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Review Article

Research Progress on the Role of the Farnesoid X Receptor in Colorectal Cancer

Yu Hong, Huang Guodong, Li Li, Lei Zhang* and Lu Hongda*

[1]The Department of Oncology, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430014, People's Republic of China
[2]Key Laboratory for Molecular Diagnosis of Hubei Province, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430014, People's Republic of China
[3]The Cancer Research Institute of Wuhan, Wuhan, 430079, People's Republic of China

Correspondence
Lu Hongdai & Lei Zhang
The Department of Oncology, The Central Hospital of Wuhan; PR China
Email: phlonda@163.com (LH) & zhanglei198121@163.com (LZ)
Tel: 027-65699953 (LH) & 027-65690401(LZ)

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Abbreviations

APC: Adenomatous polyposis coli; ASBT: Apical sodium-dependent bile acid transporter; BACS: Bile acid-CoA synthetase; BAT: Bile acid-CoA: amino acid N-acetyltransferase; CCNA2: Cyclin A2; CCNG2: Cyclin G2; CEBPB: CCAAT/enhancer-binding protein beta; CRC: Colorectal cancer; DHRS9: Dehydrogenase/reductase member 9; DR5: Death receptor 5; EGFR: Epidermal growth factor receptor; EMT: Epithelial-mesenchymal transition; ETBF:Enterotoxigenic Bacteroides fragilis; FXR: Farnesoid X receptor; IBABP: Ileal bile acid-binding protein; ISCs: Intestinal stem cells; MMP7: Matrix metalloproteinase-7; NF-κB: Nuclear transcription factor kappa B; OSTα: Organic solute transporter-α; OSTβ: Organic solute transporter-α; PD-L1: Programmed death-ligand 1; SIgA: Secretory immunoglobulin A; SOCS3: Suppressor of cytokine signaling suppressor 3; TCF/LEF: T-cell facto/lymphoid enhancerbinding factor

Abstract

Colorectal cancer is the third most common malignant tumor worldwide, ranking second in cancer-related deaths, with poor prognosis for advanced-stage patients. Farnesoid X receptor is a kind of nuclear receptor for bile acids, recent studies suggest that the farnesoid X receptor can regulate the proliferation, differentiation, invasion, and metastasis of colorectal cancer cells, thereby inhibiting the occurrence and development of colorectal cancer. The main mechanisms of action include 1) cell cycle blockade, 2) regulation of apoptosis and autophagy, 3) influence on energy metabolism, and 4) shaping the intestinal microenvironment. These mechanisms involve multiple signaling pathways such as Wnt/β-catenin, EGFR/ERK, JAK2/STAT3, etc. The anticancer effects of the farnesoid X receptor indicate its potential as a therapeutic target of colorectal cancer. Its agonists not only independently exert anti-tumor effects but also synergistically enhance the efficacy of chemotherapy and immunotherapy, offering the possibility of improving the survival and prognosis of colorectal cancer.

Introduction

Colorectal cancer (CRC) ranks as the third most prevalent malignant neoplasm globally and the second most common cause of cancer-related death, constituting approximately 10% of the overall cancer incidence and 9.4% of the overall cancer caused deaths. Over the past years, the prevalence of CRC has been steadily rising and increasingly affecting individuals at younger ages. Consequently, the identification of novel diagnostic and therapeutic targets assumes paramount importance in enhancing the prognosis and extending the survival of CRC patients [1].

The farnesoid X receptor (FXR) is a nuclear receptor that binds to endogenous ligands, specifically bile acids [2]. FXR is expressed in various tissues, including the heart, kidney, and breast, with the liver and ileum exhibiting the highest levels of expression [3-5]. As a nuclear receptor for bile acids, FXR governs the circulation and metabolism of bile acids through multiple pathways. Furthermore, recent research has revealed that FXR plays a crucial role in CRC. This article aims to critically examine the advancements made in the research of FXR in CRC and investigate its significant potential in the realms of diagnosis

The Physiological Functions of FXR

FXR, classified as a subclass of bile acid nuclear receptors, can be effectively stimulated by bile acids, subsequently governing various facets of bile acid metabolism, encompassing synthesis, transportation, and reuptake.

Firstly, The negative regulation of bile acid synthesis is mediated by FXR, which plays a crucial role in the classical pathway involving multiple enzymes, including CYP7A1, CYP8B1, and CYP27A1. FXR exerts its inhibitory effect by inducing the expression of small heterodimer partner (SHP), which effectively suppresses the activity of the enzymes essential for bile acid synthesis [6-8].

Secondly, FXR plays a crucial role in facilitating the transport of bile acids. Prior to transport, non-conjugated bile acids must undergo conversion into conjugated bile acids through the actions of bile acid-CoA synthetase (BACS) and bile acid-CoA: amino acid N-acetyltransferase (BAT) [9]. Both BACS and BAT contain functional FXR binding sites (IR-1 sequence), and the activation of FXR can stimulate their expression, thereby promoting the production of conjugated bile acids for subsequent transport [10]. Furthermore, FXR can also enhance the expression of transport-related genes, such as bile salt export pump (BSEP) and multidrug resistance 3(MDR3), through similar mechanisms, thereby further facilitating the transport of bile acids [11,12].

Finally, The FXR regulates the reabsorption of bile acids, assisting in the modulation of the enterohepatic circulation of bile acids. After exerting their physiological effects, the majority of bile acids are actively reabsorbed

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through the apical sodium-dependent bile acid transporter (ASBT) located on the apical membrane of the enterocyte [10]. Upon entry into the cytoplasm, bile acids bind to the ileal bile acid-binding protein (IBABP) and shuttle from the apical to the basolateral side [13], where they are secreted into the portal vein by the heterodimeric organic solute transporter proteins (OSTα and OSTβ) for uptake by hepatocytes, a process known as enterohepatic circulation [14]. The negative regulation of ASBT by FXR occurs via the SHP-dependent pathway, while the induction of ileal bile acid-binding protein, and organic solute transporter expression is facilitated by specific sequences in their promoters, thereby regulating bile acid reabsorption [15-17].

FXR Suppresses CRC

FXR not only possesses the capability to regulate bile acid metabolism under physiological circumstances, but it also assumes a significant role in the context of colorectal cancer. Specifically, FXR exhibits the ability to impede the proliferation and migration of colorectal cancer cells, influence the tumor microenvironment, and hinder the initiation and advancement of colorectal cancer through various mechanisms.

FXR Affects the Proliferation, Differentiation, Invasion and Metastasis of Colorectal Cancer Cells

Lgr5+ intestinal stem cells (ISCs) play a pivotal role in the formation of intestinal tumors. FXR has been demonstrated to function as a regulator of ISCs proliferation, which play a pivotal role in the formation of intestinal tumors. The absence of FXR fosters ISC proliferation, heightens DNA damage and genetic instability, and propels malignant transformation. While the activation of FXR has been shown to have the potential to restrict abnormal proliferation of intestinal stem cells ISCs, mitigate the transformation of adenoma to adenocarcinoma mediated by Lgr5+ cells [18]. Furthermore, FXR has been found to exert inhibitory effects on tumor cell proliferation while promoting differentiation. In murine models of adenomas and adenocarcinomas, the activation of FXR led to diminished proliferation, enhanced nuclear morphology, and augmented quantities of differentiated cells, including goblet cells [18,19].

FXR can inhibit the tumor progression through the modulation of tumor invasiveness and migration. The research by Sun et al. suggests that colorectal cancer cells with FXR knockout exhibit a greater number of invasive and migratory cells compared to the FXR-expressing group. Additionally, there is an increased wound healing rate, indicating enhanced invasive capabilities. In addition, the verification of FXR's impact on CRC metastasis in vivo was done by establishing a model of colon cancer lung metastasis through tail vein injection. The findings indicated that the FXR knockout group had a higher number of tumor nodules in lung metastasis compared to the control group [20]. Therefore, FXR has the ability to hinder the invasion and metastasis of colon cancer cells in both in vivo and in vitro settings, which is mainly accomplished by suppressing the epithelial-mesenchymal transition (EMT). EMT plays a crucial role in the progression and metastasis of tumors by enhancing the invasion and migration potential of cells. The downregulation of FXR leads to an upregulation of EMT markers such as Vimentin, Snail, Slug, Fibronectin, and MMP-9. Conversely, the activation of FXR can yield opposite results [20,21]. Additionally, FXR can inhibit the matrix metalloproteinase-7 (MMP-7) transcription by binding to the response elements in it promoter, and inhibit the invasion of CRC [22].

Mechanisms of FXR Inhibition in CRC

FXR Affects Cell Cycle

The regulation of the cell cycle by FXR is considered one of the mechanisms through which it inhibits proliferation. FXR has the ability to impede the transition of cells from the G0/G1 phase to the S phase, Consequently, there is an escalation in the percentage of cells residing in the G0/G1 phase, accompanied by a decrease in the proportion of cells in the S phase, and the expression levels of crucial proteins involved in the cell cycle, namely cyclin D1 and c-Myc exhibit a decline, and these alterations ultimately lead to the suppression of tumor growth [20,21,23]. Recent studies have indicated that FXR can suppress miR-135A1, leading to an increase in cyclin G2 (CCNG2) expression, thereby impeding the cell cycle and restraining tumor proliferation via the FXR/miR-135A1/CCNG2 axis [24,25]. Similarly, Wan also proposed an anti-proliferation mechanism mediated by the FXR/miR-22/CCNA2 axis. Cyclin A2 (CCNA2), a cell cycle protein, in colorectal cancer has gradually gained recognition as a novel oncogene that governs apoptosis and growth. The inhibitory effect of MiR-22 on tumor growth through its targeting of CCNA2 has been demonstrated [26]. This investigation has revealed that FXR has the ability to directly interact with the IR1 motif located upstream of miR-22, thereby regulating its expression and facilitating the inhibition of CCNA2 expression by miR-22, ultimately leading to an anti-proliferative effect [27].

FXR Regulate apoptosis and autophagy

FXR modulates extrinsic cell apoptosis to reduce cell proliferation, thereby inhibiting tumor growth. The regulation of apoptosis in colorectal cancer (CRC) cells by FXR is mediated through the BAX/caspase-3 pathway. Activation of FXR expression in CRC cell lines increases the mRNA levels of pro-apoptotic genes (FAS, BAK1, P21, KLF4, FADD, CASP9, and P27) and decreases the levels of the anti-apoptotic gene BCL2 [28,29]. Moreover, experiments conducted by Naito et al. further substantiate that FXR-mediated regulation of apoptosis in colorectal cancer cells is mediated through death receptor 5 (DR5)-mediated extrinsic apoptosis. Treatment of CRC cell lines with the FXR agonist GW4064 leads to a significant increase in DR5 protein expression along with enhanced expression of apoptosis-related molecules such as caspase-8, caspase-3, and PARP in the extrinsic death signaling pathway. However, the intrinsic death signaling pathway remains unaffected.

Furthermore, FXR can induce apoptosis by reducing autophagic activity. For some colorectal cancer cells that rely on autophagic activity for cell survival, FXR inhibition of autophagic activity demonstrates an anti-tumor effect [30,31].

FXR Influences Energy Metabolism

FXR suppresses the proliferation and invasion of colorectal cancer cells by influencing energy metabolism. The Warburg effect is a characteristic of tumor energy metabolism, indicating that even in the presence of sufficient oxygen, tumor cells tend to favor aerobic glycolysis over aerobic respiration. This metabolic preference not only provides the required energy for tumor cells but also disrupts immune cell function and promotes tumor proliferation and invasion through the accumulation of metabolic byproducts [32]. FXR silencing promotes aerobic glycolysis in colorectal cancer cells, thus participating in the regulation of colon cancer cell growth and proliferation, primarily mediated by enhanced binding of the transcription factor CCAAT/enhancer-binding protein beta (CEBPB).

Studies confirm a significant increase in CEBPB expression in colorectal cancer, where CEBPB, by binding to the FXR promoter, downregulates FXR expression, leading to tumor invasion and progression [33].

Furthermore, abnormal oxidative phosphorylation is associated with tumor proliferation, invasion, and drug resistance [34,35]. Dehydrogenase/reductase member 9 (DHRS9), a target gene of FXR, directly binds to FXR and upregulates its own expression. This interaction inhibits the oxidative phosphorylation of tumor cells, thus regulating the malignant progression of colorectal cancer [36].

FXR Modulates the Intestinal Microenvironment

Colorectal cancer resides within a complex intestinal microenvironment, and its malignant behavior is closely associated with the surrounding microenvironment. Studies have revealed that the intestinal microbiota, metabolic products, inflammatory cells, immune cells, and immune-inflammatory factors in the intestinal microenvironment are interconnected through FXR. Together, they collectively regulate the occurrence, development, invasion, and metastasis of colorectal cancer.

FXR regulates bile acid metabolism. As an important metabolite of intestinal microenvironment, bile acid not only plays a role in the digestion and absorption of fat, but also has tumor-promoting activity, it can promote CRC by inducing cell proliferation, DNA oxidative damage, and causing inflammation [37,38]. FXR can maintain bile acid homeostasis and inhibit the tumorigenic activity of bile acids. It includes three aspects. First, FXR negatively regulates bile acid synthesis, directly reducing the level of intestinal bile acids. Second, FXR downregulates the intestinal influx transporter ASBT, induces the expression of binding protein IBABP and efflux transporters OSTα/β, and reduces the toxic effect of bile acids on intestinal cells. In contrast, FXR deficiency leads to disruptions in bile acid metabolism, resulting in more exposure of intestinal cells to bile acids, thereby promoting CRC formation [39]. And last, FXR can positively regulate the secretion of secretory immunoglobulin A (SIgA) by acting on bile acids. SIgA is an important factor in the intestinal mucosal barrier, which can limit pathogen invasion and maintain intestinal microenvironment [40,41].

FXR inhibits intestinal inflammation. The inflammatory environment of the intestine is closely associated with the formation of CRC, and FXR can improve intestinal inflammation, and inhibit the formation and development of CRC. As mentioned earlier, since bile acids are important substances that lead to intestinal inflammation, and FXR can regulates various aspects of bile acid synthesis, transport, and metabolism, so FXR indirectly inhibit inflammation by regulating bile acid levels and metabolism [42]. Furthermore, FXR can inhibit intestinal inflammation through non-bile acid-dependent pathways. According to the research, activation of FXR in the intestine reduces the production of pro-inflammatory cytokines such as interleukin IL-1β, IL-2, IL-6, tumor necrosis factor-alpha, and interferon-gamma, thereby reducing local inflammation [43]. FXR plays a protective role in inflammation-related colorectal cancer, and selective activation of intestinal FXR can improve intestinal inflammation, reduce tumor numbers, and exert anti-inflammatory and anti-proliferative effects [22,43](22,43). Mechanistic studies suggest that this effect may be mediated by the nuclear transcription factor kappa B (NF-κB), as FXR downregulates the expression of inflammatory factors by inhibiting the activity of NF-Kb [44,45].

FXR affects gut microbiota. Gut microbiota as an important component of the intestinal tumor microenvironment, plays an important role in the development of tumors, and FXR is essential for maintaining intestinal flora homeostasis. Particularly, Enterotoxigenic Bacteroides fragilis (ETBF) has been shown to have a highly carcinogenic effect [46].FXR downregulation promotes the colonization of ETBF and the formation of CAC. The mechanism of action mainly involves two aspects. On the one hand, FXR downregulation can lead to bile acid disorder, and ETBF has high bile acid tolerance, therefore, the high bile acid environment formed by FXR downregulation is beneficial for the survival of ETBF. On the other hand, secretory immunoglobulin A (SIgA) plays an auxiliary role in bile acid-mediated ETBF accumulation,the decrease of FXR leads to the increase of SIgA and promote the colonization of ETBF. FXR can also affect in the number and composition of the gut microbiota.The expression of FXR in CRC mice decreased significantly, which led to the decrease of α-diversity of fecal flora, the increase of the number of Bacteroides and Proteus, and the decrease of the number of thick-walled bacteria and verrucous microbacteria. Among them, the decrease of the Firmicutes/Bacteroidetes (F/B) ratio may be related to colitis in the development of CRC. In addition, FXR is also closely related to the imbalance of metabolites in intestinal flora, the FXR downregulation group also showed a decrease in butyrate, which may be related to the potential presence of intestinal tumors [40].

FXR modulates the intestinal immune microenvironment. The immunotherapeutic challenges faced by colorectal cancer have drawn significant attention, and its immune resistance is closely linked to the immune microenvironment. Research indicates that FXR has the capability to reshape the immune microenvironment. Firstly, FXR can influence the recruitment of immune cells. In inflammatory bowel disease, FXR reduces the recruitment of immune cells such as macrophages, T cells, and B cells, maintaining the homeostasis of the intestinal immune microenvironment. Secondly, FXR can affect the status of immune cells. FXR promotes the polarization of macrophages towards the M2 phenotype, and it reduces the differentiation of monocytes into dendritic cells, thereby inhibiting inflammatory responses [47]. Lastly, FXR also influences immune regulatory molecules. As mentioned earlier, FXR leads to a reduction in dendritic cells and macrophages, inhibiting the production of immune-inflammatory factors such as TNF-α and interferon-gamma [37,48]. Additionally, FXR promotes the expression of Programmed Death-Ligand 1 (PD-L1), and activating FXR can enhance the efficacy of CRC anti-PD-L1 immunotherapy [49].

FXR Inhibits Proliferation and Invasion-Related Signaling Pathways

FXR inhibits the proliferation and invasion processes in colorectal cancer through involvement in signaling pathways such as Wnt/β-catenin, EGFR/ERK, JAK2/STAT3.

The Wnt/β-catenin signaling pathway has a close association with tumor proliferation and progression. In colorectal cancer cells, frequent mutations in the tumor suppressor gene adenomatous polyposis coli (APC) lead to the accumulation of the β-catenin complex. The complex, when bound to T-cell factor/lymphoid enhancer-binding factor (TCF/LEF), forms the β-catenin/TCF4 complex, activating the Wnt pathway and participating in tumor proliferation and invasion[50]. In this process, FXR can interact with β-catenin to inhibit the activation of the Wnt pathway (Figure). FXR can reduce the activity level

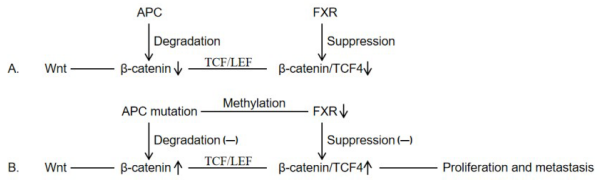

Figure. FXR Inhibition of Wat/β-catenin Signaling Pathway Mediates Proliferation and Migration of CRC Cells. A. Under physiological conditions, the tumor suppressor gene APC participates in the degradation of the β-catenin complex, reducing the formation of the β-catenin/TC4 complex. Simultaneously, FXR can decrease the activity level of the β -catenin/TCF4 complex, collectively inhibiting the Wnt/β -catenin signaling pathway. B In CRC, mutations in the tumor suppressor gene APC lead to the accumulation of β-catenin, APC mutations also inhibit the expression of FXR thereby reducing FXR's negative regulation of the β -catenin/TCF4 complex. Consequently, the Wnt pathway is activated, contributing to the proliferation and invasion of tumors.APC, Adenomatous polyposis coli; FXR, Faresoid X receptor, TCFLEF, T-cell facto/lymphoid enhancerbinding factor)

of the β-catenin/TCF4 complex, and significantly inhibiting tumor cell proliferation in a dose- and time-dependent manner. Additionally, FXR negatively regulates the Wnt signaling pathway to inhibit epithelial-mesenchymal transition (EMT), thereby reducing CRC invasion and metastasis. However, the loss of APC induces CpG methylation in the FXR promoter, suppressing FXR expression and counteracting its anti-tumor effects [20,51,52].

The EGFR/ERK pathway is one of the crucial mechanisms underlying the proliferation and metastasis of colorectal cancer. FXR, by modulating the EGFR/ERK pathway, inhibits tumor formation. Activation of FXR in colorectal cancer cells induces the phosphorylation of Src protein kinase, downregulating the levels of epidermal growth factor receptor (EGFR) and downstream kinase ERK 1/2, thereby suppressing tumor proliferation. Conversely, antagonists of FXR yield opposite results [53]. Additionally, in human colon cancer cells, MMP-7 participates in the transactivation of EGFR. FXR, acting as a transcriptional inhibitor of MMP-7, may also be involved in the regulation of the EGFR/ERK pathway, exerting an anti-tumor effect [22].

The JAK/STAT pathway is also implicated in the occurrence and progression of CRC and is negatively regulated by the suppressor of cytokine signaling 3 (SOCS3)[54]. FXR can upregulate the protein and mRNA expression levels of SOCS3 by binding to the IR-9 sequence in the SOCS3 promoter, thereby inhibiting the JAK2/STAT3 pathway [21].

The Application and Prospects of FXR in the Diagnosis and Treatment of CRC

FXR plays an anticancer role by regulating the proliferation, differentiation, invasion, and metastasis of colorectal cancer. Clinical studies have indicated a negative correlation between FXR expression levels and CRC size, TNM staging, grading, proliferation levels, as well as local recurrence and metastasis [20,55]. Analysis of CRC data from TCGA database also supports a correlation between relatively high FXR expression and longer overall survival.

However, unfortunately, the expression of FXR in colorectal cancer tissues is generally downregulated due to the combined effects of genetic mutations and epigenetic mechanisms [56-60]. Given the pivotal role of FXR in inhibiting CRC, activating FXR to improve the survival and prognosis of CRC is expected to become a novel treatment strategy.

Common FXR agonists such as acetyl cholic acid, chenodeoxycholic acid, and GW4064 have entered clinical trial phases [61]. Activating FXR promotes the circulation and metabolism of bile acids, reduces the toxic effects of bile acids on intestinal cells, facilitates intestinal mucosal repair, and inhibits inflammation and tumor cell proliferation and invasion through multiple pathways, thereby suppressing the occurrence and development of CRC [49].

In addition to its inherent anticancer effects, FXR agonists can synergize with other anti-tumor therapies. Combination chemotherapy based on oxaliplatin is a crucial approach for treating CRC, but long-term use can lead to drug resistance and side effects, impacting treatment efficacy. The FXR agonist GW4064 enhances the chemosensitivity of CRC to oxaliplatin by inducing cell apoptosis, thus complementing the therapeutic effects of oxaliplatin [62]. Furthermore, there is a synergistic effect between FXR agonists and immunotherapy, which is particularly important for colorectal cancer with immune resistance. While the development of immunotherapy has benefited many cancer patients, a significant portion of colorectal cancer patients remains insensitive to immunotherapy, highlighting the pressing need to enhance immunotherapy responsiveness [63]. Immune checkpoint inhibitors targeting PD-L1 are crucial for immunotherapy, and recent studies indicate that combined treatment with GW4064 and anti-PD-L1 achieves superior anti-tumor effects. On one hand, GW4064, as an FXR agonist, can upregulate the expression of PD-L1 in CRC cells by activating the MAPK pathway. On the other hand, FXR can reshape the immune microenvironment, potentially reversing the immune-insensitive state of CRC by influencing immune cell infiltration, status, and the production of immune-inflammatory factors [49].

In summary, FXR as a therapeutic target for CRC shows promising prospects. However, since FXR is expressed in organs other than the intestine and plays different physiological roles, non-selective activation is likely to lead to systemic side effects, such as diarrhea, itching, and elevated transaminases. Therefore, the development of highly selective FXR agonists is a crucial research direction for CRC treatment. Some intestine-specific FXR agonists, such as obeticholic acid, TC-100, and cilofexor, have been shown to play a role in CRC treatment by modulating bile acid profiles and the intestinal microenvironment [64]. However, previous studies were mainly conducted in animal models, and given the apparent species-specificity of bile acid composition, further research is needed to ensure the safety and efficacy of FXR agonists.

Conclusion

The incidence and mortality rates of colorectal cancer rank among the highest worldwide. Late-stage CRC lacks effective treatment options, leading to poor prognosis with a median overall survival of approximately 30 months, posing a significant threat to human health [65]. The search for new treatment strategies is imminent, and the pronounced anti-tumor effects of FXR underscore its potential as a therapeutic target for CRC, suggesting its potential as a therapeutic target for CRC. The inhibitory effects of FXR on CRC are multifaceted, involving multiple signaling pathways. FXR not only influences the cell cycle, autophagy, apoptosis, and energy metabolism of colorectal

cancer cells but also participates in shaping the intestinal microenvironment. The complex intestinal microenvironment is a crucial characteristic distinguishing CRC from other tumors. Factors such as gut microbiota, metabolic products, inflammatory conditions, and immune microenvironment are closely associated with CRC proliferation, invasion, and drug resistance, and are interconnected through FXR. Activating FXR not only promotes its anti-tumor effects but also facilitates the reshaping of the intestinal microenvironment, improving immune tolerance. Currently, FXR agonists have shown promising progress in experimental CRC therapy, but further research is needed to establish their role as therapeutic agents for CRC.

Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

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