Liver X receptor: A potential target for inflammatory bowel disease and colorectal cancer (Review)

YINGJIE LI[1*], XIAOYAN FU[1*], MEIWEN BAI[1*], JIAQI ZHOU[1], JIATAI QIU[1], HONGXIA ZHANG[1], SHUJUAN LIANG[1] and MEIFANG LIU[1,2]

[1]Lab for Immune Microenvironment and Inflammatory Disease Research in Universities of Shandong Province, School of Basic Medical Sciences, Shandong Second Medical University, Weifang, Shandong 261053, P.R. China; [2]Department of Nephrology, Affiliated Hospital of Shandong Second Medical University, Weifang, Shandong 261041, P.R. China

Received March 29, 2025; Accepted October 29, 2025

DOI: 10.3892/mmr.2025.13764

Abstract. Liver X receptor (LXR), comprising isoforms LXRα and LXRβ, is a member of the nuclear receptor family, which serves important roles in maintaining cholesterol and lipid metabolism homeostasis by regulating cholesterol excretion and reverse transport. LXR activation also participates in regulating the pathological processes of inflammation and tumor-related processes, such as proliferation and apoptosis. Inflammatory bowel disease (IBD) and colorectal cancer (CRC) are two common intestinal inflammatory diseases, and the occurrence of CRC is closely associated with the development of chronic inflammation, particularly IBD. To date, the pathogenesis of IBD and CRC remains to be fully elucidated, although research is being conducted in this area. LXR has been suggested to participate in regulating the pathogenesis of both IBD and CRC. Although previous findings illustrate the benefits of LXR activation on intestinal inflammatory response and cancer, there remains a lack of comprehensive understanding of how LXR exerts its properties. The present review provided an overview of the recent advances in understanding the roles of LXR in IBD and CRC, to explore the potential therapeutic strategies and targets mediated by the dual roles of LXR in immune modulation and cholesterol metabolism, and to identify the link between IBD and CRC. The present review highlighted the novel role of LXR in bridging metabolic regulation and immune homeostasis, positioning it as a promising therapeutic target for IBD and CRC.

Correspondence to: Professor Meifang Liu or Professor Shujuan Liang, Lab for Immune Microenvironment and Inflammatory Disease Research in Universities of Shandong Province, School of Basic Medical Sciences, Shandong Second Medical University, 7166 Baotong West Street, Weifang, Shandong 261053, P.R. China
E-mail: lmf00719@163.com
E-mail: liangshj@sdsmu.edu.cn

*Contributed equally

Key words: liver X receptor, inflammatory bowel disease, colorectal cancer, inflammation, intestinal

Contents

1. Introduction

Inflammatory bowel disease (IBD) is a chronic and recurrent inflammatory disorder of the gastrointestinal tract, which mainly includes Crohn's disease (CD) and ulcerative colitis (UC) (1-4). UC is an idiopathic chronic inflammatory condition affecting the colonic mucosa, characterized by alternating periods of flare-ups and remission. The disease typically originates in the rectum and extends continuously throughout the colon (5). Lesions are predominantly confined to the colonic mucosa, with ulcers manifesting as the primary symptom, alongside diarrhea, abdominal pain and weight loss, among which bloody diarrhea is a hallmark of UC (6). CD is a progressive chronic inflammatory disease that can affect any part of the gastrointestinal tract. The most commonly affected parts are the terminal ileum and colon. In addition to symptoms such as diarrhea and abdominal pain, complications such as stenosis, fistula or abscesses may occur over time (7,8). The incidence of IBD is higher in developed countries. According to recent epidemiological evidence, ~3 million individuals in the USA are affected by IBD (9). The majority of patients experience symptom onset aged 20-39 years, with a lower incidence rate observed in individuals aged >50 years (3). The pathogenesis of IBD involves multifactorial interactions, including environmental triggers, genetic susceptibility, immune dysregulation and gut microbiota alterations. Available evidence suggests that abnormal immune responses, including both innate and adaptive immune response, are important causes of chronic intestinal inflammation in patients with IBD (10,11). Chronic, persistent

inflammation is a hallmark of IBD and is associated with an increased risk of intestinal malignancies (12,13). Notably, liver X receptor (LXR), as a cholesterol sensor, has recently been shown to mitigate inflammation-driven carcinogenesis by restoring immune-metabolic balance (14). Long-term inflammation can induce damage and dysregulated proliferation of colonic mucosal cells, ultimately leading to the development of cancer, such as colorectal cancer (CRC) and colitis-associated cancer (15,16). Therefore, a major challenge in controlling IBD and colon cancer is managing the occurrence and development of intestinal inflammation, which may be an effective method to treat digestive system diseases linked to intestinal inflammation.

LXR is a ligand-activated transcription factor belonging to the nuclear hormone receptor family, comprising two subtypes: LXRα and LXRβ (17). LXRα is highly expressed in metabolically active tissues, including the liver, small intestine, kidney, adipose tissue and macrophages, while LXRβ is ubiquitously expressed throughout the body (17,18). LXR has been identified to function as a heterodimer with retinoid X receptor (RXR). The LXR/RXR heterodimer can be activated by ligands or agonists of LXR or RXR individually, or by both simultaneously, resulting in a synergistic effect (19,20). The activation of LXR has been reported to regulate the expression of a series of genes associated with cholesterol transport, glucose metabolism and the modulation of inflammatory responses (21,22). LXR regulates cholesterol metabolism by inducing the expression of a series of target genes, including adenosine triphosphate (ATP)-binding cassette transporter family members such as ATP-binding cassette transporter A1 (ABCA1), ATP-binding cassette subfamily G member (ABCG)1, ABCG5 and ABCG8, which promote the absorption, transport and excretion of cholesterol in the intestine (23,24). The LXR/RXR heterodimer has been identified as a key regulator of ABCA1 expression *in vivo* (25). In addition, the genes involved in the LXR-induced regulation of the cholesterol metabolism pathway include sterol regulatory element-binding protein (SREBP)2, which can activate cholesterol biosynthesis and uptake pathways at low cholesterol levels. These mechanisms work together to maintain the balance of cholesterol in the body (26-28). Although the most widely studied function of LXR is to regulate cholesterol metabolism, previous studies have shown that LXR is also involved in the regulation of inflammatory responses and tumor progression, particularly in enteritis and intestinal cancer (29,30). Existing studies have shown that LXR can reduce inflammatory response and intestinal mucosal injury by reducing inflammatory cell infiltration, inhibiting the secretion of pro-inflammatory cytokines and enhancing the integrity of the intestinal mucosal barrier (14,31,32). For example, LXR activation can reduce the release of inflammatory mediators by promoting macrophage polarization to anti-inflammatory phenotypes and can enhance the phagocytosis of macrophages toward tumor-related inflammatory cells (33-36). In addition, the activation of LXR can directly inhibit the proliferation or promote the apoptosis of intestinal tumor cells by regulating cholesterol metabolism or related genes, thus inhibiting tumor growth (37-39). The present review summarizes the pleiotropic effects of LXR on IBD and CRC pathogenesis, focusing on three interconnected axes: i) Intestinal barrier preservation; ii) immune cell reprogramming; and iii) metabolic regulation. Therapeutic opportunities and challenges in targeting LXR signaling are further discussed.

2. LXR and intestinal homeostasis

LXR as an intestinal barrier guardian. As a nuclear receptor superfamily member, LXR has emerged as a central regulator of intestinal homeostasis through its dual roles in metabolic regulation and immune modulation (29,40). LXR maintains mucosal integrity through dual mechanisms: The intestinal barrier serves as the first line of defense in maintaining intestinal homeostasis and it is mainly composed of the mucus layer on the surface of intestinal epithelial cells, which is formed by the synthesis and secretion of large amounts of mucin 2 (MUC2) by goblet cells. MUC2 serves a key role in protecting the intestinal tract from harmful substances and numerous microorganisms. By contrast, defects in the synthesis and secretion of MUC2, as well as alterations in its glycosylation structure, may lead to intestinal diseases (41-43). Furthermore, tight junction proteins in intestinal epithelial cells, such as tight junction protein 1 and claudins, are an important part of the intestinal barrier (44,45). Under physiological conditions, LXR, with its function primarily mediated by LXRβ, maintains MUC2 secretion from goblet cells and sustains the expression of tight junction proteins (46).

LXR as an immune modulator. The activation of LXR has emerged as a potent protective mechanism in intestinal inflammatory diseases. It is worth noting that the distinct LXR subtypes have different roles: LXRα primarily governs immune responses in myeloid immune cells, such as macrophages and dendritic cells (DCs), whereas LXRβ orchestrates immune responses within the intestinal epithelium (47). Among them, LXRα serves a notable role in modulating macrophage polarization, shifting their phenotype from pro-inflammatory M1 to anti-inflammatory M2 subtypes, which is important for resolving intestinal inflammation and maintaining immune homeostasis (29,48). LXRβ effectively mediates the initiation and progression of inflammatory responses by suppressing the transcription of inflammatory factors and chemokines in intestinal epithelial cells, thereby reducing immune cell infiltration (47). Furthermore, an imbalance between T helper 17 (Th17) and regulatory T (Treg) cells is an important factor in the pathogenesis of autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and IBD (49,50). The activation of LXRα and LXRβ alleviates the occurrence and progression of intestinal inflammatory diseases by regulating the balance of Th17/Treg cells in the intestine through distinct mechanisms. The excessive activation of Th17 cells or excessive immunosuppressive activity induced by Treg cells may contribute to the development of cancer, such as colorectal, breast and ovarian cancer. Therefore, the activation of LXR is important for regulating the balance of Th17/Treg cells, and inhibiting tumor immune escape and growth (51).

LXR as a metabolic stabilizer. LXR, which acts as a cholesterol sensor, has been reported to regulate cholesterol transport to the liver and its excretion as bile acids, so as to maintain cholesterol homeostasis. In particular, LXR is involved in

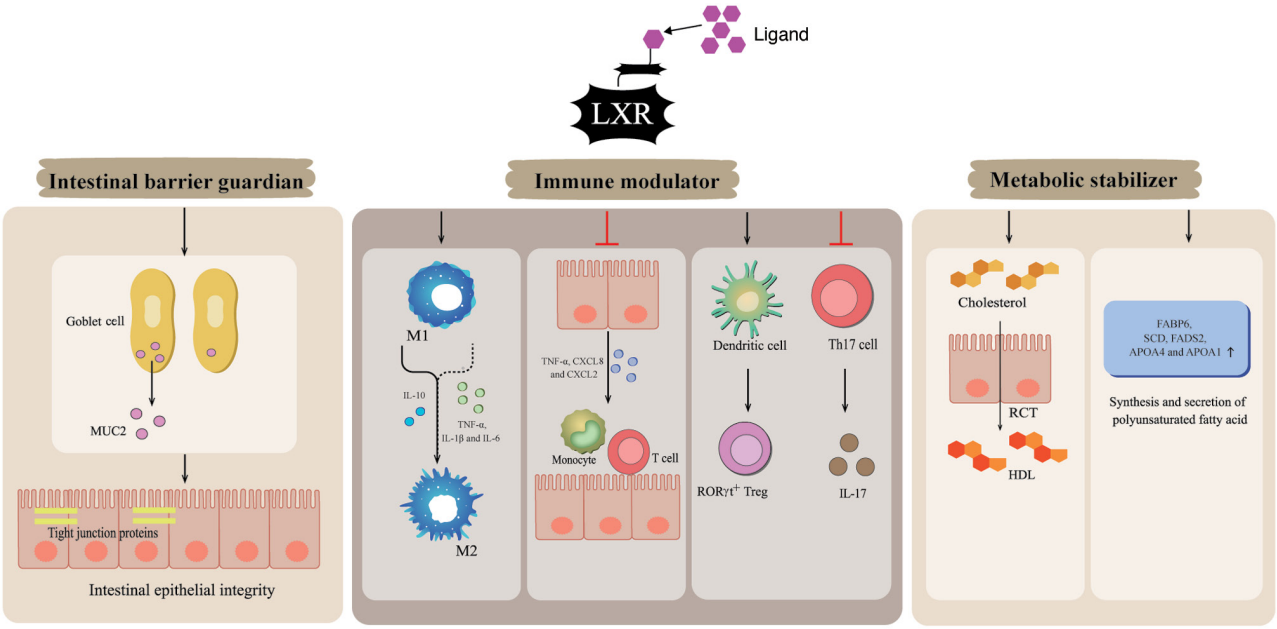

Figure 1. Role of LXR in intestinal homeostasis. LXR serves multiple key roles in intestinal homeostasis. As an intestinal barrier guardian, LXR maintains the integrity of the intestinal epithelium, promotes the secretion of MUC2 by goblet cells and upregulates the expression of tight junction proteins. As an immunomodulator, LXR regulates the intestinal immune response by influencing the polarization of monocytes into M1 and M2 macrophages, the expression of inflammatory factors in epithelial cells and subsequent immune cell infiltration, as well as the balance of Th17/Treg cells. As a metabolic stabilizer, LXR affects intestinal metabolic homeostasis by regulating RCT, and the synthesis and secretion of fatty acids. These functions of LXR work together to ensure that the intestine maintains normal physiological function and health in the face of external challenges. LXR, liver X receptor; Th17, T helper 17; RORγt$^+$ Treg, RORγt-expressing regulatory T cell; HDL, high-density lipoprotein; MUC2, mucin 2; RCT, reverse cholesterol transport; FABP6, fatty acid-binding protein 6; SCD, stearoyl-CoA desaturase; FADS2, fatty acid desaturase 2; APO, apolipoprotein.

reverse cholesterol transport (RCT), which refers to the transport of cholesterol from peripheral tissues to the liver, where it is excreted in the form of bile acid (52-54). In the intestine, LXRα is predominantly expressed in fully differentiated cells of the colonic epithelium and ileal villi, mediating the reverse excretion of cholesterol, while LXRβ is typically expressed in the intestinal mucosal epithelium, promoting cholesterol absorption. The relative distribution and interaction of these two subtypes jointly regulate the absorption and excretion of intestinal cholesterol (55).

Furthermore, the activation of LXR, particularly LXRα, promotes fatty acid desaturation and storage by upregulating fatty acid-binding protein 6, stearoyl-CoA desaturase (SCD) and fatty acid desaturase 2, thereby facilitating dynamic lipid buffering within intracellular lipid droplets. Complementing these processes, LXR stimulates the synthesis and secretion of apolipoprotein (APO)A4 and APOA1, which are important for chylomicron assembly and basolateral trafficking of dietary lipids (56-58). These synergistic mechanisms maintain the homeostatic equilibrium of intestinal lipid absorption, metabolism and excretion. Therefore, the activation of LXR can regulate intestinal cholesterol homeostasis, thus preventing the occurrence of metabolic diseases. Notably, the intestinal vs. hepatic tissue-specific effects of LXR agonists warrant further investigation, as systemic activation of LXR may lead to hepatic steatosis, a key challenge for therapeutic development (30).

Briefly, the activation of LXR inhibits intestinal inflammation and tumorigenesis by enhancing intestinal barrier function and immune regulation, as well as regulating cholesterol metabolism (Fig. 1).

3. LXR in intestinal pathologies

In the pathological process of IBD, as a nuclear receptor and transcriptional regulator, LXR ameliorates colonic pathology and intestinal inflammation by maintaining the intestinal barrier function, inhibiting the release of inflammatory mediators and modulating immune cell function. In terms of CRC, LXR activation in tumor cells is responsible for apoptosis or pyroptosis by blocking the cell cycle and regulating cholesterol metabolism, thus inhibiting tumor cell proliferation. In addition, the activation of LXR within the tumor microenvironment (TME) also inhibits tumor progression by fostering a robust antitumor immune response. The role of LXR in IBD and CRC pathogenesis is summarized as follows.

LXR in IBD

Anti-inflammatory mechanisms. Various immune factors contribute to the development of IBD. These include immune cells, such as macrophages, neutrophils and lymphocytes, as well as the inflammatory cytokines and chemokines they produce (47,59-61). Furthermore, epithelial cells can secrete a variety of cytokines and chemokines, which promote the migration and infiltration of other immune cells, thus aggravating the inflammatory response (47,59,62). Current evidence has indicated that the activation of LXR can inhibit the inflammatory response by regulating the differentiation and infiltration of lymphocytes. LXRβ activation suppresses pro-inflammatory cytokine release and CD4$^+$ T-cell infiltration, thereby preventing aberrant Th17 cell differentiation. In parallel, LXRα activation mitigates inflammation by driving

DC-dependent Treg cell differentiation. Together, these mechanisms reduce the production of inflammatory mediators, such as TNF-α (46,47,63-66). Previous studies in mice with colitis have revealed that impaired oxysterol-LXR signaling disrupts the Th17/Treg cell balance through increased Th17 polarization and diminished Treg cell populations. This imbalance is associated with elevated levels of pro-inflammatory cytokines, such as IL-17 and IL-23 (44,64,67). However, specific drug treatments, such as Si-Ni-San, can target oxysterol/LXR signaling, which helps to restore the balance of Th17/Treg cells, thus protecting the body from intestinal diseases caused by inflammatory response (44).

In addition, experimental models have shown that LXR deficiency exacerbates colitis by increasing the infiltration of immune cells and the release of inflammatory mediators into the colon (46,47). The activation of LXR, primarily of the isoform LXRα, reduces the accumulation of immune cells at inflammatory sites and inhibits the release of pro-inflammatory mediators, including IL-17, TNF-α, IL-1β, C-X-C motif chemokine (CXCL)8, CXCL10 and C-C motif chemokine (CCL)2, thus alleviating intestinal inflammation and injury (68-70). Additionally, the activation of LXR attenuates the recruitment of MyD88, an innate immune signal transduction adaptor, and TNF receptor associated factor 6 via ABCA1-dependent changes in membrane lipid tissue; furthermore, LXR activation inhibits the Toll-like receptor (TLR)2, TLR4 and TLR9 signaling pathways, particularly TLR4 signaling and the NF-κB axis, and reduces the release of pro-inflammatory factors, such as TNF-α and IL-1β (32,71). These anti-inflammatory effects following LXR activation are observed not only in immune cells, such as macrophages and DCs, but also in intestinal epithelial cells (71-74).

The anti-inflammatory effect of epithelial LXR activation is mediated through two primary mechanisms. Primarily, in response to high intracellular cholesterol, LXRα activation in intestinal epithelial cells orchestrates cholesterol homeostasis by upregulating efflux transporters, such as ABCA1 and ABCG1, and inhibiting the uptake mediator NPC1-like intracellular cholesterol transporter 1 (75). This promotes RCT and high-density lipoprotein synthesis, thereby preventing excessive accumulation of cholesterol in enterocytes and exerting an anti-inflammatory effect (56,76-79). It has been shown that the activation of LXR can regulate lipid metabolism by increasing the expression of ABCA1 and promoting the outflow of cholesterol (75,80), thus inhibiting the NF-κB signaling pathway and the release of pro-inflammatory factors (72,76,81,82). Similarly, LXRβ expression in colonic epithelial cells exerts anti-inflammatory effects. The activation of LXRβ markedly suppresses the expression of inflammatory and chemotactic factors, such as TNF-α, CXCL8 and CXCL2, thereby reducing the recruitment of immune cells, including macrophages and T cells, and ultimately curbing the propagation of inflammation (47).

Preclinical evidence. Intestinal barrier homeostasis is important for preventing IBD. Compromise of the mucosal barrier can initiate IBD and even the development of CRC. Both LXRα and LXRβ are expressed in colonic epithelial cells and work cooperatively to maintain intestinal barrier integrity (46,72). A study has shown that LXRβ deletion leads to the development of higher severity colitis than LXRα deletion (47). Further mechanistic analysis has suggested that LXRβ may directly regulate goblet cell differentiation and sustain MUC2 expression, whereas loss of LXRβ can lead to reduced goblet cell numbers and disruption of the mucus layer, thereby impairing the intestinal mucosal barrier (46). Notably, LXRα/β double knockout mice have been shown to exhibit a loss of estrogen receptor β (ERβ), which leads to the dysfunction of goblet cell secretion and the notable downregulation of the hemidesmosomal protein plectin, resulting in mucosal damage and the deterioration of epithelial cell connections, suggesting that LXRα indirectly regulates epithelial structure integrity through ERβ expression (46,47). These findings in LXR-deficient mice suggest that LXR contributes to intestinal barrier integrity not only in its activated state but also through basal expression in the absence of ligand binding. Nonetheless, the specific regulatory mechanisms of LXR isoforms in intestinal barrier function remain to be fully elucidated. Further investigations using subtype-selective genetic knockout models are required to elucidate their distinct roles in cellular differentiation.

LXR also serves as an important regulator of intestinal stem cell proliferation, differentiation dynamics and epithelial repair processes (30). In dextran sulfate sodium-induced colitis models, treatment with the LXR agonist GW3965 hydrochloride was shown to promote the proliferation of crypt cells, rather than directly mitigating damage. Upon intestinal injury, LXR activation enhances epithelial regeneration and tissue repair through modulation of cholesterol homeostasis and induction of amphiregulin expression (30,83,84). Although these findings highlight the regenerative role of LXR, the precise molecular mechanisms governing LXR-mediated intestinal regeneration require further elucidation. Additionally, one study demonstrated that LXR agonists such as T0901317 promote fecal cholesterol excretion by promoting RCT and intestinal cholesterol excretion in diabetic and obese mice, thus preventing excessive accumulation of cholesterol in intestinal epithelial cells (24).

Briefly, LXR serves an important role in regulating intestinal inflammation by maintaining the integrity of the intestinal barrier, regulating the release of chemokines and mediating the function of immune cells. Notably, chronic inflammation in IBD establishes a tumor-promoting microenvironment through sustained cytokine signaling and oxidative stress (85,86). Given the anti-inflammatory function of LXR, it is plausible that LXR activation may attenuate chronic inflammation-driven tumorigenesis during IBD progression. Therefore, LXR is not only a key molecule in the development of human intestinal inflammation and experimental colitis, but also a potential target for the treatment of intestinal cancer (Fig. 2).

LXR in CRC. CRC is a prevalent malignancy of the gastrointestinal tract, which mainly occurs in the colon (87,88). At present, CRC is one of the most common types of cancer worldwide and the second leading cause of cancer-related mortality (89,90). The incidence and mortality of CRC vary according to ethnicity and its incidence is usually closely associated with diet, such as a high consumption of red meat and processed meat, and lifestyle, including a lack of physical

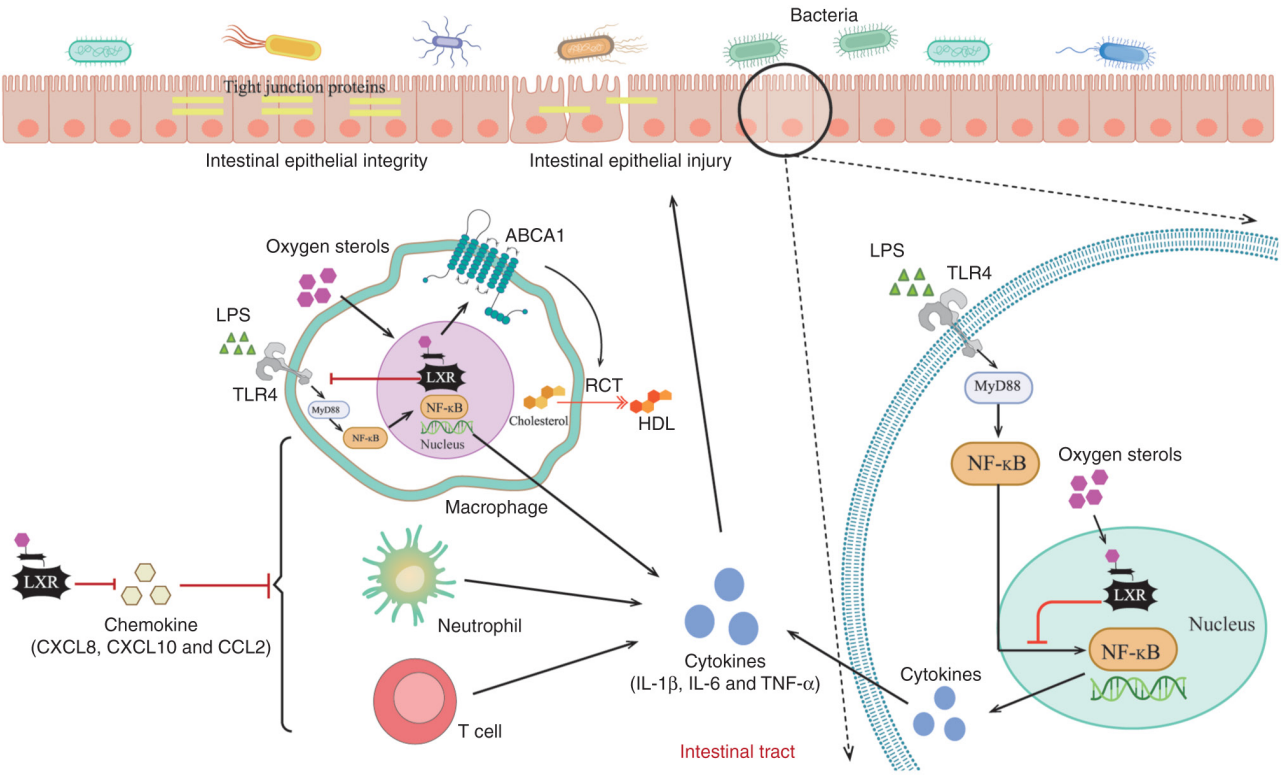

Figure 2. Mechanism of LXR participating in IBD. LXR activation regulates inflammation via two mechanisms. On one hand, the activation of LXR enhances the expression of intestinal epithelial cell tight junction proteins and inhibits the activation of intestinal epithelial cells and immune cells, such as macrophages and T cells, in the intestine, thus preventing the NF-κB pathway from releasing inflammatory cytokines and maintaining the intestinal barrier. On the other hand, the activation of LXR can regulate lipid metabolism and inhibit the NF-κB signaling pathway and the release of pro-inflammatory factors by increasing the expression of macrophage ABCA1 and promoting cholesterol outflow. The aforementioned findings suggest that LXR is a key regulator in the occurrence and development of IBD. LXR, liver X receptor; IBD, inflammatory bowel disease; HDL, high-density lipoprotein; RCT, reverse cholesterol transport; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; ABCA1, ATP-binding cassette transporter A1; CXCL, C-X-C motif chemokine; CCL2, C-C motif chemokine 2.

activity, smoking, obesity and heavy drinking (91-93). In previous years, the overall incidence of CRC, particularly rectal cancer and distal colon cancer, has decreased in individuals aged >50 years old, but increased in those aged <50 years old (94). Notably, surgery, radiotherapy, chemotherapy and other cancer treatment methods cannot cure advanced or metastatic CRC, thus identifying a target for the treatment of colon cancer is important (90,95). Recent research has demonstrated that LXR activation within tumor cells and the TME controls CRC progression, indicating that elucidating the mechanisms of LXR activity could offer promising new targets for clinical therapy (96,97).

Tumor-suppressive pathways. Studies have shown that the occurrence of intestinal tumors is associated with the loss of control of cell proliferation and with cholesterol metabolism disorders (98-100). During cell proliferation, the expression of LXRα and LXRβ is upregulated. Activation of LXR downregulates key cell cycle promoters including S-phase kinase-related protein 2, cyclin A2 and cyclin D1, while upregulating cell cycle inhibitors p27Kip1 and p53. These changes lead to G_1 phase cell cycle arrest and inhibit cell cycle progression in cancer cells (81,97,101). The antitumor effect of LXR is also dependent on inducing apoptosis by activating the caspase-3 pathway (102). A study has shown that ergosterol, as an agonist of both LXR subtypes, can induce the apoptosis of CRC cells by upregulating pro-apoptotic proteins Bax and cleaved caspase-3, downregulating the anti-apoptotic protein Bcl-2, and synergistically inhibiting pathways such as the PI3K/AKT and Ras/MAPK signaling pathways (97). In addition, the homeostatic regulation of cholesterol mediated by LXR demonstrates potent anti-neoplastic activity by inhibiting the growth of colon cancer and other tumors, as research has found that the activation of LXR can inhibit the survival of cancer cells by regulating intracellular cholesterol levels (103-107). Specifically, the activation of LXR, predominantly LXRα, mediates the upregulation of the ABCA1 and ABCG1 genes, which stimulates the reverse transport and efflux of cholesterol and damages the structure of lipid rafts, making them smaller and thinner. The decrease of the plasma membrane cholesterol steady-state level leads to the downregulation of AKT phosphorylation in the lipid layer and promotes cancer cell apoptosis (104,108).

Notably, LXR activation induces not only apoptosis but also pyroptosis in cancer cells. Specifically, in colon cancer, LXR promotes caspase-1 activation to trigger pyroptosis (107). The primary mechanism involves LXRβ activation, which facilitates the opening of the pannexin 1 channel on the cell membrane, leading to ATP release. Extracellular ATP activates P2X purinoceptor 7, thereby inducing the assembly of the NOD-like-receptor pyrin domain containing 3 (NLRP3) inflammasome and subsequent caspase-1 activation. This process ultimately results in pyroptosis of colon cancer cells (109,110). This mechanism establishes NLRP3 inflammasome activation as a novel LXR-dependent antitumor

modality, which has important clinical relevance for targeting LXR in colon cancer therapies.

Furthermore, studies have revealed that LXR activation can influence tumor progression by modulating antitumor immunity within the TME. During the development of malignant tumors, immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) expand and inhibit the antitumor immune response, thereby promoting tumor cell proliferation and metastasis (111-114). Studies have revealed that the LXRβ-selective agonist abequolixron (RGX-104) inhibits tumor growth by reducing the survival of immunosuppressive cells within the TME. Specifically, LXRβ activation upregulates the transcription of ApoE, which binds to LDL receptor-related protein 8 (LRP8) on MDSCs. This interaction impairs MDSC survival, enhances $CD8^+$ T-cell activation and potentiates antitumor immunity *in vivo* (18,111,115-117). Furthermore, in zearalenone (Zen)-induced Sprague-Dawley rats, intestinal injury, immunosuppression and dysregulated lipid metabolism have been observed. Zen can markedly reduce the level of the LXR endogenous agonist 27-hydroxycholesterol, downregulate LXRα and LXRβ, and inhibit the expression of ApoE (118). ApoE deficiency promotes the proliferation of intestinal MDSCs and inhibits T-cell function, thus increasing the risk of immunosuppressive TME formation (18,118,119). Notably, administration of either LXR or ApoE agonists can reverse T-cell suppression, restoring the core activity of this pathway in preventing tumorigenesis (118).

Clinical association. LXRα, as a transcription factor, can regulate the expression of several cancer-related genes (120,121). Epidermal growth factor receptor (EGFR) is highly expressed in several types of cancer, and is closely associated with the proliferation, invasion and metastasis of tumors (122-124). Previous studies have shown that LXRα can directly bind to the promoter region of EGFR and inhibit its transcription, thus blocking the downstream signaling pathway mediated by EGFR and inhibiting the proliferation of CRC cells (122,125). This transcriptional regulation mechanism unveils an epigenetic dimension of LXR-mediated tumor suppression, providing a possible novel target for the treatment of CRC. In addition, emerging research has revealed a context-dependent duality of LXR signaling in colorectal carcinogenesis. A recent study demonstrated that ATPase H^+ transporting V0 subunit A1 (ATP6VOA1), an intrinsic regulator in tumor cells, promotes the synthesis of cholesterol metabolite 24-hydroxycholesterol (24-OHC) by enhancing both exogenous cholesterol uptake and intracellular cholesterol accumulation in CRC cells (96). As a natural agonist of LXR, 24-OHC simultaneously activates both LXRα and LXRβ subtypes. In contrast to the conventional view of LXR-mediated tumor suppression, this activation of the LXR pathway promotes CRC cell secretion of elevated levels of TGF-β1 into the TME in a paracrine manner. The released TGF-β1 subsequently activates SMAD family member 3 signaling in $CD8^+$ T cells, ultimately suppressing their antitumor cytotoxicity. Notably, the pharmacological inhibition of the ATP6VOA1/24-OHC pathway blocks LXR activation and prevents immunosuppressive reprogramming, thereby attenuating CRC tumor growth (96,126,127). These findings demonstrate that context-specific LXR inhibition can exert antitumor effects, expanding the paradigm of LXR function in oncogenesis and highlighting the context-dependent duality of LXR activity in tumor regulation. These insights establish a novel therapeutic strategy for CRC through the precise modulation of LXR signaling pathways. Emerging evidence has suggested that the circadian regulation of LXR activity may influence therapeutic efficacy. Previous studies have demonstrated diurnal oscillation of LXRα expression in colonic epithelium, with peak activity coinciding with lipid absorption phases. This chronobiological dimension introduces new considerations for optimizing dosing schedules of LXR-targeted therapies (128-130).

In summary, LXR activation exerts multifaceted antitumor effects by inducing cell cycle arrest, promoting apoptosis and pyroptosis via NLRP3 inflammasome activation, and suppressing cholesterol metabolism in cancer cells. LXR also enhances antitumor immunity by inhibiting MDSCs and dampening EGFR-mediated proliferation. It is worth noting that all aforementioned pleiotropic effects are contingent upon LXR activation status and cellular context. However, emerging evidence has suggested a context-dependent dual role for LXR: The activation of LXR may also promote the secretion of immunosuppressive factors by tumor cells, thereby undermining antitumor immunity. These pleiotropic actions highlight the therapeutic potential of targeting LXR in CRC, although its precise mechanisms require further elucidation. Continued research is important to fully exploit LXR as a novel therapeutic target or agent (Fig. 3).

4. Therapeutic strategies targeting LXR

Given the notable role of the LXR pathway in combating IBD and CRC, the discovery and development of LXR agonists holds considerable therapeutic potential for intestinal diseases. As a nuclear transcription factor, LXR is activated by its natural ligand oxysterol, a cholesterol derivative that regulates the transcription of target genes (131). Commonly used synthetic agonists, such as T0901317 and GW3965 hydrochloride, activate the downstream pathway of LXR by simulating the activity of oxysterols, the natural ligands for LXR, subsequently regulating immune function and lipid homeostasis (31,72). For example, the synthetic ligand GW3965 hydrochloride promotes RCT, inhibits the NF-κB signal cascade by activating the LXR/ABCA1 pathway and inhibits the production of pro-inflammatory factors, such as IL-8 and CCL28 (72). T0901317 inhibits the proliferation of colon cancer stem cells by activating LXR signaling, and upregulates ABCA1, ABCG5 and ABCG8, disrupting membrane integrity in CRC cells and inducing apoptosis (58). Subtype-selective agonists offer improved safety profiles compared with general LXR agonists. The LXRβ-specific agonist RGX-104 depletes MDSCs through the LXRβ/ApoE/LRP8 axis, enhances $CD8^+$ T-cell activity and suppresses tumor growth in CRC models, and has advanced to phase Ib/II clinical trials (trial no. NCT02922764), suggesting superior tumor suppression compared with non-selective agonists (18). However, to date, no agonists specifically targeting LXRα for alleviating IBD or CRC have been identified. Sterol-based LXR agonists, such as DMHCA and MePipHCA, have been shown to alleviate intestinal inflammation in DSS-induced IBD mouse model of IBD by activating ABCA1 and ABCG1, and inhibiting pro-inflammatory factors, such as IL-1β and CCL2, without

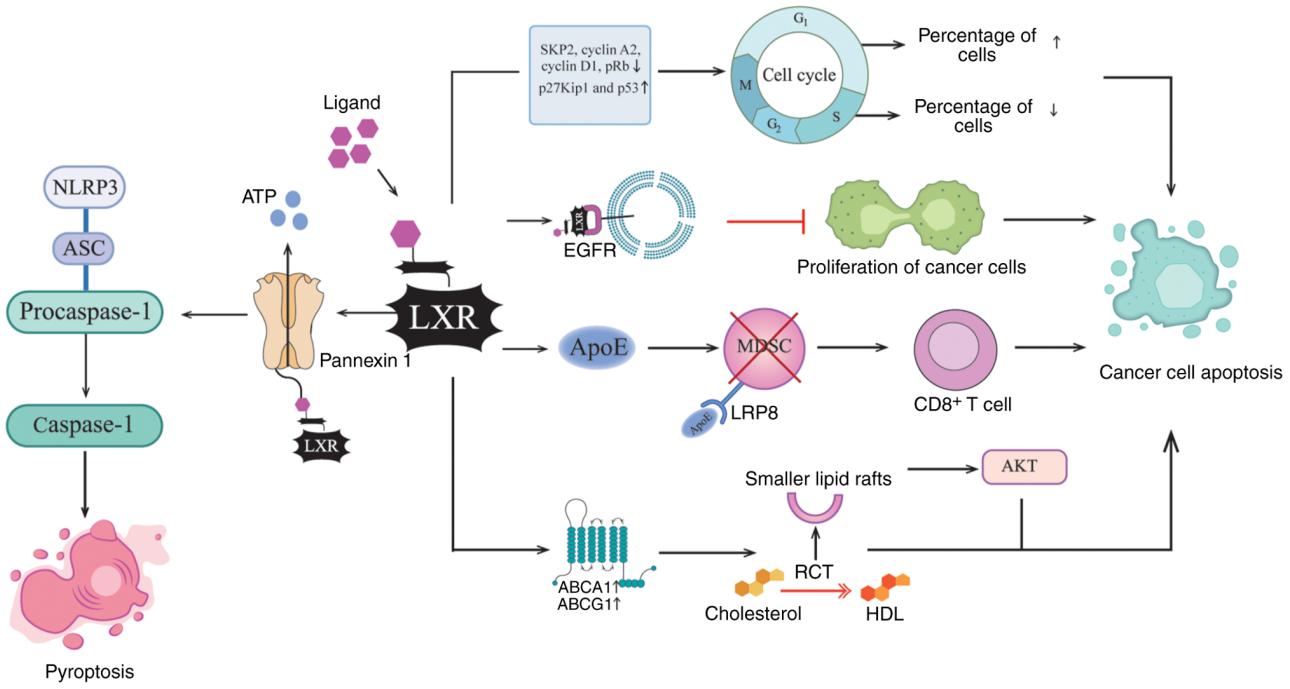

Figure 3. LXR participates in the mechanism of intestinal cancer. LXR activation has multiple mechanisms in the development of colon cancer. On one hand, following its activation, LXR can induce the programmed death of colon cancer cells by binding to EGFR on the surface of cancer cells, regulating their growth cycle, inhibiting the survival of MDSCs and promoting genes such as ABCA1. On the other hand, the combination of LXR activation and the opening of pannexin 1 channels induces caspase-1 activation, leading to cancer cell pyroptosis. These findings provide novel foundations for the treatment of colon cancer. LXR, liver X receptor; NLRP3, NOD-like-receptor pyrin domain containing 3; MDSCs, myeloid-derived suppressor cells; ABCA1, ATP-binding cassette transporter A1; ApoE, apolipoprotein E; ASC, apoptosis-associated speck-like protein containing a CARD; EGFR, epidermal growth factor receptor; LRP8, LDL receptor-related protein 8; HDL, high-density lipoprotein; RCT, reverse cholesterol transport; ABCG1, ATP binding cassette subfamily G member; SKP2, S-phase kinase-related protein 2.

inducing SREBP1c-mediated lipogenic pathways, thereby avoiding hepatotoxicity (31).

Although LXR synthetic agonists have shown potential in treating IBD and CRC in preclinical studies, LXR targeted therapy still faces notable obstacles. Synthetic agonists may promote hepatic steatosis via lipogenesis mediated by LXRα/SREBP1c (132), and cholestasis via ABCG5 and ABCG8 upregulation, leading to hepatotoxicity (133). LXRα predominantly regulates lipid metabolism, while LXRβ mainly regulates immune cells; both LXRα and LXRβ are widely co-expressed in the body, so the design of LXR-targeting subtype-selective drugs is complex (120). Furthermore, LXR activation in CRC may paradoxically promote immunosuppression via the ATP6V0A1/LXR/TGF-β1 axis, thereby inhibiting $CD8^+$ T-cell function and undermining antitumor immunity, which complicates the development of LXR-targeted therapies (96).

Combination strategies represent promising approaches to enhance LXR-directed therapy. RGX-104 combined with photosensitizer Ce6-mediated photodynamic therapy depletes MDSCs and activates the caspase-3/gasdermin-E-dependent cell apoptosis pathway (119). Further synergy with anti-programmed cell death-1 antibody treatment could promote $CD8^+$ T-cell infiltration and activation, amplifying systemic antitumor immunity, although this strategy remains unexplored in IBD and CRC contexts (119,134). In addition, the LXR inverse agonist SR9243 specifically targets CRC stem cells (CSCs) and inhibits the expression of lipid synthesis genes SCD1 and fatty acid synthase by specifically binding to the allosteric site of LXR, resulting in the obstruction of lipid production and metabolism. However, this inhibitory effect does not affect the LXR-mediated RCT pathway. This inhibition of lipid metabolism leads to the accumulation of reactive oxygen species in CSCs, which eventually induces apoptosis (39,58). This discovery provides a novel concept for targeted therapy based on LXR allosteric inhibition.

5. Conclusion

LXR serves a notable role at the intersection of lipid metabolism and immune regulation, positioning it as a promising therapeutic target linking IBD and CRC. Current understanding of LXR function predominantly depends on animal model research and no LXR agonist has progressed to phase III clinical trials of IBD or CRC. Given that LXR is widely expressed in the body, existing agonists are often accompanied by the risk of hepatotoxicity. Furthermore, there is insufficient targeted research on LXR subtypes, which makes it difficult to develop intestine-specific treatments. Nevertheless, the latest progress in subtype selection and combination therapy provides a feasible way forward. Developing intestine-specific agonists and combined regimens may be key strategies in unlocking the potential of metabolism and immunotherapy in treating IBD and CRC. However, the ways in which LXR activation and inhibition affect the progress of enteritis through interactions with intestinal microflora remain to be fully elucidated. Clarifying the role of LXR in IBD and CRC may provide new targets for the treatment of these diseases and broaden the application prospects of LXR.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant nos. 82000525 and 81873883), the Science and Technology Support Plan for Youth Innovation of Colleges and Universities of Shandong Province of China (grant no. 2021KJ106) and the Shandong Provincial Natural Science Foundation (grant no. ZR2023MH359). In addition, the present study was funded by the Youth Innovation Team Project for Talent Introduction and Cultivation in Universities of Shandong Province.

Availability of data and materials

Not applicable.

Authors' contributions

YL, ML and SL conceived the study and edited the manuscript. MB, JZ, JQ, HZ and XF contributed to the search and analysis of literature and the review of the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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