receptor known as VDR. Calcitriol engages the VDR to regulate calcium and phosphate levels essential for human homeostasis. VDR can be activated by LCA and its metabolites (78–80). VDR can regulate various diseases of the gut, kidneys, bones, skin, heart, and various other organs (80). For example, the absence of specific VDR in the breast epithelium significantly inhibits pubertal mammary gland development. Lack of VDR in the lungs of mice can lead to early onset of COPD/emphysema, accompanied by chronic inflammatory responses, immune dysregulation, and lung destruction. By decreasing oxidative stress and blocking the autophagy and apoptosis pathways of cardiomyocytes, VDR activation guards against cardiac ischemia/reperfusion injury.

VDR is primarily studied as a bile acid sensor in the gut and is widely expressed in the gastrointestinal tract (81, 82). Its protective effect against colitis and colon cancer has been established (83). Numerous immune cells have the VDR/JAK/STAT signaling pathway, which controls cell activity and has significant implications for improving illness. Previous research indicated that toll-like receptors on monocytes and macrophages detect bacterial,

viral, and fungal components, leading to increased expression of the vitamin D receptor (VDR) and CYP27B1 (84). Activation of VDR results in its heterodimerization with the retinoid X receptor (RXR). Heterodimers interact with DNA to stimulate the production of antibiotic peptides, leading to antibiotic-like effects (85, 86). Then, using mice with deficient vitamin D receptor (VDR) in colonic epithelial cells (CEC-VDRKO) or non-intestinal epithelial cells (NEC-VDRKO), the study found that activation of vitamin D receptor can reduce the symptoms and inflammation of colitis and promote the repair of intestinal tissue. 1, 25-dihydroxyvitamin D had anti-inflammatory effects by directly inhibiting M1-type macrophage polarization and promoting M2-type macrophage polarization in mice treated with DSS (Figure 5) (87, 88). Through its modulation of the JAK/STAT signaling pathway, VDR can affect the growth of tumors. However, Lu et al. found that Monotropein can regulate macrophage M1-type polarization via VDR/JAK1/STAT1 and inhibit colitis-related cancers (89), it is still necessary to investigate the molecular mechanism of VDR. VDR also regulates the composition and function of gut bacterial communities. Oral 1,25 (OH)₂D₃ supplementation has an effect on the gut microbiota of the human digestive tract, reducing opportunistic pathogens and increasing bacterial abundance.

5.4 S1PR2

S1PR2 is a G-protein-coupled receptor, which is activated by the bioactive lipid sphingosine 1-phosphate (S1P), and has various functions such as participating in metabolism, regulating muscle function, and regulating immune cell transport (90–94). Conjugated bile acids with taurine or glycine can also activate S1PR2. Hepatocytes, sinusoidal endothelial cells, bile duct cells, hepatic stellate cells, and macrophages all express S1PR2.

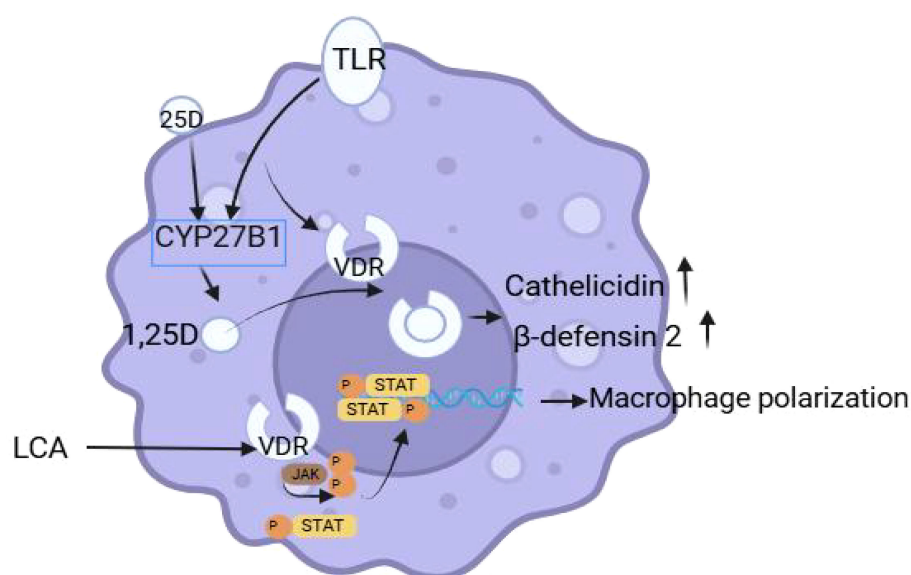


FIGURE 5
VDR regulates macrophages.

There are five subtypes of the G-protein-coupled receptor S1PR: S1PR1, S1PR2, S1PR3, S1PR4, and S1PR5. S1PR1 signals coordinate the transformation of macrophages into M2 type and the conversion of macrophages into M1 type is regulated by S1PR3 (95–97). By altering signaling pathways and enzymes, S1PR has been shown in numerous studies to have a significant effect on the movement of immune cells, tumor cells and so on. S1PR controls the body's relative reaction in this manner. Consequently, S1PR has been identified as a potential target for treating autoimmune, lung, liver diseases, and cancer (98).

Both intestinal mucosal macrophages from IBD patients and mice with DSS-induced colitis, as well as LPS-treated macrophages *in vitro*, showed markedly increased expression of S1PR2. The S1PR2/RhoA/ROCK1 signaling pathway potentially contributes to IBD development by influencing M1 macrophage polarization (99). Additionally, S1PR2 is a significant target for IBD treatment due to its functions in regulating vascular permeability, immune cell transport, and preserving intestinal epithelial barrier integrity. Research indicates that S1PR2-/- deficient mice exhibit heightened sensitivity to dextran sulfate-induced colitis, characterized by increased intestinal permeability and CD4+ T cell proliferation (100). Another study showed that neither the inhibition of FXR nor the knockdown of TGR5 expression in a high-fat diet had a notable effect on the production of DCA-promoted proinflammatory cytokine IL-1 β . According to the study, DCA induces the release of pepsin B, at least partially, through S1PR2, which in turn activates the NLRP3 inflammasome (Figure 6). This, in turn, causes the macrophages to produce IL-1 β in a dose-dependent manner. Given that colitis-associated cancer (CAC) is closely linked

to persistent, uncontrolled intestinal inflammation, this may also be another possible mechanism by which secondary bile acid DCA is involved in colon cancer development.

6 Treatment

The global incidence of IBD has been rising annually, predominantly affecting young individuals. Most IBD patients have repeated attacks and are not cured, and inflammatory bowel disease is progressive. A considerable number of patients need surgical treatment due to complications, such as ileostomy, subtotal colectomy or total colectomy. If left untreated, it may lead to a series of irreversible long-term complications, such as colitis-related colorectal cancer (101). With the development of science and technology, the treatment of IBD has kept pace with The Times. In the early 20th century, colitis treatment primarily involved bed rest and enemas. After 1930, the surgical treatment of UC has made great progress, and ileostomy, subtotal colectomy or total colectomy are still retained (102). The discovery of sulfonamides and antibiotics contributed to the emergence of the first effective UC treatment drugs, and subsequently, glucocorticoids, immunosuppressants and other drugs were found to be successfully used in the treatment of IBD, and the introduction of anti-tumor necrosis factor α (TNF- α) monoclonal antibodies made the treatment of IBD enter the era of biological agents. Currently, IBD treatment drugs are categorized into para-aminosalicylic acid, glucocorticoids, immunosuppressants, biologics, and small molecule drugs (Table 2).

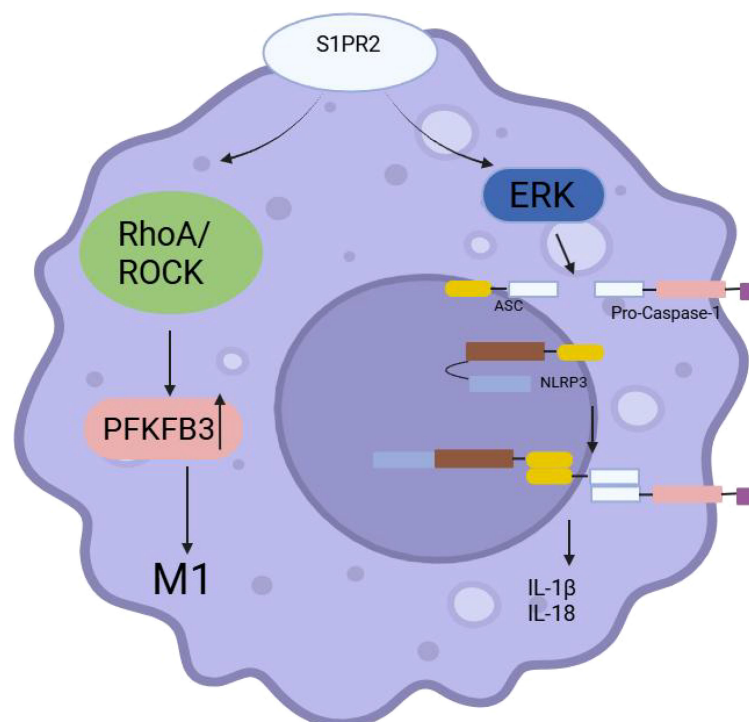


FIGURE 6
S1PR2 regulates macrophages.

The active ingredient in aminosalicic acid, 5 aminosalicic acid (5 ASA), reduces inflammation and antioxidant to treat IBD. In addition, 5 ASA can regulate the immunity and correct the imbalance of intestinal flora in UC patients, and play a role in preventing colon cancer (109). Among them, sulfasalazine (SASP) is the first drug discovered, and its therapeutic effect on UC and active CD has been confirmed in a number of studies (103, 110, 111). Only a small fraction of SASP is absorbed in the small intestine. Most of the drugs are decomposed by bacteria after reaching the colon and release 5 ASA and SP. The former plays a therapeutic role locally in the colon mucosa, while the latter acts as an inert carrier to ensure the release of 5 ASA in the colon. The side effects of SASP include gastrointestinal reactions, rash, headache, reversible male infertility, allergic reactions, hepatotoxicity, hematological toxicity, aseptic pneumonia, etc. The

occurrence of these adverse reactions is considered to be closely related to the blood concentration of SP, so the development of new preparations of 5-ASA without SP to reduce adverse reactions is the focus of research (112).

Cytoplasmic glucocorticoid receptor (GR) can regulate the transcription of anti-inflammatory protein genes by binding to glucocorticoids. This process inhibits pro-inflammatory gene activation and promotes the degradation of their mRNA, resulting in significant anti-inflammatory effects (105). As early as the 1950s, glucocorticoids were found to have a positive effect on symptom improvement in UC patients. The dose, manner, and duration of administration all affect the likelihood and intensity of the majority of glucocorticoid-related adverse effects (113). At the same time, hormone resistance is another concern in hormone therapy (114).

TABLE 2 Drug therapy for inflammatory bowel disease.

Type	Medicine	Characteristics	Common adverse reactions	Precaution	References
Para-aminosalicylic acid	Sulfasalazine	Colon release	Gastrointestinal reactions, rash, headache, reversible male infertility, allergic reactions, hepatotoxicity, hematological toxicity, aseptic pneumonia	Not for use in children under 2 years old, as it has many drug interactions, including with oral hypoglycemic agents and oral anticoagulants.	Kirsner JB (103), Ko CW (104)
	Mesalazine	Ileum and colon release	Diarrhea, nausea and headache	Combined use with adrenaline and anticoagulants increases the tendency to bleed and enhances the hypoglycemic effect of sulfonylureas.	
	Olsalazine	Release at distal jejunum, ileum and colon	Diarrhea, nausea and headache	Not for use in patients with severe liver or kidney dysfunction.	
Glucocorticoid	Budesonide	The doses of other types of systemic action hormones are converted based on the dose of prednisone	Hypercortical syndrome induces or aggravates infection, osteoporosis, muscle atrophy, and delayed wound healing	Gradually reduce the dosage until the medication is stopped as the symptoms ease. It cannot be used for maintenance treatment.	Kadmiel M et al. (105)
Immunosuppressant	Tacrolimus, Thalidomide	Suitable for those who are ineffective or dependent on glucocorticoid	Gastrointestinal reactions, hepatotoxicity, infection, bone marrow suppression, and pancreatitis	For patients with hormone-dependent UC, a low dose of [1.3mg/(kg.d)] azathioprine can effectively maintain disease remission; Thalidomide is suitable for the treatment of refractory UC	Lichtiger S (106), Singh S (107)
Biologics and small molecule drugs	Adalimumab, certolizumab pegol, golimumab	Glucocorticoid and the above-mentioned immunosuppressants are ineffective or glucocorticoid-dependent or intolerant to the above-mentioned drugs	Infection, gastrointestinal discomfort, allergies, headaches, malignant tumors	Contraindications: ① Active infection, chronic infection or a history of repeated infections in the recent period; ② Congestive heart failure ③ Malignant tumors (including current symptoms and past medical history); ④ Demyelinating lesions of the nervous system; ⑤ Allergic to murine protein components; ⑥ Pregnancy period.	Peyrin-Biroulet L (108)

Immunosuppressants are the third class of drugs introduced for the treatment of IBD, but the initial indications of this class of drugs do not include IBD. With the development and widespread clinical application of biologics, the positioning of immunosuppressants in the treatment of IBD has changed, and the combination treatment with biologics may be more effective and beneficial, but more evidence is needed. 6-mercaptopurine (6-MP) and azathioprine (AZA) have been shown to be effective and relatively safe in the induction and maintenance of remission of IBD, postoperative maintenance therapy of CD, and chemoprophylaxis of colorectal cancer (115–117). Hepatotoxicity, infection, pancreatitis, bone marrow suppression, and gastrointestinal problems are among the common side effects of AZA and 6-MP. Long-term use may raise the chance of developing cancerous growths such as skin cancer and lymphoma (118).

Biologics and small molecule drugs can bind to specific targets to effectively control clinical symptoms and disease progression in patients with IBD by blocking downstream inflammatory responses and lymphocyte migration. The first biologics introduced for IBD treatment were anti-TNF- α drugs. Common adverse reactions of biologics and small molecule drugs include infection, gastrointestinal discomfort, allergy, headache, etc. Common serious adverse events include severe infection, opportunistic infection, and malignant tumor. The production of anti-antibodies are closely related to the loss of response to biologic agents and allergy, and combined immunosuppressive therapy can significantly reduce the production of anti-antibodies (119). The development of medications that target bile acid receptors to treat cholestasis and metabolic disorders has advanced recently (46, 47). Currently, various bile acid receptor ligands have demonstrated potential in experimentally treating diseases such as IBD. A derivative of the anthocyanide oxycholic acid, obeticholic acid (OCA) is an FXR agonist, has been utilized in clinical studies to treat NASH. The intestinal environment's stability is maintained via the JAK/STAT-mediated signaling system. A novel oral JAK inhibitor called tofacitinib has been approved in clinical studies to treat UC and may potentially be useful in treating CD (120). Tofacitinib decreased intestinal inflammatory response in UC patients by inhibiting M1 macrophage polarization, which in turn decreased the production of inflammatory markers. Meanwhile, *in vitro* studies indicate that vitamin D influences macrophage polarization, warranting further investigation into its role as an immunomodulator in IBD treatment.

7 Conclusions and perspectives

Maintaining bile acid homeostasis in life is crucial since studies conducted in recent decades have shown how vital bile acids are for immunity. The importance of bile acids interacting with the gut microbiome is well understood and extensively studied.

In addition to their role in lipid metabolism, bile acids have become important metabolites of pleiotropic signals as important regulators of intestinal immune system and intestinal microbiota. Bile acids can regulate the development and function of intestinal immune cells by acting as natural ligands on bile acid receptors that exist in these cells. This impacts the gut's immunological homeostasis.

In this review, the latest advances in bile acid metabolism and bile acid receptor regulation of intestinal macrophages are reviewed. Although important advances have been made in past studies, many important questions remain. Due to its low specificity, bile acids can bind to various bile acid receptors and have immunomodulatory effects. Bile acid receptors are widely distributed in the body and exist in various tissues and organs. Secondly, due to the cytotoxic effects of bile acids and their metabolites themselves, the use of bile acids in the treatment of IBD still requires further research. The intestinal microbiota, intestinal immune cells and intestinal microenvironment interact and influence each other, making it still difficult to use bile acids in the treatment of IBD. The search for new, safe and effective targeted drugs is the focus of the next research. As mentioned in the article, some targeted drugs have been proven to have good therapeutic effects on inflammatory bowel disease. Some of the latest studies also indicate that bile acid receptor dual agonists have therapeutic potential in IBD models. Dual-target drugs or multi-target drugs, especially those with synergistic effects, will have greater advantages in improving therapeutic efficacy and reducing drug resistance. In conclusion, although there are still some difficulties in the treatment of IBD with bile acid receptors, there is strong evidence supporting the role of bile acid receptors in regulating macrophages and IBD. Discovering and validating brand-new dual-target or multi-target drugs and developing highly specific targeted drugs is one of the main development directions in the future, which has significant clinical significance.

Author contributions

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Conflict of interest

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References

- Fiorucci S, Biagioli M, Zampella A, Distrutti E, et al. Bile acids activated receptors regulate innate immunity. *Front Immunol.* (2018) 9:1853. doi: 10.3389/fimmu.2018.01853
- He S, Li J, Yao Z, Gao Z, Jiang Y, Chen X, et al. Insulin alleviates murine colitis through microbiome alterations and bile acid metabolism. *J Transl Med.* (2023) 21:498. doi: 10.1186/s12967-023-04214-3
- Biagioli M, Di Giorgio C, Massa C, Marchiano S, Bellini R, Bordoni M, et al. Microbial-derived bile acid reverses inflammation in IBD via GPBAR1 agonism and RORgammat inverse agonism. *BioMed Pharmacother.* (2024) 181:117731. doi: 10.1016/j.biopha.2024.117731
- He Q, Wu J, Ke J, Zhang Q, Zeng W, Luo Z, et al. Therapeutic role of ursodeoxycholic acid in colitis-associated cancer via gut microbiota modulation. *Mol Ther.* (2023) 31:585–98. doi: 10.1016/j.yjmt.2022.10.014
- Dong X, Qi M, Cai C, Zhu Y, Li Y, Coulter S, et al. Farnesoid X receptor mediates macrophage-intrinsic responses to suppress colitis-induced colon cancer progression. *JCI Insight.* (2024) 9. doi: 10.1172/jci.insight.170428
- Biagioli M, Di Giorgio C, Morretta E, Bellini R, Massa C, Urbani G, et al. Development of dual GPBAR1 agonist and RORgammat inverse agonist for the treatment of inflammatory bowel diseases. *Pharmacol Res.* (2024) 208:107403. doi: 10.1016/j.phrs.2024.107403
- Huang Y, Chen Z, et al. Inflammatory bowel disease related innate immunity and adaptive immunity. *Am J Transl Res.* (2016) 8:2490–7.
- de Souza HS, Fiocchi C, et al. Immunopathogenesis of IBD: current state of the art. *Nat Rev Gastroenterol Hepatol.* (2016) 13:13–27. doi: 10.1038/nrgastro.2015.186
- Lee SH, Kwon JE, Cho ML, et al. Immunological pathogenesis of inflammatory bowel disease. *Intest Res.* (2018) 16:26–42. doi: 10.5217/ir.2018.16.1.26
- Chiang JY, et al. Bile acids: regulation of synthesis. *J Lipid Res.* (2009) 50:1955–66. doi: 10.1194/jlr.R900010-JLR200
- Fiorucci S, Carino A, Baldoni M, Santucci L, Costanzi E, Graziosi L, et al. Bile acid signaling in inflammatory bowel diseases. *Dig Dis Sci.* (2021) 66:674–93. doi: 10.1007/s10620-020-06715-3
- Quinn RA, Melnik AV, Vrbancac A, Fu T, Patras KA, Christy MP, et al. Global chemical effects of the microbiome include new bile-acid conjugations. *Nature.* (2020) 579:123–9. doi: 10.1038/s41586-020-2047-9
- Russell DW, et al. The enzymes, regulation, and genetics of bile acid synthesis. *Annu Rev Biochem.* (2003) 72:137–74. doi: 10.1146/annurev.biochem.72.121801.161712
- Kiriyama Y, Nochi H, et al. Physiological role of bile acids modified by the gut microbiome. *Microorganisms.* (2021) 10. doi: 10.3390/microorganisms10010068
- Fiorucci S, Distrutti E, et al. Bile acid-activated receptors, intestinal microbiota, and the treatment of metabolic disorders. *Trends Mol Med.* (2015) 21:702–14. doi: 10.1016/j.molmed.2015.09.001
- Guzior DV, Quinn RA, et al. Review: microbial transformations of human bile acids. *Microbiome.* (2021) 9:140. doi: 10.1186/s40168-021-01101-1
- Chiang JY, et al. Bile acid metabolism and signaling. *Compr Physiol.* (2013) 3:1191–212. doi: 10.1002/cphy.c120023
- Li T, Chiang JY, et al. Bile acid signaling in metabolic disease and drug therapy. *Pharmacol Rev.* (2014) 66:948–83. doi: 10.1124/pr.113.008201
- Chiang JY, et al. Recent advances in understanding bile acid homeostasis. *F1000Res.* (2017) 6:2029. doi: 10.12688/f1000research.12449.1
- Fiorucci S, Distrutti E, et al. Chenodeoxycholic acid: an update on its therapeutic applications. *Handb Exp Pharmacol.* (2019) 256:265–82. doi: 10.1007/164_2019_226
- Di Ciaula A, Wang DQ, Portincasa P, et al. An update on the pathogenesis of cholesterol gallstone disease. *Curr Opin Gastroenterol.* (2018) 34:71–80. doi: 10.1097/MOG.0000000000000423
- Vitek L, Carey MC, et al. New pathophysiological concepts underlying pathogenesis of pigment gallstones. *Clin Res Hepatol Gastroenterol.* (2012) 36:122–9. doi: 10.1016/j.clinre.2011.08.010
- Tazuma S, et al. Gallstone disease: Epidemiology, pathogenesis, and classification of biliary stones (common bile duct and intrahepatic). *Best Pract Res Clin Gastroenterol.* (2006) 20:1075–83. doi: 10.1016/j.bpg.2006.05.009
- Lefebvre P, Cariou B, Lien F, Kuipers F, Stals B, et al. Role of bile acids and bile acid receptors in metabolic regulation. *Physiol Rev.* (2009) 89:147–91. doi: 10.1152/physrev.00010.2008
- Makishima M, Okamoto AY, Repa JJ, Tu H, Learned RM, Luk A, et al. Identification of a nuclear receptor for bile acids. *Science.* (1999) 284:1362–5. doi: 10.1126/science.284.5418.1362
- Fiorucci S, Baldoni M, Ricci P, Zampella A, Distrutti E, Biagioli M, et al. Bile acid-activated receptors and the regulation of macrophages function in metabolic disorders. *Curr Opin Pharmacol.* (2020) 53:45–54. doi: 10.1016/j.coph.2020.04.008
- Muller PA, Matheis F, Mucida D, et al. Gut macrophages: key players in intestinal immunity and tissue physiology. *Curr Opin Immunol.* (2020) 62:54–61. doi: 10.1016/j.coi.2019.11.011
- Gomez Perdiguero E, Klapproth K, Schulz C, Busch K, Azzoni E, Crozet L, et al. Tissue-resident macrophages originate from yolk-sac-derived erythro-myeloid progenitors. *Nature.* (2015) 518:547–51. doi: 10.1038/nature13989
- Ginhoux F, Williams M, et al. Tissue-Resident macrophage ontogeny and homeostasis. *Immunity.* (2016) 44:439–49. doi: 10.1016/j.immuni.2016.02.024
- Mills CD, Kincaid K, Alt JM, Heilman MJ, Hill AM, et al. M-1/M-2 macrophages and the Th1/Th2 paradigm. *J Immunol.* (2000) 164:6166–73. doi: 10.4049/jimmunol.164.12.6166
- Martinez FO, Gordon S, et al. The M1 and M2 paradigm of macrophage activation: time for reassessment. *F1000Prime Rep.* (2014) 6:13. doi: 10.12703/P6-13
- Anders CB, Lawton TMW, Smith HL, Garret J, Doucette MM, Ammons MCB, et al. Use of integrated metabolomics, transcriptomics, and signal protein profile to characterize the effector function and associated metabotype of polarized macrophage phenotypes. *J Leukoc Biol.* (2022) 111:667–93. doi: 10.1002/JLB.6A1120-744R
- Mosser DM, Edwards JP, et al. Exploring the full spectrum of macrophage activation. *Nat Rev Immunol.* (2008) 8:958–69. doi: 10.1038/nri2448
- Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaili SA, Mardani F, et al. Macrophage plasticity, polarization, and function in health and disease. *J Cell Physiol.* (2018) 233:6425–40. doi: 10.1002/jcp.26429
- Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M, et al. The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol.* (2004) 25:677–86. doi: 10.1016/j.it.2004.09.015
- Biswas SK, Mantovani A, et al. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. *Nat Immunol.* (2010) 11:889–96. doi: 10.1038/ni.1937
- Wynn TA, Vannella KM, et al. Macrophages in tissue repair, regeneration, and fibrosis. *Immunity.* (2016) 44:450–62. doi: 10.1016/j.immuni.2016.02.015
- Yue Y, Yang X, Feng K, Wang L, Hou J, Mei B, et al. M2b macrophages reduce early reperfusion injury after myocardial ischemia in mice: A predominant role of inhibiting apoptosis via A20. *Int J Cardiol.* (2017) 245:228–35. doi: 10.1016/j.ijcard.2017.07.085
- Zizzo G, Hilliard BA, Monestier M, Cohen PL, et al. Efficient clearance of early apoptotic cells by human macrophages requires M2c polarization and MerTK induction. *J Immunol.* (2012) 189:3508–20. doi: 10.4049/jimmunol.1200662
- Wu H, Xu JB, He YL, Peng JJ, Zhang XH, Chen CQ, et al. Tumor-associated macrophages promote angiogenesis and lymphangiogenesis of gastric cancer. *J Surg Oncol.* (2012) 106:462–8. doi: 10.1002/jso.23110
- Wang Q, Ni H, Lan L, Wei X, Xiang R, Wang Y, et al. Fra-1 protooncogene regulates IL-6 expression in macrophages and promotes the generation of M2d macrophages. *Cell Res.* (2010) 20:701–12. doi: 10.1038/cr.2010.52
- Forman BM, Goode E, Chen J, Oro AE, Bradley DJ, Perlmann T, et al. Identification of a nuclear receptor that is activated by farnesol metabolites. *Cell.* (1995) 81:687–93. doi: 10.1016/0092-8674(95)90530-8
- Distrutti E, Santucci L, Cipriani S, Renga B, Schiaroli E, Ricci P, et al. Bile acid activated receptors are targets for regulation of integrity of gastrointestinal mucosa. *J Gastroenterol.* (2015) 50:707–19. doi: 10.1007/s00535-015-1041-8
- Wang L, Lee YK, Bundman D, Han Y, Thevananthi S, Kim C S, et al. Redundant pathways for negative feedback regulation of bile acid production. *Dev Cell.* (2002) 2:721–31. doi: 10.1016/s1534-5807(02)00187-9
- Fiorucci S, Distrutti E, Biagioli M, et al. Special FX: harnessing the farnesoid-X-receptor to control bile acid synthesis. *Dig Dis Sci.* (2021) 66:3668–71. doi: 10.1007/s10620-021-06840-7
- Teodoro JS, Rolo AP, Palmeira CM, et al. Hepatic FXR: key regulator of whole-body energy metabolism. *Trends Endocrinol Metab.* (2011) 22:458–66. doi: 10.1016/j.tem.2011.07.002

47. Chavez-Talavera O, Tailleux A, Lefebvre P, Staels B, et al. Bile acid control of metabolism and inflammation in obesity, type 2 diabetes, dyslipidemia, and nonalcoholic fatty liver disease. *Gastroenterology*. (2017) 152:1679–1694 e3. doi: 10.1053/j.gastro.2017.01.055
48. Lee FY, Lee H, Hubbert ML, Edwards PA, Zhang Y, et al. FXR, a multipurpose nuclear receptor. *Trends Biochem Sci*. (2006) 31:572–80. doi: 10.1016/j.tibs.2006.08.002
49. Islam KB, Fukiya S, Hagio M, Fujii N, Ishizuka S, Ooka T, et al. Bile acid is a host factor that regulates the composition of the cecal microbiota in rats. *Gastroenterology*. (2011) 141:1773–81. doi: 10.1053/j.gastro.2011.07.046
50. Inagaki T, Choi M, Moschetta A, Peng L, Cummins CL, McDonald JG, et al. Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. *Cell Metab*. (2005) 2:217–25. doi: 10.1016/j.cmet.2005.09.001
51. Lu TT, Makishima M, Repa JJ, Schoonjans K, Kerr TA, Auwerx J, et al. Molecular basis for feedback regulation of bile acid synthesis by nuclear receptors. *Mol Cell*. (2000) 6:507–15. doi: 10.1016/S1097-2765(00)00050-2
52. Fang S, Miao J, Xiang L, Ponugoti B, Treuter E, Kemper JK, et al. Coordinated recruitment of histone methyltransferase G9a and other chromatin-modifying enzymes in SHP-mediated regulation of hepatic bile acid metabolism. *Mol Cell Biol*. (2007) 27:1407–24. doi: 10.1128/MCB.00944-06
53. Song KH, Li T, Owsley E, Strom S, Chiang JY, et al. Bile acids activate fibroblast growth factor 19 signaling in human hepatocytes to inhibit cholesterol 7 α -hydroxylase gene expression. *Hepatology*. (2009) 49:297–305. doi: 10.1002/hep.22627
54. Kim I, Ahn SH, Inagaki T, Choi M, Ito S, Guo GL, et al. Differential regulation of bile acid homeostasis by the farnesoid X receptor in liver and intestine. *J Lipid Res*. (2007) 48:2664–72. doi: 10.1194/jlr.M700330-JLR200
55. Holt JA, Luo G, Billin AN, Bisi J, McNeill YY, Kozarsky KF, et al. Definition of a novel growth factor-dependent signal cascade for the suppression of bile acid biosynthesis. *Genes Dev*. (2003) 17:1581–91. doi: 10.1101/gad.1083503
56. Guo C, Xie S, Chi Z, Zhang J, Liu Y, Zhang L, et al. Bile acids control inflammation and metabolic disorder through inhibition of NLRP3 inflammasome. *Immunity*. (2016) 45:944. doi: 10.1016/j.immuni.2016.10.009
57. Hao H, Cao L, Jiang C, Che Y, Zhang S, Takahashi S, et al. Farnesoid X receptor regulation of the NLRP3 inflammasome underlies cholestasis-associated sepsis. *Cell Metab*. (2017) 25:856–867 e5. doi: 10.1016/j.cmet.2017.03.007
58. Yang CS, Kim JJ, Kim TS, Lee PY, Kim SY, Lee HM, et al. Small heterodimer partner interacts with NLRP3 and negatively regulates activation of the NLRP3 inflammasome. *Nat Commun*. (2015) 6:6115. doi: 10.1038/ncomms7115
59. Fang S, Suh JM, Reilly SM, Yu E, Osborn O, Lackey D, et al. Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance. *Nat Med*. (2015) 21:159–65. doi: 10.1038/nm.3760
60. Maruyama T, Miyamoto Y, Nakamura T, Tamai Y, Okada H, Sugiyama E, et al. Identification of membrane-type receptor for bile acids (M-BAR). *Biochem Biophys Res Commun*. (2002) 298:714–9. doi: 10.1016/S0006-291X(02)02550-0
61. Kawamata Y, Fujii R, Hosoya M, Harada M, Yoshida H, Miwa M, et al. A G protein-coupled receptor responsive to bile acids. *J Biol Chem*. (2003) 278:9435–40. doi: 10.1074/jbc.M209706200
62. Cipriani S, Mencarelli A, Chini MG, Distrutti E, Renga B, Bifulco G, et al. The bile acid receptor GPBAR-1 (TGR5) modulates integrity of intestinal barrier and immune response to experimental colitis. *PLoS One*. (2011) 6:e25637. doi: 10.1371/journal.pone.0025637
63. Maruyama T, Tanaka K, Suzuki J, Miyoshi H, Harada N, Nakamura T, et al. Targeted disruption of G protein-coupled bile acid receptor 1 (Gpbar1/M-Bar) in mice. *J Endocrinol*. (2006) 191:197–205. doi: 10.1677/joe.1.06546
64. Ichikawa R, Takayama T, Yoneno K, Kamada N, Kitazume MT, Higuchi H, et al. Bile acids induce monocyte differentiation toward interleukin-12 hypo-producing dendritic cells via a TGR5-dependent pathway. *Immunology*. (2012) 136:153–62. doi: 10.1111/j.1365-2567.2012.03554.x
65. Mencarelli A, Renga B, Migliorati M, Cipriani S, Distrutti E, Santucci L, et al. The bile acid sensor farnesoid X receptor is a modulator of liver immunity in a rodent model of acute hepatitis. *J Immunol*. (2009) 183:6657–66. doi: 10.4049/jimmunol.0901347
66. Biagioli M, Carino A, Fiorucci C, Marchiano S, Di Giorgio C, Bordonni M, et al. The bile acid receptor GPBAR1 modulates CCL2/CCR2 signaling at the liver sinusoidal/macrophage interface and reverses acetaminophen-induced liver toxicity. *J Immunol*. (2020) 204:2535–51. doi: 10.4049/jimmunol.1901427
67. Biagioli M, Carino A, Fiorucci C, Marchiano S, Di Giorgio C, Roselli R, et al. GPBAR1 functions as gatekeeper for liver NKT cells and provides counterregulatory signals in mouse models of immune-mediated hepatitis. *Cell Mol Gastroenterol Hepatol*. (2019) 8:447–73. doi: 10.1016/j.jcmgh.2019.06.003
68. Biagioli M, Carino A, Cipriani S, Francisci D, Marchiano S, Scarpelli P, et al. The bile acid receptor GPBAR1 regulates the M1/M2 phenotype of intestinal macrophages and activation of GPBAR1 rescues mice from murine colitis. *J Immunol*. (2017) 199:718–33. doi: 10.4049/jimmunol.1700183
69. Fiorucci S, Mencarelli A, Palladino G, Cipriani S, et al. Bile-acid-activated receptors: targeting TGR5 and farnesoid-X-receptor in lipid and glucose disorders. *Trends Pharmacol Sci*. (2009) 30:570–80. doi: 10.1016/j.tips.2009.08.001
70. Chen Y, Le TH, Du Q, Zhao Z, Liu Y, Zou J, et al. Genistein protects against DSS-induced colitis by inhibiting NLRP3 inflammasome via TGR5-cAMP signaling. *Int Immunopharmacol*. (2019) 71:144–54. doi: 10.1016/j.intimp.2019.01.021
71. Haselow K, Bode JG, Wammers M, Ehling C, Keitel V, Kleinebrecht L, et al. Bile acids PKA-dependently induce a switch of the IL-10/IL-12 ratio and reduce proinflammatory capability of human macrophages. *J Leukoc Biol*. (2013) 94:1253–64. doi: 10.1189/jlb.0812396
72. Watanabe M, Houten SM, Matak C, Christoffolete MA, Kim BW, Sato H, et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature*. (2006) 439:484–9. doi: 10.1038/nature04330
73. Velazquez-Villegas LA, Perino A, Lemos V, Zietak M, Nomura M, Pols TWH, et al. TGR5 signalling promotes mitochondrial fission and beige remodelling of white adipose tissue. *Nat Commun*. (2018) 9:245. doi: 10.1038/s41467-017-02068-0
74. Donkers JM, Kooijman S, Slijepcevic D, Kunst RF, Roscam Abbing RL, Haazen L, et al. NTCP deficiency in mice protects against obesity and hepatosteatosis. *JCI Insight*. (2019) 5. doi: 10.1172/jci.insight.127197
75. Chaudhari SN, Harris DA, Aliakbarian H, Luo JN, Henke MT, Subramaniam R, et al. Bariatric surgery reveals a gut-restricted TGR5 agonist with anti-diabetic effects. *Nat Chem Biol*. (2021) 17:20–9. doi: 10.1038/s41589-020-0604-z
76. Pols TW, Noriega LG, Nomura M, Auwerx J, Schoonjans K, et al. The bile acid membrane receptor TGR5 as an emerging target in metabolism and inflammation. *J Hepatol*. (2011) 54:1263–72. doi: 10.1016/j.jhep.2010.12.004
77. Brumbaugh PF, Haussler MR, et al. 1 α ,25-dihydroxycholecalciferol receptors in intestine. II. Temperature-dependent transfer of the hormone to chromatin via a specific cytosol receptor. *J Biol Chem*. (1974) 249:1258–62. doi: 10.1016/S0021-9258(19)42969-4
78. Makishima M, Lu TT, Xie W, Whitfield GK, Domoto H, Evans RM, et al. Vitamin D receptor as an intestinal bile acid sensor. *Science*. (2002) 296:1313–6. doi: 10.1126/science.1070477
79. Adachi R, Honma Y, Masuno H, Kawana K, Shimomura I, Yamada S, et al. Selective activation of vitamin D receptor by lithocholic acid acetate, a bile acid derivative. *J Lipid Res*. (2005) 46:46–57. doi: 10.1194/jlr.M400294-JLR200
80. Li N, Ma P, Li Y, Shang X, Nan X, Shi L, et al. Gut microbiota-derived 12-ketolithocholic acid suppresses the IL-17A secretion from colonic group 3 innate lymphoid cells to prevent the acute exacerbation of ulcerative colitis. *Gut Microbes*. (2023) 15:2290315. doi: 10.1080/19490976.2023.2290315
81. Bookout AL, Jeong Y, Downes M, Yu RT, Evans RM, Mangelsdorf DJ, et al. Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network. *Cell*. (2006) 126:789–99. doi: 10.1016/j.cell.2006.06.049
82. Nagpal S, Na S, Rathnachalam R, et al. Noncalcemic actions of vitamin D receptor ligands. *Endocr Rev*. (2005) 26:662–87. doi: 10.1210/er.2004-0002
83. Takada I, Makishima M, et al. Control of inflammatory bowel disease and colorectal cancer by synthetic vitamin D receptor ligands. *Curr Med Chem*. (2017) 24:868–75. doi: 10.1217/0929867323666161202145509
84. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science*. (2006) 311:1770–3. doi: 10.1126/science.1123933
85. Gombart AF, Borregaard N, Koeffler HP, et al. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. *FASEB J*. (2005) 19:1067–77. doi: 10.1096/fj.04-3284com
86. Yuk JM, Shin DM, Lee HM, Yang CS, Jin HS, Kim KK, et al. Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin. *Cell Host Microbe*. (2009) 6:231–43. doi: 10.1016/j.chom.2009.08.004
87. Wang F, Johnson RL, DeSmet ML, Snyder PW, Fairfax KC, Fleet JC, et al. Vitamin D receptor-dependent signaling protects mice from dextran sulfate sodium-induced colitis. *Endocrinology*. (2017) 158:1951–63. doi: 10.1210/en.2016-1913
88. Carlberg C, et al. Vitamin D signaling in the context of innate immunity: focus on human monocytes. *Front Immunol*. (2019) 10:2211. doi: 10.3389/fimmu.2019.02211
89. Lu Y, Chen Y, Li Y, Xu S, Lian D, Liang J, et al. Monotropein inhibits colitis associated cancer through VDR/JAK1/STAT1 regulation of macrophage polarization. *Int Immunopharmacol*. (2023) 124, 110838. doi: 10.1016/j.intimp.2023.110838
90. Studer E, Zhou X, Zhao R, Wang Y, Takabe K, Nagahashi M, et al. Conjugated bile acids activate the sphingosine-1-phosphate receptor 2 in primary rodent hepatocytes. *Hepatology*. (2012) 55:267–76. doi: 10.1002/hep.24681
91. Nagahashi M, Takabe K, Liu R, Peng K, Wang X, Wang Y, et al. Conjugated bile acid-activated S1P receptor 2 is a key regulator of sphingosine kinase 2 and hepatic gene expression. *Hepatology*. (2015) 61:1216–26. doi: 10.1002/hep.27592
92. Lu H, Yuan H, Chen S, Huang L, Xiang H, Yang G, et al. Senescent endothelial dysfunction is attributed to the up-regulation of sphingosine-1-phosphate receptor-2 in aged rats. *Mol Cell Biochem*. (2012) 363:217–24. doi: 10.1007/s11010-011-1173-y
93. Zhang L, Dong Y, Wang Y, Hu W, Dong S, Chen Y, et al. Sphingosine-1-phosphate (S1P) receptors: Promising drug targets for treating bone-related diseases. *J Cell Mol Med*. (2020) 24:4389–401. doi: 10.1111/jcmm.15155

94. Roberts E, Guerrero M, Urbano M, Rosen H, et al. Sphingosine 1-phosphate receptor agonists: a patent review, (2010-2012). *Expert Opin Ther Pat.* (2013) 23:817–41. doi: 10.1517/13543776.2013.783022
95. Nagahashi M, Yamada A, Katsuta E, Aoyagi T, Huang WC, Terracina KP, et al. Targeting the sphK1/S1P/S1PR1 axis that links obesity, chronic inflammation, and breast cancer metastasis. *Cancer Res.* (2018) 78:1713–25. doi: 10.1158/0008-5472.CAN-17-1423
96. Yang J, Yang L, Tian L, Ji X, Yang L, Li L, et al. Sphingosine 1-phosphate (S1P)/S1P receptor2/3 axis promotes inflammatory M1 polarization of bone marrow-derived monocyte/macrophage via G(alpha)i/o/PI3K/JNK pathway. *Cell Physiol Biochem.* (2018) 49:1677–93. doi: 10.1159/000493611
97. Deng S, Zhou X, Ge Z, Song Y, Wang H, Liu X, et al. Exosomes from adipose-derived mesenchymal stem cells ameliorate cardiac damage after myocardial infarction by activating S1P/SK1/S1PR1 signaling and promoting macrophage M2 polarization. *Int J Biochem Cell Biol.* (2019) 114:105564. doi: 10.1016/j.biocel.2019.105564
98. Chen H, Wang J, Zhang C, Ding P, Tian S, Chen J, et al. Sphingosine 1-phosphate receptor, a new therapeutic direction in different diseases. *BioMed Pharmacother.* (2022) 153:113341. doi: 10.1016/j.biopha.2022.113341
99. Wang X, Chen S, Xiang H, Wang X, Xiao J, Zhao S, et al. S1PR2/RhoA/ROCK1 pathway promotes inflammatory bowel disease by inducing intestinal vascular endothelial barrier damage and M1 macrophage polarization. *Biochem Pharmacol.* (2022) 201:115077. doi: 10.1016/j.bcp.2022.115077
100. Zhao S, Gong Z, Zhou J, Tian C, Gao Y, Xu C, et al. Deoxycholic acid triggers NLRP3 inflammasome activation and aggravates DSS-Induced colitis in mice. *Front Immunol.* (2016) 7:536. doi: 10.3389/fimmu.2016.00536
101. Chan SSM, et al. Editorial: differences in sex-based incidence of inflammatory bowel diseases between Asia-Pacific and Western countries - are these due to differences in environment, access to healthcare, or pathophysiology? *Aliment Pharmacol Ther.* (2019) 49:1098–9. doi: 10.1111/apt.15203
102. Actis GC, Pellicano R, Fagoonee S, Ribaldone DG, et al. History of inflammatory bowel diseases. *J Clin Med.* (2019) 8. doi: 10.3390/jcm8111970
103. Kirsner JB, et al. Historical origins of medical and surgical therapy of inflammatory bowel disease. *Lancet.* (1998) 352:1303–5. doi: 10.1016/S0140-6736(98)11132-7
104. Ko CW, Singh S, Feuerstein JD, Falck-Ytter C, Falck-Ytter Y, Cross RK, et al. AGA Clinical Practice Guidelines on the Management of Mild-to-Moderate Ulcerative Colitis. *Gastroenterology.* (2019) 156(3):748–64. doi: 10.1053/j.gastro.2018.12.009
105. Kadmiel M, Cidlowski JA, et al. Glucocorticoid receptor signaling in health and disease. *Trends Pharmacol Sci.* (2013) 34:518–30. doi: 10.1016/j.tips.2013.07.003
106. Lichtiger S, Present DH. Preliminary report: cyclosporin in treatment of severe active ulcerative colitis. *Lancet.* (1990) 336(8706):16–9. doi: 10.1016/0140-6736(90)91521-b
107. Singh S, Allegretti JR, Siddique SM, Terdiman JP. AGA Technical review on the management of moderate to severe ulcerative colitis. *Gastroenterology.* (2020) 158(5):1465–96.e17. doi: 10.1053/j.gastro.2020.01.007
108. Peyrin-Biroulet L, Sandborn WJ, Panaccione R, Domenech E, Pouillon L, Siegmund B, et al. Tumour necrosis factor inhibitors in inflammatory bowel disease: the story continues. *Therap Adv Gastroenterol.* (2021) 14:17562848211059954. doi: 10.1177/17562848211059954
109. Beiranvand M, et al. A review of the biological and pharmacological activities of mesalazine or 5-aminosalicylic acid (5-ASA): an anti-ulcer and anti-oxidant drug. *Inflammopharmacology.* (2021) 29:1279–90. doi: 10.1007/s10787-021-00856-1
110. Baron JH, Connell AM, Lennard-Jones JE, Jones FA, et al. Sulphasalazine and salicylazosulphadimidine in ulcerative colitis. *Lancet.* (1962) 1:1094–6. doi: 10.1016/s0140-6736(62)92080-9
111. Dick AP, Grayson MJ, Carpenter RG, Petrie A, et al. Controlled trial of sulphasalazine in the treatment of ulcerative colitis. *Gut.* (1964) 5:437–42. doi: 10.1136/gut.5.5.437
112. Watkinson G, et al. Sulphasalazine: a review of 40 years' experience. *Drugs.* (1986) 32 Suppl 1:1–11. doi: 10.2165/00003495-198600321-00003
113. Keenan GF, et al. Management of complications of glucocorticoid therapy. *Clin Chest Med.* (1997) 18:507–20. doi: 10.1016/s0272-5231(05)70398-1
114. Farrell RJ, Kelleher D, et al. Glucocorticoid resistance in inflammatory bowel disease. *J Endocrinol.* (2003) 178:339–46. doi: 10.1677/joe.0.1780339
115. Bean RH, et al. The treatment of chronic ulcerative colitis with 6-mercaptopurine. *Med J Aust.* (1962) 49:592–3. doi: 10.5694/j.1326-5377.1962.tb20590.x
116. Summers RW, Switz DM, Sessions JT Jr., Beckett JM, Best WR, Kern FJ, et al. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology.* (1979) 77:847–69. doi: 10.1016/0016-5085(79)90385-8
117. Axelrad JE, Roy A, Lawlor G, Korelitz B, Lichtiger S, et al. Thiopurines and inflammatory bowel disease: Current evidence and a historical perspective. *World J Gastroenterol.* (2016) 22:10103–17. doi: 10.3748/wjg.v22.i46.10103
118. Goldberg R, Irving PM, et al. Toxicity and response to thiopurines in patients with inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol.* (2015) 9:891–900. doi: 10.1586/17474124.2015.1039987
119. Bots SJ, Parker CE, Brandse JF, Lowenberg M, Feagan BG, Sandborn WJ, et al. Anti-drug antibody formation against biologic agents in inflammatory bowel disease: A systematic review and meta-analysis. *BioDrugs.* (2021) 35:715–33. doi: 10.1007/s40259-021-00507-5
120. Salas A, Hernandez-Rocha C, Duijvestein M, Faubion W, McGovern D, Vermeire S, et al. JAK-STAT pathway targeting for the treatment of inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol.* (2020) 17:323–37. doi: 10.1038/s41575-020-0273-0