Emerging role of bile acids in colorectal liver metastasis: From molecular mechanism to clinical significance (Review)

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Abstract. Liver metastasis is the leading cause of colorectal cancer (CRC)-related mortality. Microbiota dysbiosis serves a role in the pathogenesis of colorectal liver metastases. Bile acids (BAs), cholesterol metabolites synthesized by intestinal bacteria, contribute to the metastatic cascade of CRC, encompassing colorectal invasion, migration, angiogenesis, anoikis resistance and the establishment of a hepatic pre-metastatic niche. BAs impact inflammation and modulate the immune landscape within the tumor microenvironment by activating signaling pathways, which are used by tumor cells to facilitate metastasis. Given the widespread distribution of BA-activated receptors in both tumor and immune cells, strategies aimed at restoring BA homeostasis and blocking metastasis-associated signaling are of importance in cancer therapy. The present study summarizes the specific role of BAs in each step of colorectal liver metastasis, elucidating the association between BA and CRC progression to highlight the potential of BAs as predictive biomarkers for colorectal liver metastasis and their therapeutic potential in developing novel treatment strategies.

Contents

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1. Introduction

According to the latest global statistics, 1,926,118 patients were diagnosed with colorectal cancer (CRC) and 903,859 patients died of CRC; CRC is the third most commonly diagnosed cancer and the second leading cause of cancer-associated death (1). Notably, nearly half of patients with CRC are either diagnosed with metastatic CRC at the outset or develop metastases during the course of the illness. As the most frequent metastatic site, liver metastasis worsens prognosis, with <20% of patients with colorectal liver metastasis surviving >5 years (2). Furthermore, CRC with liver metastases exhibits decreased antitumor immunity and efficacy of immunotherapy (3,4). Understanding the regulatory mechanisms governing each stage of colorectal liver metastasis is key for developing strategies to disrupt the metastatic cascade.

Bile acid (BA) is a cholesterol metabolite that emulsifies lipids to facilitate digestion and absorption. BA is classified into primary and secondary BA based on the dehydroxylation at C7 (Table I). Primary BAs, including cholic acid (CA) and chenodeoxycholic acid (CDCA), are initially synthesized in the liver and conjugated with taurine or glycine. These conjugated primary BAs are stored in the gallbladder and released into the duodenum upon ingestion. During their journey through the small intestine, most primary BAs undergo deconjugation, mediated by bile salt hydrolase, which is harbored by the gut microbiota *Bacteroidetes, Firmicutes and Actinobacteria* (5). The deconjugated BAs are reabsorbed to replenish the liver BA pool via enterohepatic circulation. A total of ~5% of primary BAs escape reabsorption and enter the colon. The gut microbiota, especially *Clostridium and Eubacterium*, use 7α-dehydroxylation to transform CA and CDCA into secondary BAs deoxycholic acid (DCA) and lithocholic acid (LCA). This endows BAs with hydrophobic properties, enabling secondary BAs to be passively absorbed into the portal vein and enter

the liver (6,7). The enterohepatic circulation transports intestinal metabolites into the liver and constitutes the anatomical basis of the gut-liver axis (Fig. 1). Therefore, the intestinal and hepatic BA pools interact dynamically.

BAs are natural ligands of receptors, including the farnesoid X receptor (FXR), Takeda G protein-coupled receptor 5 (TGR5), the vitamin D3 receptor (VDR), sphingosine-1-phosphate receptor 2 (S1PR2) and retinoid-related orphan receptor-γt (RORγt). Most BA receptors are involved in the regulation of gut-associated inflammation (8) and glucose and lipid metabolism (9). Additionally, by interacting with BA receptors, BAs can modulate the functional state of immune cells, thereby influencing host immunity (6). In recent years, increasing evidence has implicated BAs in tumor development (10-12). BAs stimulate the pro-inflammatory signaling in the intestine and facilitate acquisition of a malignant phenotype (13). Previous reviews have clarified the association between BA metabolism and colorectal carcinogenesis (14-16). However, a comprehensive review summarizing the role of BAs in the progression of CRC remains lacking. In addition, the immunomodulatory effects of BAs are primarily discussed in the context of inflammatory bowel disease, with a focus on intestinal mucosal immunity (17). To the best of our knowledge, few reviews have concluded the involvement of BAs in regulating the antitumor immunity (18,19), particularly within the gut-liver axis. The present review aimed to explore the regulatory role of BAs at each stage of the colorectal metastatic cascade, from tumor invasion to impairment of antitumor immunity, to provide a foundation for development of novel therapeutic strategies for treating colorectal liver metastasis.

2. Dysregulated BA metabolism in CRC

CRC is associated with an augmented BA pool and increased proportions of secondary BAs in both serum and feces (20,21). This is likely due to long-term adoption of a high-fat diet in populations at a high risk of CRC. Individuals who adopt a high-fat diet acquire ample cholesterol for BA synthesis, resulting in increased BAs that escape into the colon, where primary BAs are converted to secondary BAs (22,23). A study confirmed that diets high in fat and low in fiber lead to higher levels of intestinal BAs in African Americans than in rural Africans who follow a low-fat diet (24).

In addition, gut microbiota in patients with CRC exhibits active catalytic activity for 7α-dehydroxylation, the key step in producing secondary BAs (25-28). *In vitro* cultures of bacteria derived from human CRC tissues have a stronger capacity for DCA production than those from normal mucosa (25). A meta-analysis of fecal metagenomes indicated that bacteria containing the BA-inducible gene operon, which encodes enzymes for 7α-dehydroxylation, are enriched in patients with CRC (26). *Clostridium* species catalyze 7α-dehydroxylation (27). Abundance of *Clostridium symbiosum* is significantly increased in the feces of patients with CRC (28), confirming the oncogenic properties of secondary BAs. A recent study (29) also highlighted the pro-carcinogenic role of the increased abundance of *Bacteroides* in the feces of patients with CRC, which contains bile salt hydrolase and facilitates BA deconjugation. Accumulated deconjugated DCA and LCA dampen antitumor immunity in patients with CRC (29). These findings suggest that alterations in the intestinal microbiome during CRC pathogenesis enhance the production of unconjugated secondary BA.

Furthermore, mutations in tumor suppressor genes are involved in BA metabolism by regulating the FXR-SHP axis. Under physiological conditions, FXR activation in enterocytes triggers fibroblast growth factor (FGF) secretion into enterohepatic circulation, which inhibits expression of cholesterol 7α-hydroxylase (CYP7A1) by binding to hepatic membrane receptor FGF receptor (FGFR)4, thereby limiting BA synthesis (30). Specific suppression of FXR in the intestinal epithelium of mice has been shown to result in increased DCA excretion in feces (31). However, FXR expression is downregulated in patients with CRC and is inversely associated with tumor stage (32). Adenomatous polyposis coli (Apc) mutations occur in ~85% of patients with CRC, resulting in intestinal FXR inactivation (33). Knockdown of Apc in mice silences FXR by stimulating CpG methylation in both tumor tissue and normal colonic mucosa (34), increasing total serum BAs (33). In addition, the tumor suppressor p53, which is mutated in almost half of patients with CRC, is key for BA homeostasis. Kim and Lee reported that p53 significantly decreases BA synthesis in mice by upregulating SHP expression, which directly inhibits the function of CYP7A1 (35).

Collectively, a high-fat diet, intestinal dysbiosis and tumor suppressor gene mutations contribute to aberrant BA metabolism and expanded BA pool (Fig. 2).

3. Clinical implications of BA in patients with CRC

Circulating BA levels serve as indicators of CRC risk. A prospective study reported that high pre-diagnostic concentrations of most conjugated BAs in serum are positively associated with an increased risk of colon cancer (36). Unconjugated DCA and glycolithocholic acid (GLCA) show no significant associations with colon cancer risk (36). This contradicts previous reports supporting the toxicity and carcinogenicity of secondary BAs (37,38). Secondary BAs have anti-inflammatory effects, and a decreased ratio of fecal secondary to primary BA may facilitate colitis-associated cancer progression (39). Therefore, secondary BAs serve a dual role in colorectal carcinogenesis. Investigating the optimal secondary BA levels to attenuate systemic inflammation without triggering cytotoxicity is important in clinical practice.

Moreover, accumulated BAs in serum and tumor tissues are associated with poor prognosis and predict early recurrence in postoperative patients with CRC. A retrospective analysis demonstrated that increased total serum BA levels are associated with lower overall survival (OS) and disease-free survival rates in patients with CRC (40). Notably, patients with high total BA levels have significantly higher TNM stages than those with low total BA levels. The proportion of patients with TNM stage IV CRC in patients with high total BA is almost twice as large as that in patients with low total BA, implying a possible role for BAs in distant metastasis of CRC (40). In addition, the total BA and systemic immune-inflammation index exhibit good predictive capacity for early recurrence of CRC after surgical resection (41). Targeted liquid chromatography-mass spectrometry enables precise measurement of BA

Table I. Classification and source of common bile acids and their derivatives found in human body.

Bile acid	Class	Conjugated form	Source	(Refs.)
CA	Primary	TCA, GCA	Cholesterol	(6,7)
CDCA	Primary	TCDCA, GCDCA	Cholesterol	
DCA	Secondary	TDCA, GDCA	CA	
LCA	Secondary	TLCA, GLCA	CDCA	
UDCA	Secondary	TUDCA, GUDCA	CDCA	
IsoLCA	Derivative	-	LCA	(110)
IsoalloLCA	Derivative	-	LCA	(109)
3-oxoLCA	Derivative	-	LCA	(109)
LCA-3-S	Derivative	-	LCA	(111)

3-oxoLCA, 3-oxolithocholic acid; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; GLCA, glycolithocholic acid; GUDCA, glycoursodeoxycholic acid; isoLCA, isolithocholic acid; isoalloLCA, isoallolithocholic acid; LCA, lithocholic acid; LCA-3-S, lithocholic acid 3-sulfate; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TDCA, taurodeoxycholic acid; TLCA, taurolithocholic acid; TUDCA, tauroursodeoxycholic acid; UDCA, ursodeoxycholic acid.

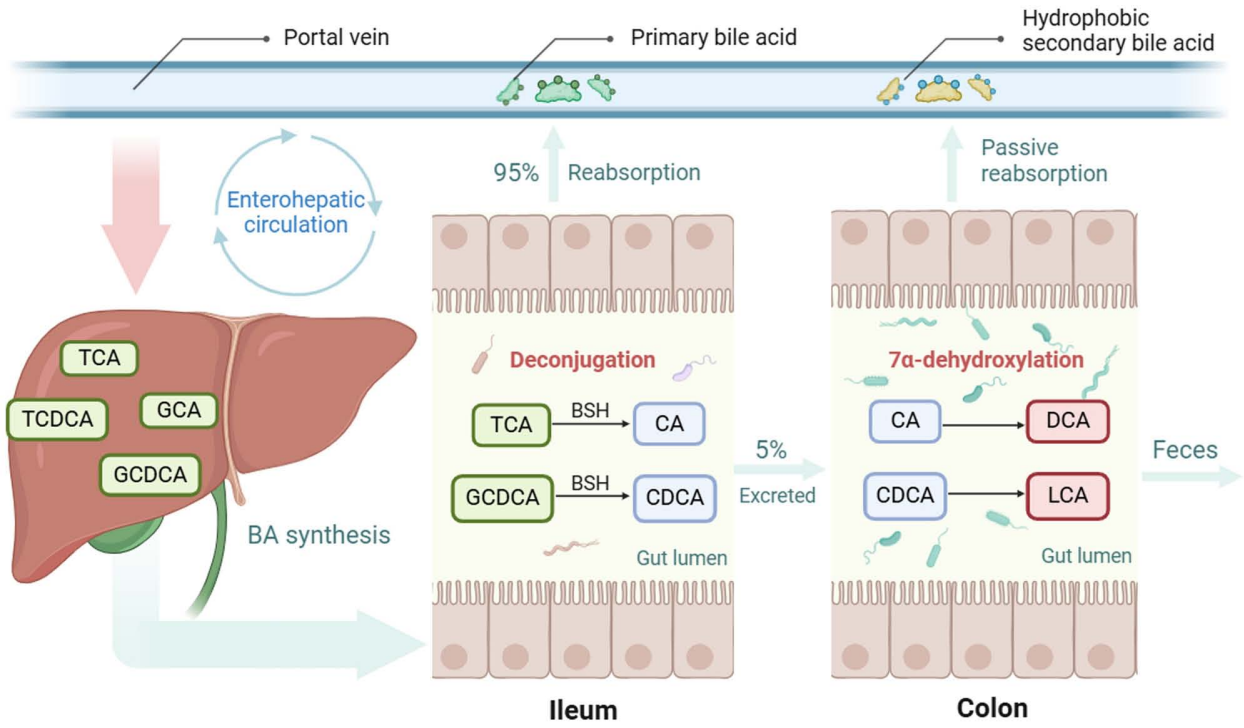

Figure 1. Normal BA metabolism in human body. Conjugated primary BAs are initially synthesized in the liver and released into the duodenum. Upon reaching the gut, BAs undergo modifications influenced by intestinal bacteria, thereby enriching the diversity of the BA pool. While a small fraction of BAs is excreted in feces, the majority are reabsorbed into the enterohepatic circulation, returning to the liver for processing. BSH, bile salt hydrolase; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; LCA, lithocholic acid; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid.

abundance in tumor tissue. It has been shown that a high ratio of glycoursodeoxycholic acid (GUDCA) to ursodeoxycholic acid (UDCA) in colon tumor tissue is positively associated with shorter 5-year OS and a high ratio of glycochenodeoxycholic acid (GCDCA) to CDCA is associated with shortened 5-year recurrence-free survival (RFS) (42). Alterations in fecal BA composition also warrant attention, given that BAs in feces are in direct contact with colonic mucosa and can directly regulate the gut inflammation (43). However, whether BAs in plasma and feces have different effects on CRC prognosis requires further investigation.

The distribution of BAs within the colon shows spatial specificity. A study on a cohort of patients with CRC (stages I-III) found that the levels of most BA species are elevated in tumor lesions from right-sided colon cancer (RCC) compared with those in left-sided colon cancer (LCC) (42). Furthermore, Morris *et al* (44) reported that BAs are more abundant in liver metastasis samples from patients with RCC than those from

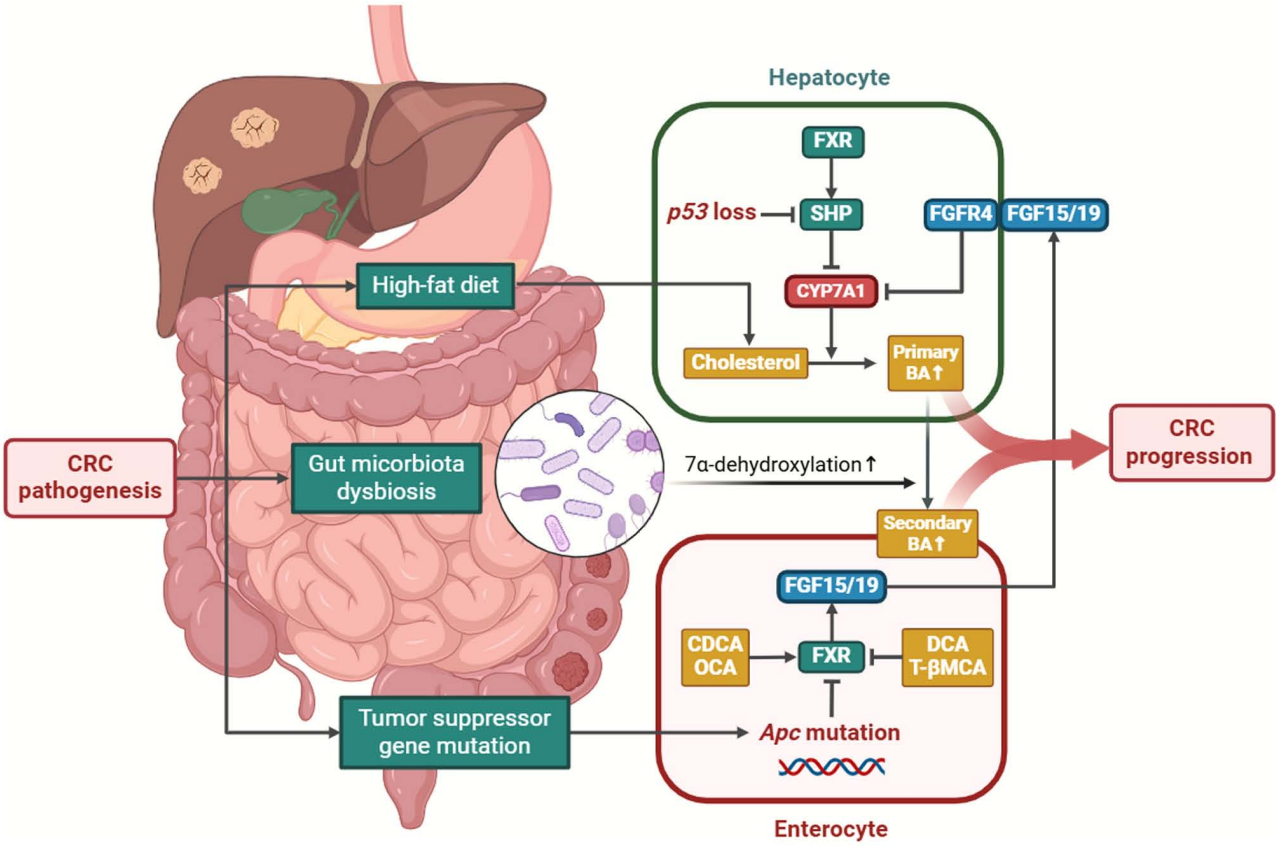

Figure 2. Dysregulated BA metabolism in CRC. Association between BA metabolism and CRC development is bidirectional and mutually reinforcing. In CRC, the expansion of BA pool primarily results from three factors. First, the long-term consumption of a high-fat diet provides a source of cholesterol for BA synthesis. Second, Apc mutation leads to silencing of intestinal FXR, a key regulator of BA synthesis in the liver. Third, alterations in gut microbiota composition in patients with CRC are characterized by an enhanced 7α-dehydroxylation capacity, leading to increased secondary BA levels, which suppress intestinal FXR. The aberrant BA metabolism favors CRC metastasis and is associated with poor prognosis. Apc, adenomatous polyposis coli; CDCA, chenodeoxycholic acid; CRC, colorectal cancer; CYP7A1, cholesterol 7α-hydroxylase; DCA, deoxycholic acid; FGFR, fibroblast growth factor receptor; FXR, farnesoid X receptor; OCA, obeticholic acid; SHP, small heterodimer partner; T-βMCA, tauro-β-muricholic acid.

patients with LCC. Metastatic liver RCC typically features more metastatic lesions, a more extensively involved segment and a poorer 5-year OS than LCC (45,46). However, whether a biased distribution of BAs contributes to metastatic features of RCC remains unclear. Lee *et al* (47) suggested that metastatic tumor cells may be capable of producing BAs to support malignant behavior. Further investigating the mechanism by which metastatic tumor cells generate BAs could provide valuable insight into targeting the colorectal liver metastasis.

Taken together, serum BAs are implicated in tumorigenesis and progression of CRC, and the abundance of BAs in CRC tumor tissue varies between different tumor locations (Table II). Although no prospective cohort studies have been conducted on the impact of BA levels on liver metastasis, experiments in mice have demonstrated that pathologically increased BA levels facilitate liver metastasis (48,49).

4. BAs induce CRC cell invasion

Invasion is a hallmark of tumor malignancy and the initial step of the metastatic cascade (50). BAs have been shown to stimulate CRC cell invasion. Treatment with pharmacological inhibitors indicates that BA-induced invasion involves MAPK, PI3K, PKC, COX2 and Rho/ROCK signaling cascades (51). The invasion and migration of CRC cells rely on acquisition of a mesenchymal phenotype and degradation of extracellular matrix (ECM), which is mediated by MMPs and urokinase-type plasminogen activators (uPAs).

Epithelial-mesenchymal transition (EMT). EMT is a cellular program involved in embryonic development and wound healing and is used by tumor cells to promote invasion and metastasis (52). Activation of EMT in tumor cells results in loss of apical-basal polarity and intercellular adhesion, endowing them with mobility and dissemination ability (52). A recent study demonstrated that high-fat diet (HFD)-induced DCA accumulation facilitates EMT in $Apc^{min/+}$ mice, indicated by downregulation of E-cadherin and upregulation of vimentin and fibronectin expression in intestinal tumor tissue (53). DCA exposure activates vascular endothelial growth factor receptor 2 (VEGFR2) in intestinal tumors of mice, resulting in expression of the EMT-inducing transcription factors ZEB1 and ZEB2 (53). Receptor tyrosine kinases, such as VEGFR and epithelial growth factor receptor (EGFR), serve key roles in proliferation and migration of CRC cells. The PI3K/AKT/mTOR and RAS/RAF/MEK/ERK signaling pathways, which are typically downstream of receptor tyrosine kinases, are implicated in BA-induced CRC invasion (54,55).

Table II. Clinical role of BAs in CRC.

Cohort	Sample	Detection method	Clinical implication	(Refs.)
Healthy controls	Serum	Liquid chromatography-mass spectrometry	High conjugated BA levels are associated with low OS and high CRC risk	(25)
CRC	Serum	Enzymatic assays	High total BA levels are associated with high TNM stage IV proportion	(29)
Postoperative CRC	Serum	Enzymatic assays	High total BA levels predict early recurrence of CRC	(30)
Stage I-III CRC	Primary tumor tissues	Liquid chromatography-mass spectrometry	BAs are more abundant in right-sided CRC, which features higher metastasis frequency, than left-sided CRC	(31)
Stage IV CRC	Metastatic tumor tissue	Liquid chromatography-mass spectrometry	BAs are more abundant in liver metastasis tissues derived from right-sided CRC compared with left-sided CRC	(32)

BA, bile acid; CRC, colorectal cancer, OS, overall survival; RFS, recurrence-free survival.

DCA activates EGFR in CRC cells, whereas ursodeoxycholic acid (UDCA) inhibits EGFR (56). UDCA has also been reported to antagonize EGFR/MAPK signaling and abrogate EGF-induced EMT in bile duct cancer cells (57); however, its protective role in regulating EMT in CRC cells remains unclear.

FXR, a BA receptor predominantly distributed in the liver and intestine, has been shown to suppress tumor invasion (58). Decreased FXR expression in CRC tumor tissues is associated with poor prognosis (59). FXR activation by obeticholic acid (OCA) suppresses the EMT process, compromising CRC invasion and migration (60), whereas FXR inhibition potentiates CRC invasion both *in vitro* and *in vivo* (58). The underlying mechanism involves FXR interaction with β-catenin to disable the transcriptional activity of the β-catenin/transcriptional factor 4 complex (58), which mediates the expression of key EMT transcription factors (52). In addition, DCA suppresses FXR expression, activating Wnt/β-catenin signaling and promoting the EMT process (12,58), further demonstrating the role of secondary BAs in inducing invasiveness of CRC cells.

Tumor cells undergoing EMT generally acquire a hybrid phenotype between epithelial and mesenchymal states, which enables them to function as cancer stem cells and increase metastatic efficacy (52). Farhana *et al* (61) demonstrated that incubating human colonic epithelial cells with 100 μM DCA or LCA for 7 days is sufficient to induce cancer stem cell transformation, with concomitantly increased expression of EMT-inducing transcription factors, including SLUG, ZEB2 and TWIST.

MMPs. The MMP family of zinc-dependent endopeptidases can break down ECM components, creating a pathway for tumor cells to invade underlying stroma. MMPs serve key roles in CRC metastasis by regulating proteinases, cellular receptors, growth factors and chemokines (62). MMPs are also regulated by BAs and, therefore, affect CRC progression. CA treatment results in an MMP-9-dependent increase in the invasiveness of human colon SW620 cells (63). Li *et al* (63) reported that CA-activated NADPH oxidase generates reactive oxygen species (ROS). p38 MAPK, ERK 1/2 and JNK 1/2, as the downstream signaling pathways of ROS, are activated and induce NF-κB and AP-1 DNA binding. As a result, expression of MMP-9 is notably enhanced (63). By contrast, activating FXR with CDCA or OCA notably suppresses MMP-7 and MMP-9 expression and inhibits CRC invasion (60,64). Additionally, Halvorsen *et al* (65) demonstrated that LCA, but not sulfated LCA, treatment increases MMP-2 secretion in CaCo-2 cells *in vitro*, suggesting intestinal microbiota-mediated BA sulfation may help regulate CRC invasion.

uPAs. The interaction between uPA and uPA receptor (uPAR) indirectly promotes ECM degradation and tumor invasion via MMP activation (66). BA-mediated tumor invasion is achieved by stimulating the expression of uPA and uPAR. A previous study showed that low DCA concentrations notably enhance invasiveness of CRC cells by stimulating uPAR expression (67). Incubating SW480 and LoVo cell lines with low concentrations of DCA for 30 min facilitates tyrosine phosphorylation and nuclear translocation of β-catenin, which directly regulates uPAR expression and is associated with invasion and migration of CRC cells (67). Baek *et al* (68) found that LCA facilitates SW620 cell invasiveness by upregulating uPAR in an AP-1-dependent manner. This may involve MAPK signaling, as ERK 1/2 and p38 inhibitors block LCA-triggered uPAR upregulation (68). BAs, especially secondary BAs, promote invasiveness of CRC cells by initiating pro-inflammatory and oncogenic signaling pathways (Fig. 3).

5. BAs facilitate angiogenesis

Tumor-associated angiogenesis is a key step in hematogenous dissemination, as demonstrated by colorectal liver metastasis (69). Neovascularization around the primary tumor renders CRC cells more likely to enter circulation. Angiogenesis in the pre-metastatic niche provides CRC cells with nutrients and

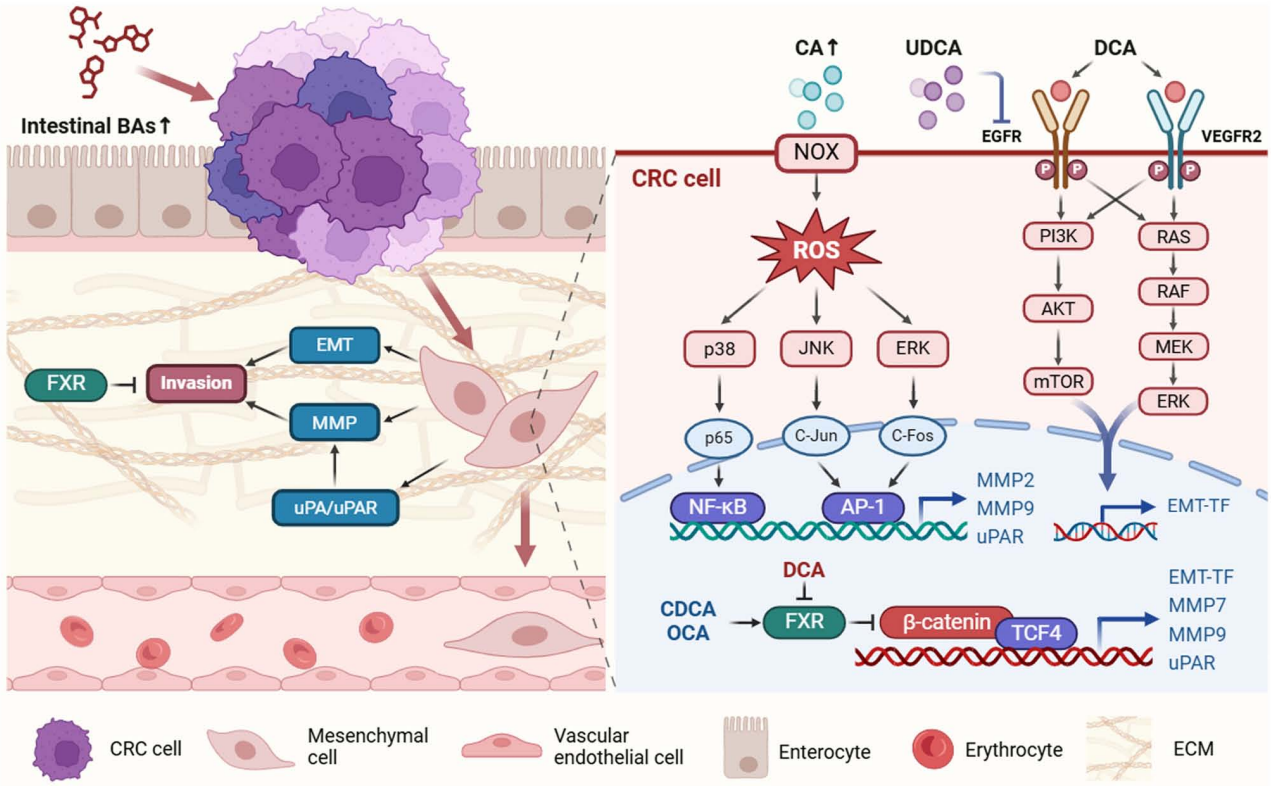

Figure 3. BAs and CRC invasion. Accumulated intestinal BAs facilitate CRC cell invasion primarily by inducing EMT and MMP-mediated ECM degradation. Activation of uPAR can promote MMP maturation. BAs can initiate inflammation and proliferation-associated signaling pathways to increase the expression of EMT-TFs, MMP and uPAR in CRC cells. This effect is ascribed to the activation of receptor tyrosine kinases, such as VEGFR2 and EGFR, and NOX-dependent ROS production. FXR hampers β-catenin-mediated EMT and ECM degradation. BAs can regulate tumor invasion by modulating the activity of FXR in CRC cells. BA, bile acid; CA, cholic acid; CDCA, chenodeoxycholic acid; CRC, colorectal cancer; DCA, deoxycholic acid; ECM, extracellular matrix; EGFR, epithelial growth factor receptor; EMT-TF, epithelial-mesenchymal transition-inducing transcriptional factor; FXR, farnesoid X receptor; NOX, NADPH oxidase; OCA, obeticholic acid; ROS, reactive oxygen species; UDCA, ursodeoxycholic acid; uPAR, urokinase-type plasminogen activator receptor; VEGFR2, vascular endothelial growth factor receptor 2.

oxygen to sustain development (69). Song *et al* (53) reported that oral administration of DCA in $Apc^{min/+}$ mice induces more vasculogenic mimicry channel formation around tumor lesions than in the control group. This effect is blocked by VEGFR2 inactivation, suggesting that DCA facilitates angiogenesis via the VEGFR2-mediated signaling pathway in CRC (53). Previous studies have shown that LCA stimulates CRC cells to secrete IL-8 *in vitro*, which is associated with angiogenesis, and endothelial cells treated with LCA exhibit an IL-8-dependent increase in tube formation (70,71). By contrast, LCA inhibits IL-1β-induced IL-8 production via interaction with VDR in colon cancer cells (72). However, the exact role of BAs in IL-8 expression in patients with CRC requires further investigation. In addition, cyclooxygenase-2 and its product, prostaglandin E2, are implicated in angiogenesis and associated with VEGF expression and microvessel density in CRC tissue (73). Studies have shown that LCA treatment promotes COX-2 expression in CRC cells by activating peroxisome proliferator-activated receptor α (74), whereas UDCA downregulates cyclooxygenase-2 expression by inhibiting p38 MAPK activation in CRC cells (75). These results suggest the potential of BAs to induce CRC angiogenesis. To the best of our knowledge, however, evidence concerning the direct angiogenic effect of BAs is lacking, and the underlying mechanisms require further investigation.

6. BAs improve survival of circulating tumor cells (CTCs)

During the metastatic cascade, CTCs that lose attachment to ECM) are subject to multiple forms of cell death. Redox imbalance, nutrient stress and anoikis compromise cell viability and hinder CTC survival (76,77). BAs can rectify defects and shield CTCs from cell death.

Metabolic characteristics of CTCs influence their metastatic processes. CTCs remodel metabolism to resist oxidative stress, adapt to specific demands of different organs and enhance their survival and metastatic potential (78). Upregulation of fatty acid oxidation (FAO) promotes CTC survival by increasing NADPH generation, which enhances defense against ROS and rebalances the redox state of CTCs (78). The blockade of FAO aggravates oxidative stress in detached CRC cells and diminishes distant metastasis (79). BAs trigger tumor metastasis by affecting FAO. Lee *et al* (47) demonstrated that in mice, taurodeoxycholic acid (TDCA) potentiates FAO in tumor cells via YAP signaling and facilitates lymph node metastasis. Metastatic tumor cells in lymph nodes can generate TDCA in an autocrine manner, which then activates VDR to facilitate translocation of YAP into the nucleus (47). Therefore, it is hypothesized that high levels of FAO, which are controlled by BAs, contribute to oxidative stress resistance in CTCs (47). In addition, aerobic glycolysis, also known as the Warburg effect,

blocks pyruvate from the tricarboxylic acid cycle, bypassing mitochondrial oxidative phosphorylation-induced ROS generation (80). Lactate and pyruvate production serve a role in the elimination of ROS (80). A recent study revealed that silencing FXR expression potentiates aerobic glycolysis in human colon cancer cells (81), which may favor survival during detachment from the ECM. Collectively, BAs promote the metabolic transformation of CTCs towards FAO and aerobic glycolysis, thereby controlling oxidative stress.

In the absence of the ECM, tumor cells are deprived of nutrients (82). In addition to adopting FAO-based metabolism, which enhances ATP production, tumor cells initiate autophagy to mitigate nutrient stress. By recycling byproducts of autophagic degradation, CTCs sustain metabolic sufficiency and survive nutrient deprivation (76). Hepatic FXR activation can notably decrease the expression of autophagy-related genes by impeding transcriptional activity of cAMP-response element binding protein (CREB), whereas TGR5 activation reverses this effect by recruiting CREB (83,84). This suggests BAs may protect CTCs from nutrient stress by affecting tumor autophagy in an FXR-dependent manner. Therefore, involvement of BA-activated receptors in regulating autophagy in metastatic CRC cells requires further investigation.

Due to loss of EGFR and β1 integrin during ECM detachment, CTCs undergo anoikis, a caspase-dependent programmed cell death. The activation of ERK signaling diminishes BCL-2 activity, which triggers apoptosis by inducing cytochrome c release (76). Given the considerable ability of DCA to stimulate EGFR/MAPK signaling, increased circulating DCA may promote anoikis resistance in CTCs. By contrast, UDCA facilitates the ubiquitination and degradation of EGFR in CRC cells, indicating an unfavorable effect on CTC survival (56). However, these hypotheses require further evidence. High DCA concentrations trigger ROS generation and induce cancer cell apoptosis (56), suggesting that both the species and dose of BAs affect CTC survival and should be considered in future studies. Collectively, BAs may promote survival of CTCs in circulation by facilitating metabolic adaptation, autophagy and anoikis resistance (Fig. 4).

7. Role of BAs in immune evasion and pre-metastatic niche formation

To survive anti-tumor immunity and seed in the liver, CRC cells downregulate their immunogenicity and recruit immunosuppressive cells to construct a compatible environment that favors colonization (85). Many studies (29,86-89) have focused on the role of BAs in regulating anti-tumor immunity and reshaping the tumor microenvironment (TME) (Fig. 5). Kawarabayashi *et al* (48) showed that elevated serum and hepatic BAs levels in bile duct-ligated (BDL) mice facilitates liver metastasis. A recent study in mice suggested that taurocholic acid (TCA) expansion facilitates colorectal liver metastasis by creating a hepatic immunosuppressive microenvironment (49). These studies provide evidence of the association between BAs and hepatic pre-metastatic niche construction. A variety of immune cells serve a role in colorectal liver metastasis (90). The tumor microenvironment is complex and it is difficult to pinpoint a single cell type responsible for metastasis (90,91). It is likely that BAs reshape the tumor microenvironment by simultaneously regulating the function of diverse immune cells (Table III).

Tumor-associated macrophages (TAMs). TAMs that are extensively present in the TME are primarily derived from circulating monocytes, which are recruited by pro-inflammatory signaling molecules, such as CCL2, CCL5 and colony stimulating factor 1 (CSF1). Based on features of the TME, macrophages polarize into two subsets: Anti-tumor M1 and pro-tumor M2. M1 TAMs exert tumoricidal activity by releasing ROS and NO, whereas M2 TAMs trigger anergy of cytotoxic T lymphocytes (CTLs) by competitively consuming L-arginine or recruiting immunosuppressive cells (92). M2 TAMs promote colorectal liver metastasis by creating a hepatic pre-metastatic niche (93).

BAs influence macrophage polarization. An *in vivo* study (94) revealed that TCA accumulation in the liver creates an immunosuppressive environment by inducing M2 macrophage polarization. The removal of BAs using cholestyramine, an American Food and Drug Administration-approved BA sequestrant, attenuates the proportion of M2 TAMs and downregulates PD-L1 expression in macrophages (94). BA-mediated TAM polarization relies on BA receptor activation. TGR5 is extensively expressed in macrophages (95). Zhao *et al* (96) demonstrated that CDCA stimulates TGR5 expression in murine bone marrow-derived macrophages *in vitro* and induces M2 polarization via the cAMP/STAT3/STAT6 signaling pathway by increasing IL-10 and ARG-1 levels and decreasing IL-6 and inducible NO synthase (iNOS) expression. Pharmacological inhibition of TGR5 by SBI 115 reverses this effect and the cytotoxicity of $CD8^+$ T cells (96). In mice, BDL-induced cholestasis, which increases serum BA concentration, increases TGR5 expression in Kupffer cells (97). Future research should focus on the role of BAs in Kupffer cell polarization and the potential association with hepatic immune tolerance. Sun *et al* (94) found that FXR plays an indispensable role in TCA-promoted M2-like macrophage polarization in the presence of IL-4. Inhibition of FXR attenuates the promoting role of TCA (94).

In addition to activating BA receptors, BAs control phenotypic conversion by regulating macrophage metabolism. Shao *et al* (98) demonstrated that LCA-treated macrophages undergo metabolic transformation from glycolysis to oxidative phosphorylation, thereby skewing polarization of macrophages towards the M2 phenotype. This suggests that accumulated BAs induce M2 TAM polarization by altering the metabolic pattern in macrophages, in addition to interacting with BA receptors.

Secondary BAs induce chronic intestinal inflammation and drive the recruitment of TAMs. Cao *et al* (99) discovered that BA-induced alterations in gut microbiota are involved in TAM accumulation. Feeding DCA changes the proportion of intestinal bacteria in mice, indicated by increased abundance of Clostridium and a reduced abundance of butyrate-producing bacteria (99). Transferring fecal microbiota from DCA-treated to $Apc^{min/+}$ mice results in low-grade intestinal inflammation, leading to an increase in infiltration of M2 TAMs by amplifying CCL2 signaling (99). This suggests that in addition to polarization, BAs facilitate monocyte trafficking from the blood and educate them to immunosuppressive M2 TAMs by regulating the gut microbiota.

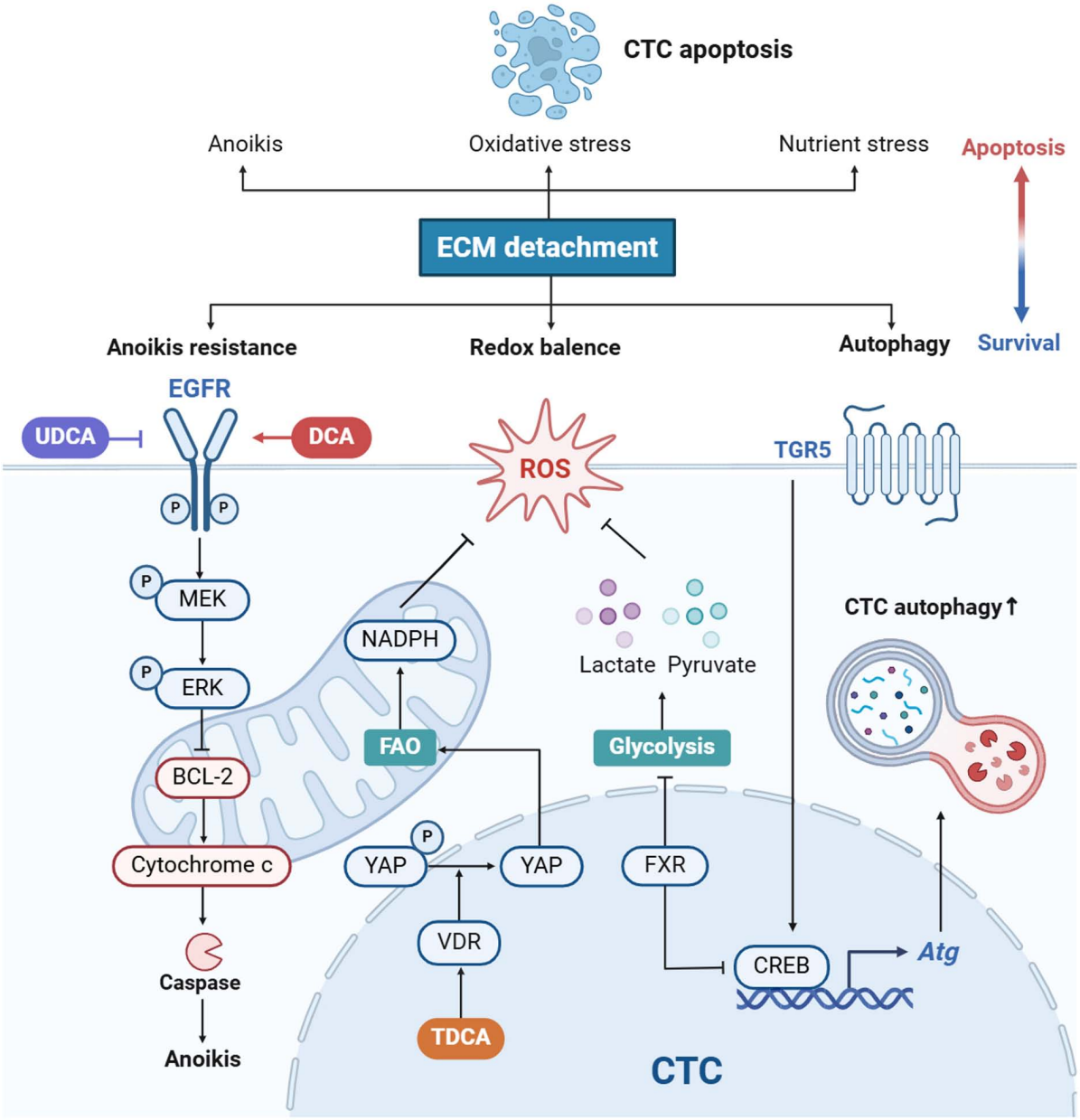

Figure 4. BAs facilitate CTC survival during ECM detachment. Following detachment from ECM, CTCs undergo anoikis and oxidative and nutrient stress. Circulating BAs can activate EGFR/MAPK signaling in CTCs to abrogate the BCL-2-mediated cytochrome c release from mitochondria, thereby diminishing caspase-dependent anoikis. DCA can potentiate FAO-derived NADPH generation via VDR/YAP signaling and increase lactate and pyruvate production by enhancing FXR-regulated aerobic glycolysis. These products eliminate excessive intracellular ROS and sustain the redox homeostasis. FXR impedes Atg expression by disrupting CREB transcriptional activity, while TGR5 activation induces CREB recruitment and drives autophagy. Atg, autophagy-related gene; CREB, cAMP-response element binding protein; CTC, circulating tumor cell; DCA, deoxycholic acid; ECM, extracellular matrix; EGFR, epithelial growth factor receptor; FAO, fatty acid oxidation; FXR, farnesoid X receptor; ROS, reactive oxygen species; TDCA, taurodeoxycholic acid; UDCA, ursodeoxycholic acid; VDR, vitamin D3 receptor; YAP, yes-associated protein.

Tumor-associated neutrophils (TANs). TANs recruited to the TME attain a pro-tumor phenotype, contributing to colorectal liver metastasis by impairing anti-tumor immunity, ECM remodulation and angiogenesis (100). In addition, TANs can facilitate the adhesion and intravasation of circulating CRC cells by extruding neutrophil extracellular traps (101). A multivariate analysis of patients with CRC showed that an elevated neutrophil-to-lymphocyte ratio is associated with liver metastasis and poor overall survival (102).

Our recent study (89) revealed that TANs lead to colorectal liver metastasis. We found that neutrophils were recruited to the liver of mice under cholestatic conditions. Further experiments demonstrated that cholestasis-related primary BAs, including tauro-β-muricholic acid (Tβ-MCA) and glycocholic acid (GCA), facilitated the immunosuppressive phenotype conversion of neutrophils via the p38 MAPK signaling pathway (89). The high expression of Arg-1 and iNOS by infiltrated neutrophils inhibits anti-tumor activity of $CD8^+$ T cells and contributes to the liver metastasis of colorectal cancer (89). TCA elevation has also been shown to trigger hepatic neutrophil infiltration in BDL mice. Mechanistically, TCA activates ERK1/2 in hepatocytes,

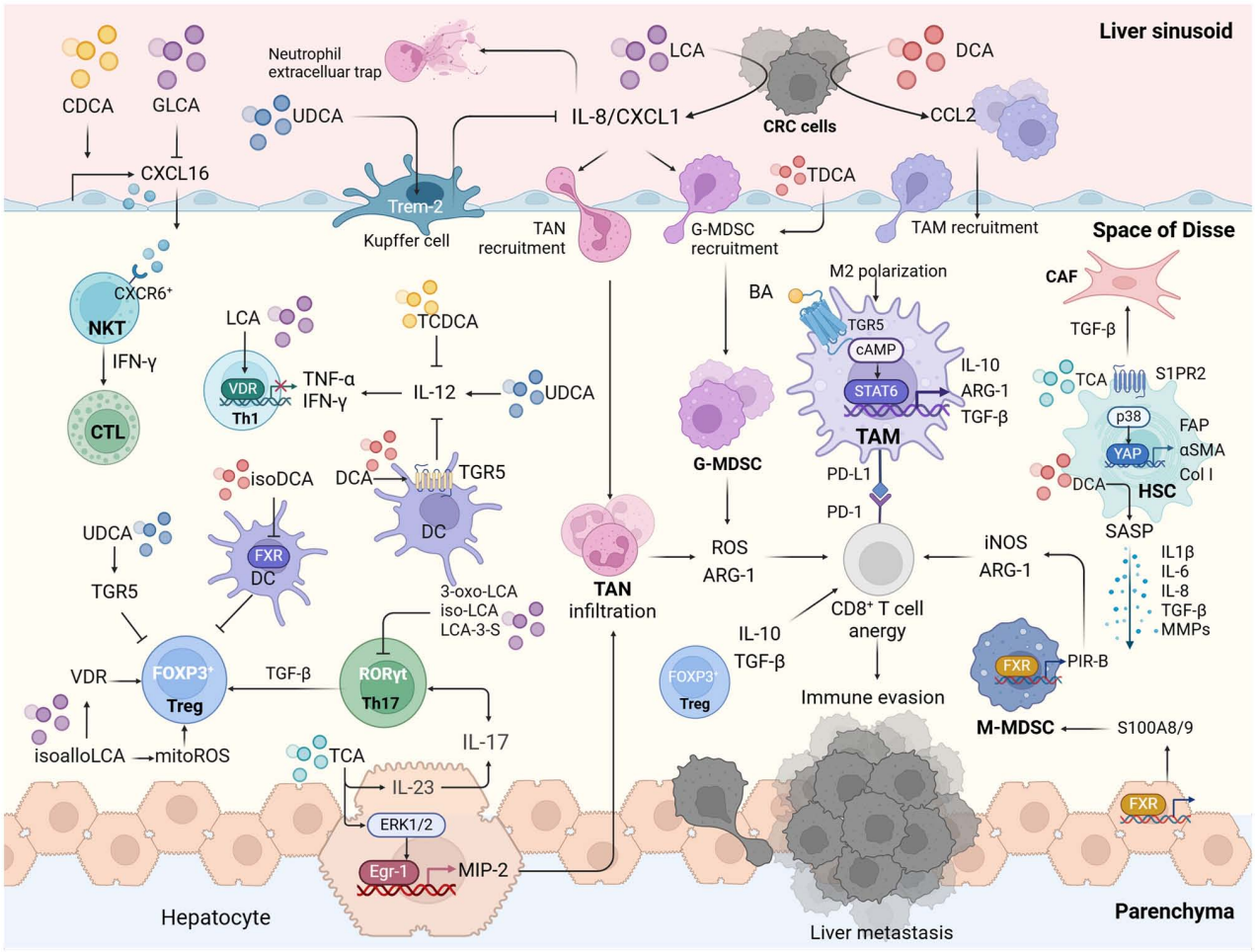

Figure 5. BAs reshape the TME. BAs, particularly secondary BAs, instigate a pro-tumor immune response by interacting with BA receptors that are extensively expressed in the TME. Accumulation of BAs triggers inflammation, facilitating the recruitment of immunosuppressive cells into the liver and creating an optimal hepatic pre-metastatic niche. 3-oxoLCA, 3-oxolithocholic acid; Arg-1, arginase-1; BA, bile acid; CAF, cancer-associated fibroblast; CDCA, chenodeoxycholic acid; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DCA, deoxycholic acid; Egr-1, early growth response factor 1; FXR, farnesoid X receptor; GLCA, glycolithocholic acid; HSC, hepatic stellate cell; iNOS, inducible nitric oxide synthase; isoLCA, isolithocholic acid; LCA, lithocholic acid; LCA-3-S, lithocholic acid 3-sulfate; LSEC, liver sinusoidal endothelial cell; MDSC, myeloid-derived suppressor cell; MIP2, macrophage inflammatory protein 2; mitoROS, mitochondrial reactive oxygen species; NKT, natural killer T cell; NLRP3, NOD-like receptor thermal protein domain associated protein 3; PIR-B, paired immunoglobin receptor-b; RORγt, retinoid related orphan receptor-γt; SASP, senescence-associated secretory phenotype; S1PR2, sphingosine-1-phosphate receptor 2; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TDCA, taurodeoxycholic acid; TGF-β, transforming growth factor-β; TGR5, Takeda G protein-coupled receptor 5; TME, tumor microenvironment; Treg, regulatory T cell; TREM2, triggering receptor expressed in myeloid cells 2; UDCA, ursodeoxycholic acid; VDR, vitamin D3 receptor.

resulting in upregulation of early growth response factor 1 transcription factor. This increases expression of macrophage inflammatory protein 2 (MIP2), which induces neutrophil migration into the liver (103). IL-17A is upregulated during cholestasis and synergizes with TCAs to induce MIP2 expression (103).

CXCL1 is a potent chemoattractant of neutrophils. UDCA may ameliorate cholestasis-induced neutrophil infiltration by upregulating expression of Trem-2, which negatively regulates CXCL1 expression in Kupffer cells (104). Pathological accumulation of BAs in the liver is associated with hepatic inflammation and neutrophil recruitment in colon cancer cachexia (105). Treatment with cholestyramine or anti-IL-6 can relieve hepatic neutrophil accumulation (105). These findings indicate an association between BA-triggered inflammation and increased levels of hepatic neutrophils and that neutrophil accumulation during cholestasis may drive colorectal liver metastasis.

Myeloid-derived suppressor cells (MDSCs). MDSCs are a subset of immature monocytes and granulocytes that express CD11b and Ly-6G, respectively. MDSCs are recruited by TME-derived pro-inflammatory signaling and contribute to metastatic CRC (106). Similarly to TAMs and TANs, MDSCs facilitate tumor evasion, with granulocytic MDSCs (G-MDSCs) generating ROS and monocytic MDSCs (M-MDSCs) producing arginase and iNOS (106). Depleting G-MDSCs in transgenic mice significantly decreases colorectal liver metastasis by restoring antitumor immunity (107).

Intraperitoneal injection of TCA increases the proportion of liver-infiltrating MDSCs in mice and facilitates experimental colorectal liver metastasis (49). This may involve FXR activation, as the intraperitoneal injection of FXR agonist induces $CD11b^{+}$ $Ly6C^{high}$ MDSC infiltration by increasing S100A8 and S100A9 expression in the liver (49). Furthermore, FXR activation triggers paired immunoglobulin receptor-b expression, which potentiates immunosuppressive function

Table III. Impact of bile acids on immune cells.

Immune cell	Bile acid	Effect	(Refs.)
TAM	CDCA, TCA, LCA	M2 TAM polarization	(76,78-80)
	DCA	Recruit M2 TAMs via upregulating CCL2	(81)
TAN	GCA	TAN immunosuppressive phenotype conversion	(85)
	TCA	Recruit neutrophils via upregulating CXCL2	(86)
	UDCA	Inhibit neutrophils recruitment	(87)
MDSC	TCA, TDCA	MDSC recruitment	(37,92)
DC	DCA, isoDCA	Impair antigen presentation ability	(96-98)
Th1	LCA	Inhibit Th1 activation	(106)
Th17	IsoLCA, 3-oxoLCA, LCA-3-S	Inhibit Th17 differentiation	(109-111)
	TCA	Indirectly recruit Th17 cells	(86)
Treg	DCA, LCA	Recruit Treg via upregulating CCL28	(18)
	IsoalloLCA	Promote Treg differentiation	(109)
	UDCA	Inhibit Treg differentiation	(120)
CTL	DCA	Inhibit tumoricidal activity of CTLs	(122)
NKT	GLCA	Inhibit NKT recruitment via downregulating CXCL16	(125)
HSC	TCA	Promote HSC proliferation, migration and extracellular matrix secretion	(133)

3-oxoLCA, 3-oxolithocholic acid; CA, cholic acid; CDCA, chenodeoxycholic acid; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DCA, deoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; GLCA, glycolithocholic acid; HSC, hepatic stellate cell; isoDCA, isodeoxycholic acid; isoLCA, isolithocholic acid; isoalloLCA, isoallolithocholic acid; LCA, lithocholic acid; LCA-3-S, lithocholic acid 3-sulfate; MDSC, myeloid-derived suppressive cell; NKT, natural killer T cell; TAM, tumor associated macrophage; TAN, tumor associated neutrophil; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TDCA, taurodeoxycholic acid; Th, T helper cell; Treg, regulatory T cell; UDCA, ursodeoxycholic acid.

of MDSCs (108). In mice, the intravenous injection of TDCA increases levels of splenic MDSCs during sepsis (109). Following TDCA treatment, purified splenic MDSCs display an amplified ROS-mediated immune regulatory capacity similar to that of G-MDSCs (109). Furthermore, IL-8 exerts potent chemoattractant activity on both neutrophils and MDSCs and induces neutrophil extracellular trap extrusion by TANs or G-MDSCs to shield circulating tumor cells from attack (110). A large-scale retrospective analysis of patients with advanced cancer revealed that IL-8 levels in the serum are associated with tumor-infiltrating immunosuppressive myeloid cells and serve as a circulating biomarker of the therapeutic effects of immune checkpoint blockade (111). LCA treatment increases IL-8 expression in CRC cells. This effect is dependent on suppression of STAT3 phosphorylation, which follows LCA-induced ERK1/2 activation (71). These findings suggest that the BA-induced increase in MDSCs could be attributed to hepatic FXR activation and IL-8 release following secondary BA-triggered inflammation.

Dendritic cells (DCs). DCs are essential for tumor-adaptive immunity. Conventional DCs transport and present tumor antigens in draining lymph nodes to activate T cells via costimulatory signaling (112). However, treatment with BAs compromises the antigen-presenting function of DCs. The secondary BA 3β-hydroxydeoxycholic acid (isoDCA) antagonizes FXR in DCs and suppresses the transcriptional activity of genes associated with antigen presentation. Consequently, despite the presence of DCs, isoDCA exposure inhibits T cell proliferation and increases the frequency of peripherally induced regulatory T cells (Tregs) (113). DCA confers an anti-inflammatory phenotype to DCs via TGR5/cAMP/PKA signaling. By activating TGR5, DCA treatment decreases the expression of IL-1β, IL-6, tumor necrosis factor-α (TNF-α), IL-12p70 and co-stimulatory molecules, such as CD40 and CD86, in bone marrow-derived DCs (BMDCs) (114). Furthermore, LCA-treated murine BMDCs undergo TGR5-dependent apoptosis and autophagy (115). With impaired glutathione production and increased ROS accumulation, LCA-treated BMDCs downregulate the expression of proinflammatory cytokines, resulting in inhibition of T helper (Th)1 and Th17 cell differentiation and a decrease in IFN-γ and IL-17 secretion (115). IL-12 participate in Th1 cell polarization and IFN-γ secretion (116). Taurochenodeoxycholic acid decreases IL-12 secretion in DCs via the TGR5/cAMP signaling pathway (117), whereas UDCA-treated BMDCs restore release of IL-12 in a concentration-dependent manner (118). These results demonstrate that BAs inhibit adaptive antitumor immunity by impairing the antigen-presenting capacity of DCs.

Th cells. $CD4^+$ Th cells are key members of the tumor-adaptive immune system. Th1 cells facilitate maturation and functional maintenance of cytotoxic $CD8^+$ T lymphocytes and upregulate major histocompatibility complex class molecules expressed on tumor cells via secreted IFN-γ to augment tumor recognition (119). High levels of circulating Th1 cells predict better prognosis in cancer (120) and are an important target in

metastasis treatment (121,122). It is reported that LCA can inhibit Th1 cell activation by suppressing VDR-dependent ERK1/2 phosphorylation and LCA treatment can down-regulate expression of Th1-related genes STAT1 and T-box expressed in T cells and secretion of cytokines IFN-γ and TNF-α in Jurkat T cells (123). This indicates that LCA may impair adaptive antitumor immunity by mediating Th1 cell inactivation.

By contrast, high expression of Th17 cluster genes and levels of IL-17A cells in tumor tissue are associated with poor CRC prognosis (124). Th17 cells can secrete TWEAK, a cytokine that induces epithelial-mesenchymal transition of CRC cells, to facilitate colorectal liver metastasis (125). Isolithocholic acid, 3-oxolithocholic acid and lithocholic acid 3-sulfate have affinity for the key transcription factor RORγt. They physically interact with RORγt and inhibit its transcriptional activity, thereby inhibiting Th17 cell differentiation and IL-17A expression (126-128). TCAs, which accumulate during cholestasis, mediate Th17 cell infiltration into the liver. Additionally, TCA promotes IL-23 production by hepatocytes, which stimulates IL-17A secretion by Th17 cells (103). IL-17A facilitates IL-23 expression in hepatocytes, thereby forming a positive feedback loop in which IL-17 and IL-23 are mutually activated (103). IL-17-enriched environment may be associated with immune suppression as elevated hepatic IL-17A increases mobilization and recruitment of G-MDSC (129) and Th17 cells can transdifferentiate into Tregs in a TGF-β-enriched environment (130). These results indicate that Th17 cell overload during cholestasis may lead to inflammatory immunosuppression in the TME and is of predictive value in response to anti-PD-1 immunotherapy (131,132).

Tregs. Tregs, the predominant source of IL-10 in the TME, serve a dual role in CRC progression (133). In the colon, a higher frequency of tumor-infiltrating FOXP3$^+$ Tregs and IL-10 levels predict better prognosis in patients with CRC (134), potentially due to suppression of Th17-mediated inflammation (135). By contrast, Sun *et al* (29) showed that immunosuppressive Tregs recruited to colon tumors promote CRC progression. In addition, hepatic Treg-derived IL-10 is key in liver metastasis. It contributes to the systemic upregulation of PD-L1 in monocytes (133), which may explain liver metastasis-mediated CD8$^+$ T cell anergy and immunotherapy resistance (7).

Unconjugated DCA and LCA increase recruitment of CD25$^+$FOXP3$^+$ Tregs to colonic tumor lesions (29). DCA and LCA activate TGR5 in CRC cells and downstream WNT/β-catenin signaling, resulting in expression of CCL28, an important chemokine that participates in Treg trafficking (29). IsoalloLCA promotes Treg differentiation and inhibits proliferation of effector T cells by increasing mitochondrial oxidative phosphorylation and generating mitochondria-derived ROS, leading to upregulation of FOXP3 (126). VDR activation may involve Treg differentiation; VDR knockout impairs LCA-mediated colonic Treg amplification (136). By contrast, UDCA inhibits Treg expansion (87). A recent study (87) reported that UDCA induces TGF-β1 autophagosomal localization and promotes subsequent degradation of TGF-β1 via the TGR5/cAMP/PKA signaling pathway in tumor-bearing mice. Owing to diminished TGF-β1 signaling, UDCA decreases Treg cell differentiation and proliferation, and the oral administration of UDCA synergizes with the immune checkpoint blockade to drive colorectal tumor suppression (87). A high GUDCA/UDCA ratio in colon tumors is associated with levels of FoxP3$^+$ Treg cells and poor prognosis in CRC (42), implying a role of BA deconjugation in antitumor immunity. These results suggest novel therapeutic strategies for treating colorectal liver metastasis and resistance to immunotherapy in patients with CRC. However, whether BA regulates hepatic Treg differentiation remains unclear.

CD8$^+$ T cells. CD8$^+$ T cells serve a predominant role in tumor immune surveillance. A higher frequency of tumor-infiltrating CD8$^+$ T cells is associated with reduced metastasis in CRC (137). A recent study (88) has shown that DCA directly suppresses tumoricidal activity of CD8$^+$ T cells by potentiating the efflux of intracellular calcium. Under physiological conditions, cytosolic Ca^{2+} accumulates upon T cell receptor activation and the nuclear factor of activated T cell 2 is dephosphorylated and translocated into the nucleus to enhance IFN-γ and TNF-α expression. DCA inhibits this process by activating plasma membrane Ca^{2+} ATPase and inhibiting Ca^{2+} accumulation, leading to CD8$^+$ T cell dysfunction (88). Cholestasis reduces anti-tumor immunity and inhibits CD8$^+$ T cell activity. PD-1 knockout in mice decreases cholestasis-induced Th17 cell proliferation and restores CD8$^+$ T cells function with no notable impact on Treg expansion (138). Therefore, PD-1 blockade is a promising approach for enhancing the antitumor immunity in the intrahepatic immunosuppressive environment during cholestasis.

Natural killer T (NKT) cells. NKT cells exert tumoricidal activity, reeducate the TME and acquire immunogenic properties (139). BA metabolism, modulated by intestinal bacteria, affects CXCR6$^+$NKT cells. BAs affect NKT cell recruitment by regulating expression of CXCL16 in liver sinusoidal endothelial cells (LSECs), the only known ligands for CXCR6 (86). *In vivo* experiments suggest feeding mice primary BAs facilitates CXCL16 expression and NKT cell accumulation, whereas feeding mice secondary BAs reverses this effect (86). Consistent with these results, a study of a liver cancer cohort showed that CDCA is positively associated with CXCL16 expression in human non-tumor liver tissue, whereas GLCA is inversely associated (86). Targeting *Clostridium*, which facilitates the conversion of primary BAs into secondary BAs, enhances hepatic NKT cell infiltration as well as their IFN-γ production (86). Based on these results and the ability of LSECs to capture nanoparticles in circulation, Ji *et al* (140) developed an OCA-nanoemulsion using an ultrasonic emulsification method for drug delivery. This nanoemulsion successfully increases expression of CXCL16 in LSECs and the accumulation of NKT cells, with higher secretion of IFN-γ in tumors of mice (140). Cheng *et al* (141) used a mouse metastasis model to demonstrate that long-term capsaicin-containing diet can contribute to the hepatic pre-metastatic niche, characterized by decreased levels of NKT cells and accumulated neutrophils and monocytes, by increasing secondary BAs generated by the gut microbiota. Oral treatment with OCA abolishes this effect and decreases liver metastasis (141). These results indicate that the intestinal

microbiota serves a key role in regulating antitumor immunity, with BAs acting as a bridge for communication.

Hepatic stellate cells (HSCs). HSCs are perisinusoidal non-parenchymal liver cells located in the space of Disse. They are the primary precursors of cancer-associated fibroblasts and facilitate colorectal liver metastasis (142). Primed HSCs contribute to tumor immune evasion by stimulating Treg expansion (142). Additionally, activated HSCs facilitate angiogenesis and form a fibrotic environment that promotes CTC adhesion, favoring hepatic disseminated CRC cell colonization (143,144). Targeting HSCs may enhance efficacy of antiangiogenic therapy in patients with colorectal liver metastasis (145).

BAs can stimulate the activation of HSC. Under cholestatic conditions, mast cells are recruited to the liver to activate HSCs (146). Incubation with TCA upregulates the expression of fibroblast activation protein, α-smooth muscle actin and collagen I in LX2 cells (human-originated HSCs) in a dose-dependent manner (146). Similar results are observed in the livers of mice treated with TCA *in vivo* (49). TCA-induced HSC activation is controlled by S1PR2/p38/MAPK/YAP signaling; JTE-013, an S1PR2 inhibitor, inhibits this TCA-mediated effect (147). Unconjugated secondary BAs exhibit greater efficiency in inducing primed HSCs than conjugated primary BAs, which involve TNF and NF-κB signaling activation (148). DCA treatment of LX2 cells triggers the secretion of the senescence-associated secretory phenotype factors and significantly upregulates expression of IL-1β, IL-6, IL-8, CXCL1, TGF-β, MMP-2, MMP-7 and MMP-9 (149). These findings indicate the potential role of HSCs in promoting liver metastasis by reshaping the hepatic pre-metastatic niche; however, evidence regarding the function of HSCs in CRC is lacking, and the specific regulatory mechanisms require further exploration.

NLRP3. The NLRP3 inflammasome is a cytoplasmic multimeric protein complex that amplifies inflammation via caspase-1-dependent IL-1β and IL-18 secretion (150). According to a recent study, targeting NLRP3 signaling diminishes PMN-MDSC recruitment, thereby inhibiting pre-metastatic niche formation (150). BAs, as danger-associated molecular patterns, participate in NLRP3 inflammasome activation. Increased CDCA levels during cholestasis activate the NLRP3 inflammasome in macrophages and potentiate cholestasis-associated liver inflammation (151). By contrast, FXR may rescue cholestasis-triggered inflammation because it impairs NLRP3 assembly by physically interacting with its components (152). DCA activates the NLRP3 inflammasome via S1PR2-mediated cathepsin B release independent of FXR or TGR5 (153). The role of BAs in stimulating NLRP3 is further demonstrated *in vivo*. NLRP3 was significantly activated in the liver of mice fed with LCA (154). However, Guo *et al* (155) suggested that BAs, especially LCA and TLCA, suppress NLRP3 activation in macrophages by facilitating NLRP3 ubiquitination via the TGR5-cAMP-PKA axis and decreasing IL-1β expression. This discrepancy may be due to the addition of LPS and NLRP3 agonist nigericin. Given the crucial role of proinflammatory signaling in immature myeloid cell recruitment, the effect of NLRP3 on the pre-metastatic niche warrants further exploration.

8. Promising BA-associated therapeutics for CRC treatment

FXR agonists. FXR functions as a tumor suppressor in CRC (156); downregulation of FXR in patients with CRC indicates poor prognosis (59). OCA, a potent synthetic FXR agonist, has been approved by the US Food and Drug Administration to treat primary biliary cholangitis (157). OCA decreases BA synthesis by activating FXR in the liver and alleviating hepatic inflammation (158). This makes it a promising therapeutic agent for treating colorectal liver metastasis, although clinical trials have not yet been conducted. Our previous study (89) provided evidence that OCA abrogates colorectal liver metastasis by suppressing BA accumulation in a cholestatic mouse model. OCA reverses the immunosuppressive microenvironment in the liver (89). Liver metastasis can compromise antitumor immunity and efficacy of immunotherapy (7). OCA notably enhances the efficacy of immune checkpoint blockade, prolonging survival of mice (89).

Additionally, the FXR agonist GW4064 has been shown to upregulate PD-L1 expression in CRC cells, thereby potentiating the efficacy of PD-L1 immune checkpoint blockade in CRC treatment (159). However, despite promising preclinical results, concerns regarding systemic use of FXR agonists persist due to their potential side effects (156). FXR agonists induce hepatocyte apoptosis by impairing mitochondrial function (160). Therefore, designing FXR agonists with higher tissue or cell specificity (161) and developing drug delivery systems to target tumor lesions (140,162) is important.

UDCA. UDCA improves BA homeostasis by facilitating BA secretion and excretion and is used for cholestasis treatment (163). Previous studies have confirmed that UDCA influences the fecal microbiota composition and reduces the risk of colorectal adenoma (164,165). In a mouse model of DSS-induced colitis, UDCA alleviates colonic inflammation and prevents colitis-associated cancer (165). By stimulating TGR5, UDCA inhibits the Hippo/YAP signaling pathway in CRC cells, thereby suppressing malignant progression of CRC (166). UDCA treatment induces anti-tumor immunity in CRC; this effect is more potent when UDCA is combined with an anti-PD treatment (87). Previous studies have elucidated the protective role of UDCA in CRC carcinogenesis (75,164,167); to the best of our knowledge, however, few (87) have focused on the association between UDCA and antitumor immunity in patients with CRC. The discovery that UDCA enhances the efficacy of immunotherapy provides new avenues for CRC treatment. As patients with liver metastasis are more likely to develop cholestasis and are refractory to immunotherapy, such as anti-PD treatment (89), the addition of UDCA to therapeutics may be beneficial.

Modulating gut microbiota. Recently, the gut microbiota associated with BA metabolism has gained increasing attention in CRC development research (6,168,169). *Clostridium* amplification, which catalyzes the 7α-dehydroxylation pathway, contributes to elevated secondary BA levels and facilitates CRC progression (170). Vancomycin, neomycin, and primaxin decrease liver metastasis by impeding secondary BA production (86). Non-absorbable antibiotic treatment has the same effect of suppressing liver metastasis of CRC as classic antibiotic cocktail

treatment (171), with fewer systemic side effects, making it a promising candidate for clinical use. Moreover, a recent study demonstrated that withdrawal of broad-spectrum antibiotics increases the abundance of *E. clostridioformis* and secondary BA production, compromising the therapeutic response to PD-1 blockade (172). This suggests that targeting harmful gut bacteria and maintaining BA homeostasis are conducive to enhancing the immunotherapy response in treating CRC.

Fecal microbiota transplantation (FMT) is the most direct method for altering gut microbiome composition to improve prognosis of patients with CRC (173). Clinical research has confirmed that FMT protects patients who receive immune checkpoint inhibitor (ICI) treatment for ICI-associated colitis (174). In addition, the abundance of *Akkermansia muciniphila* is associated with active response to ICI therapy (174,175). Transplanting *A. muciniphila* into unresponsive patients can restore sensitivity to immunotherapy. However, the safety of FMT remains controversial (174). Adverse events include fever, vomiting, infection, relapse of inflammatory bowel disease and *C. difficile* infection (176). Further randomized controlled trials are required before FMT can be widely used in clinical practice.

9. Conclusion

The key role of intestinal microbiota in CRC development is gaining increasing attention (6). As one of the primary metabolites of gut bacteria, BAs drive CRC metastasis and may be predictive biomarkers for colorectal liver metastasis (89). The present review summarizes the specific roles of BAs in regulating tumor invasion, angiogenesis, anoikis and immune evasion. Mechanistically, BAs serve as signaling molecules to induce inflammation by activating transcription factors such as NF-κB, AP-1 and STAT3 (43). In addition, pathologically accumulated hydrophobic BAs cause cell membrane perturbations and trigger the release of large amounts of pro-inflammatory mediators (43). Tumor cells harness these pro-inflammatory signaling pathways to facilitate malignant behaviors. Inflammation in the TME triggers trafficking of immune cells, which are reeducated to acquire immunosuppressive properties with the help of Bas (18). Additionally, BA exerts modulatory effects on metabolism of CRC cells and macrophages by interacting with BA receptors (177). Given the key role of metabolism in antitumor immunity, the mechanisms by which BAs serve as metabolic mediators facilitating liver metastasis warrant further exploration.

BA metabolism disorders, such as cholestasis, are one of the most common complications in patients with liver metastasis (178). Accumulated BAs contribute to the hepatic colonization of tumor cells. Secondary BAs in feces play an anti-inflammatory role in colitis-associated CRC (179), whereas secondary BAs in serum can be transported into the liver and induce an immunosuppressive pre-metastatic niche (86). Therapeutic agents that can reduce the reabsorption of secondary BA in the colon may hold promise for treatment of CRC. Therefore, the prognostic value of fecal and serum BA levels needs to be clarified in patients with colorectal liver metastases.

Clinicians should consider BAs when managing patients with advanced-stage CRC. As aforementioned, elevated serum levels of total BAs are associated with lower OS and RFS and an increased incidence of distant metastasis (40). High levels of BAs, particularly secondary BAs, may impair antitumor immunity and compromise efficacy of immunotherapy (86). Therefore, in patients with elevated serum BAs, use of BA synthesis inhibitors such as OCA and BA secretion promoters such as UDCA may improve OS and enhance immunotherapeutic outcomes (87,89). Furthermore, expression of BA receptors in CRC tissue has prognostic implications. Given the tumor-suppressive role of FXR (159,161,180) and tumor-promoting role of TGR5 (166), immunohistochemical analysis of these receptors may provide value for CRC prognosis.

In conclusion, the present review summarizes the role of BAs in promotion of liver metastasis, as well as promising therapeutic agents. Future research should focus on the regulatory mechanisms of BA synthesis and metabolism to develop more approaches to rebalance BA homeostasis and inhibit colorectal liver metastasis.

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Authors' contributions

LS conceived the study and edited the manuscript. ZL performed the literature review and wrote the manuscript. LD, MC and XY performed the literature review. NY and ZF revised the manuscript. Data authentication is not applicable. All authors have read and approved the final 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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