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REVIEW

Role of bile acids in colon carcinogenesis

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Abstract

Bile acids (BAs) are cholesterol derivatives synthesized in the liver and then secreted into the intestine for lipid absorption. There are numerous scientific reports describing BAs, especially secondary BAs, as strong carcinogens or promoters of colon cancers. Firstly, BAs act as strong stimulators of colorectal cancer (CRC) initiation by damaging colonic epithelial cells, and inducing reactive oxygen species production, genomic destabilization, apoptosis resistance, and cancer stem cells-like formation. Consequently, BAs promote CRC progression *via* multiple mechanisms, including inhibiting apoptosis, enhancing cancer cell proliferation, invasion, and angiogenesis. There are diverse signals involved in the carcinogenesis mechanism of BAs, with a major role of epidermal growth factor receptor, and its down-stream signaling, involving mitogen-activated protein kinase, phosphoinositide 3-kinase/Akt, and nuclear factor kappa-light-chain-enhancer of activated B cells. BAs regulate numerous genes including the human leukocyte antigen class I gene, p53, matrix metalloprotease, urokinase plasminogen activator receptor, Cyclin D1, cyclooxygenase-2, interleukin-8, and miRNAs of CRC cells, leading to CRC promotion. These evidence suggests that targeting BAs is an efficacious strategies for CRC prevention and treatment.

Key words: Apoptosis resistance; Cancer stemness; Bile acids; Colorectal cancer; Reactive oxygen species; Angiogenesis

Core tip: Even though there is a close relationship between a high concentration of bile acids (BAs) and high risk of colorectal cancer (CRC), the mechanism of BAs promoting colon carcinogenesis is still not fully understood. In this review paper, we discuss molecular mechanisms of BAs as CRC promoters, their role in CRC progression, the oncogenic genes and signaling

pathways involved, and important therapies against BA-related CRC.

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INTRODUCTION

Bile acids: Biochemistry and physiology

Bile acids (BAs) are amphipathic molecules synthesized from cholesterols in the liver, stored in the gallbladder, and released into the intestinal lumen after food ingestion. Their major functions are facilitating intestinal digestion and absorption of dietary fat, steroids, drugs, and lipophilic vitamins. In addition, through their nuclear receptors, including farnesoid X receptor (FXR), pregnane X receptor, vitamin D3 receptor (VDR), and constitutive androstane receptor, BAs also act as signaling molecules regulating their own synthesis, transport, homeostasis, and other metabolic processes such as energy-related metabolism and glucose handling[1,2].

BAs have a steroid nucleus formed by three 6-carbon rings and one 5-carbon ring[1]. They are mainly synthesized by two biosynthetic pathways: Classical and alternative pathways. Classical pathway, also called neutral pathways, occurs in the liver and is responsible for the majority of BA synthesis. This pathway is initiated by cholesterol 7-alpha-hydroxylase enzyme (encoded by CYP7A1) and results in the formation of the primary BAs, cholic acid (CA) and chenodeoxycholic acid (CDCA). Key enzymes required for the formation of CA and CDCA are sterol 12-alpha-hydroxylase (CYP8B1) and sterol-27-hydroxylase (CYP27A1), respectively. An alternative pathway for BA synthesis occurs in other tissues besides the liver. This pathway is initiated by CYP27A1 and also involves CYP7B1. After several metabolic steps, CDCA is formed. Recently, another BA synthesis pathway was discovered, called the neuronal pathway, and it is believed to be important for neuronal cholesterol clearance. This pathway requires cholesterol 24-hydroxylase (CYP46A1) and 24-hydroxycholesterol 7-alpha-hydroxylase (CYP39A1), which play major roles, and its final product is also CDCA[3]. In this review, we focus on BAs synthesized in hepatocytes *via* the classical pathway.

After their synthesis in hepatocytes, primary BAs (CA and CDCA) are conjugated with glycine or taurine, and are excreted in the bile *via* the canalicular bile-salt export pump and stored in the gallbladder[4]. After a meal, cholecystokinin secreted from the duodenum stimulates gallbladder contraction and the release of bile salts into the intestinal tract. In the small intestinal tract, micellar BAs act as effective detergents facilitating the solubilizing of fatty acids and monoacylglycerols, digestion, and absorption of dietary lipids and fat-soluble vitamins. Then, BAs are efficiently reabsorbed in the ileum and transported back to the liver *via* the hepatic portal vein, where they are cleared, re-secreted in the bile, and ready for new circulation. This is called enterohepatic circulation[5] (Figure 1). BAs are extensively reclaimed by the terminal ileum *via* the apical Na^+-dependent bile-salt transporter (ASBT) and effluxed by OST-α/β, MRP3, and a truncated form of ASBT (t-ASBT). In the ileocytes, the ileal bile-acid-binding protein (FABP6) promotes BA flux and protects ileocytes against the deleterious effect of BAs[6].

In addition to enterohepatic circulation, about 10% of the total BA pool that has not been cleared by the hepatic system reaches the systemic circulation to the kidney, where it is filtrated by the renal glomeruli and reabsorbed by epithelial cells of the proximal convoluted tubules of the kidney. This BA then returns to the liver *via* systemic circulation and is ready for subsequent circulation (Figure 1). In healthy individuals, BAs are virtually absent in the urine, but they become easily detectable upon cholestasis. This is due to the decreased renal absorption of systemic BAs in order to promote the urinary excretion of toxic BAs accumulating in the liver[6] .

A small amount of BA, which escapes from ileum re-absorption, flows to the large intestines, where some of it is de-conjugated by bacterial bile salt hydrolases to become free BA. Consequently, bacterial 7α-dehydroxylase removes a hydroxyl group from C-7 and converts CA to deoxycholic acid (DCA) and CDCA to lithocholic acid (LCA). These are called secondary BAs[5]. They are then reabsorbed into colonocytes *via* both passive absorption as well as active transporters similar to ileocytes to return to the liver for detoxification and then recycling[5,6]. Only a small amount of these BAs (about 5%-10%) are lost *via* feces (Figure 1). This is compensated by the amount of BA newly synthesized by the liver to maintain a constant BA pool size under physiological conditions[5].

For detoxification, secondary BAs, especially LCA, are sulfated and N-acylamidated in the liver and then secreted into bile. A small amount of LCA (approximately 1%) circulated to the liver is sulfated and efficiently secreted into circulation for renal excretion. In the intestine, cytochrome P450 3A4 (CYP3A4), cytochrome P450 2B (CYP2B), cytochrome P450 2C (CYP2C), and epimerases are involved in detoxification of LCA to more soluble hydrochloric acid and ursodeoxycholic acid (UDCA)[5].

Bile acid synthesis regulation and changes in bile acid pool size

Regulation of bile acid synthesis is performed mainly by a negative feedback mechanism exerted by them own FXR receptor and CYP7A1 enzyme. In this mechanism, FXR, once activated, elicits transcriptional up-regulation of hepatic small heterodimer partner (SHP) protein

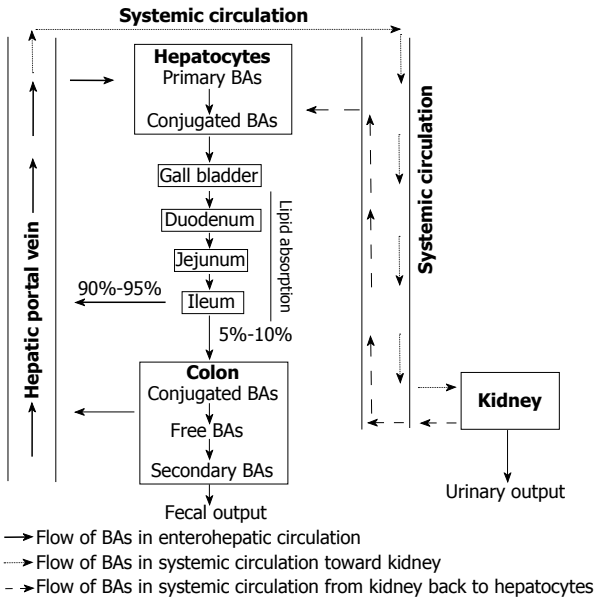

Figure 1 Bile acid circulation. Primary bile acids (BAs) are mainly synthesized in liver from cholesterols. After that, they are conjugated with glycine or taurine, excreted in the bile, and stored in the gallbladder. After a meal, conjugated BAs are stimulated to release into the intestinal tract for facilitating the digestion of dietary lipids and fat-soluble vitamins. Then, BAs are efficiently reabsorbed in the ileum and most of them (90%-95%) is transported back to the liver *via* the hepatic portal vein to be cleared, re-secreted in the bile, and ready for new circulation. This is called enterohepatic circulation. In addition to enterohepatic circulation, about 10% of the total BA pool reaches the systemic circulation to the kidney to be filtrated by the renal glomeruli and then return to the liver for subsequent circulation. A small amount of BAs (5%-10%), which escapes from ileum re-absorption, flows to the large intestines, where some of it is de-conjugated by bacterial bile salt hydrolases to become free BA and converted to secondary BAs. They are then reabsorbed into colonocytes to return to the liver for detoxification and then re-cycling. Only a small amount of these BAs (about 5%-10%) are lost *via* feces. BAs: Bile acids.

and ileal fibroblast growth factor 19 (FGF-19). SHP and FGF-19 in turn negatively regulate the expression of CYP7A1, thus resulting in repression of BA synthesis[1,2]. Otherwise, BAs act as signaling molecules to induce protein kinase C (PKC), or inflammatory cytokines, such as tumor necrosis factor (TNF)-α and Interleukin (IL)-1β, that stimulate JNK signaling for final CYP7A1 down-regulation[7].

In addition to BAs, hormones and exogenous compounds may also affect BA synthesis, such as insulin[8], thyroid hormones[9], or some drugs like phenobarbital[10] and rifampicin[11,12]. All of them also target CYP7A1 to affect BA synthesis. Additionally, BA synthesis is also regulated by CYP7A1 diurnal variation that leads to a change in CYP7A1 enzymatic activity within a day. It was revealed that there are two peaks in CYP7A1 activity, the first at midday and the second around 10:00 p.m.[13,14].

Because BAs are cholesterol derivatives, their synthesis is stimulated by high fat diets. Population-based studies have shown that subjects who consume high-fat and high-beef foods display elevated levels of fecal secondary BAs, mostly DCA and LCA, as do patients diagnosed with colonic carcinomas[15-20]. Conversely, diets rich in vegetables and fruits are linked to a decreased BA concentration because dietary fibers (from vegetables and fruits) can bind to LCA and aid in its excretion[21,22]. Otherwise, vitamin D and high dietary calcium supplementation have been proven to alter BA composition and inhibit colon carcinogenesis induced by either high-fat diets or intrarectal instillation of LCA[23]. Vitamin D activates the VDR receptor, which may activate a feed-forward catabolic pathway that leads to the detoxification of LCA[24-26]. High dietary calcium leads to the formation of insoluble calcium soaps, and this in turn decreases the concentration of free BAs in the intestinal lumen, which ultimately may protect against the formation of colon cancer[27].

MOLECULAR MECHANISM OF BILE ACIDS IN COLON CARCINOGENESIS

Bile acids initiate colon cancer

BAs are cholesterol derivatives with detergent properties, so when present at high concentrations, they could cause cell membrane damage resulting in focal destruction of intestinal epithelium[28]. This damage subsequently stimulates repair mechanisms involving inflammatory reactions and hyperproliferation of undifferentiated cells[29]. These processes could cause a cell transition into a precancerous state and are considered as an early priming step in colorectal tumorigenesis (Figure 2).

BAs are well-known as strong stimulators of reactive oxygen species (ROS) and reactive nitrogen species (RNS) production, causing oxidative stress that damages DNA, disrupting the base excision repair pathway[30]. Otherwise, BAs have also been demonstrated to cause colon cell genomic instability and mutation *via* multiple mechanisms, including mitosis disruption (aneuploidy, micronuclei formation), defects in spindle assembly checkpoints, cell cycle arrest at G1 and/or G2, and improper alignment of chromosomes at the metaphase plate and multipolar division[31] (Figure 2).

Additionally, after chronic exposure to BAs at physiological concentration, colon epithelial cells become resistant to apoptosis[32]. This is because BAs induce the degradation of tumor suppressor p53, which monitors cell processing of DNA repair and initiates apoptosis if DNA damage proves to be irreparable[33]. Additionally, BAs up-regulate X-linked inhibitor of apoptosis protein, that in turn inhibits caspase-3 activation, protecting cells against apoptosis[34]. Thus, because of its role in promoting genomic instability coupled with apoptosis resistance, BAs drive colon cells to a dangerous state that can lead to further mutation and ultimately cancer (Figure 2).

BAs are also reported to induce colonic epithelial cells into becoming cancer stem cells (CSCs)[35] that are able to self-renew and are capable of initiating carcinogenesis and sustaining tumor growth. It has been revealed that BAs, specifically DCA and LCA, induce cancer stemness, evidenced by an increased proportion of CSCs, elevated levels of CSC markers,

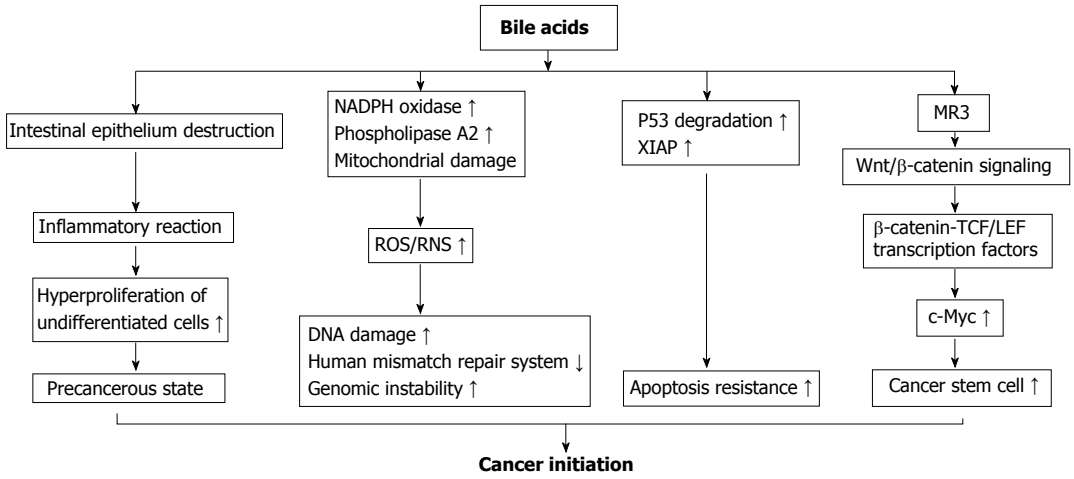

Figure 2 Mechanisms of bile acids initiating colorectal cancer development. (1) High concentrations of bile acids (BAs) could cause a focal destruction of intestinal epithelium, subsequently stimulate repair mechanisms involving inflammatory reactions and hyper-proliferation of undifferentiated cells. These processes could cause a cell transition into a precancerous state and are considered as an early priming step in colorectal tumorigenesis; (2) BAs strongly induce reactive oxygenic species and reactive nitrogen species production *via* its stimulatory effect on nicotinamide adenine dinucleotide phosphate oxidase and phospholipase A2, and mitochondrial damage. These reactive species cause damage on DNA, and disrupt the base excision repair pathways; (3) After chronic exposure to BAs at physiological concentration, colon epithelial cells become resistant to apoptosis. This is because BAs induce the degradation of tumor suppressor p53, and up-regulate the expression of X-linked inhibitor of apoptosis protein protein. The cells with genomic errors coupled with apoptosis resistance ability rapidly get much further mutation and ultimately become cancer cells; (4) BAs induce colonic epithelial cells becoming CSCs through muscarinic cholinergic receptor receptor and Wnt/β-catenin signaling. This pathway leads to nuclear translocation of β-catenin to form a complex with T cell factor/lymphoid enhancer factor family transcription factors that acts as a co-activator to express c-Myc, a gene regulating cell stemness. NADPH oxidase: Nicotinamide adenine dinucleotide phosphate oxidase; MR3: Muscarinic cholinergic receptor 3; ROS: Reactive oxygenic species; RNS: Reactive nitrogen species; XIAP: X-linked inhibitor of apoptosis protein; TCF/LEF: T cell factor/lymphoid enhancer factor.

epithelial mesenchymal transition markers, and increased colonosphere formation. These are mediated through muscarinic receptor 3 (MR3) and Wnt/β-catenin signaling[35] (Figure 2).

Bile acids promote colon cancer progression

BAs, especially DCA and LCA, are well-known as toxic BAs to colonic cells. They induce cell death through two basic pathways involving either death receptors or mitochondrial[36]. BAs induce apoptosis is a result of ROS generation, cytochrome C release, and activation of cytosolic caspase[37]. However, a biphasic effect of cytoprotection and induction of apoptosis by BAs was reported depending on BA concentration[38]. It was proven that at high concentrations, BAs strongly induce cell death, but in normal physiological conditions, epithelial cells are exposed to BAs at a low concentration. As discussed above, BAs at physiological concentration make cells become apoptosis-resistant. This process is mediated by epidermal growth factor receptor (EGFR)/phosphoinositide 3-kinase (PI3K)/Akt/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling[39,40]. These findings indicate how BAs increase resistance of colorectal cancer (CRC) to chemotherapy and radiation.

Proliferation plays a central role in cancer development and progression. BAs have been proven to stimulate the proliferation of CRC cells, H508 that abundant expressed both MR3 and EGFR. But they did not stimulate proliferation of SNU-C4 CRC cells that express EGFR but not muscarinic receptor, indicating BA-induced CRC cell proliferation is MR3-dependent and is mediated by transactivation of EGFR[41]. However, a study by Cao *et al*[42] on $Apc^{min/+}$ mice model proved that DCA stimulates tumor cell proliferation *via* Wnt signaling activation, thus enhancing the multiplicity of intestinal tumor and accelerating intestinal adenoma-adenocarcinoma sequence. Another study performed a long-term diet study in mice also showed that western-style diets, that is high in fat and scarce in fiber and vitamin D, caused an increased luminal BA, thus increasing colon tumor numbers, and activating cell proliferation[43].

BAs are proven to stimulate CRC cell invasiveness. A study by Pai *et al*[44] revealed that DCA significantly stimulates β-catenin signaling, and in turn induces urokinase plasminogen activator receptor (uPAR) expression and finally stimulates cell invasiveness. However, our study demonstrated that LCA induces uPAR expression *via* the Erk-1/2 and AP-1 pathway and in turn, stimulates invasiveness of human CRC cells[45]. Otherwise, Debruyne *et al*[46] demonstrated that LCA stimulates CRC cell invasion through haptotaxis stimulation, which is dependent on multiple oncogenic signaling pathways including the RhoA/Rho-kinase pathway, protein kinase C signaling cascades, mitogen-activated protein kinase (MAPK), and cyclooxygenase-2 (Cox-2). Activation of Rac1, RhoA GTPase, and FXR also involves this mechanism of BAs.

For tumor growth and metastasis, growth of the vascular network is important. The process whereby new blood vessels are formed is called angiogenesis. This process has an essential role in the formation of a new vascular network to supply nutrients and oxygen, and also remove waste products. More than a dozen different proteins have been identified as angiogenic

activators, including vascular endothelial growth factor, basic fibroblast growth factor, angiogenin, transforming growth factor (TGF)-α, TGF-β, TNF-α, platelet-derived endothelial growth factor, granulocyte colony-stimulating factor, placental growth factor, IL-8, hepatocyte growth factor, and epidermal growth factor[47]. BAs such as DCA, taurodeoxycholic acid, or LCA were proven to stimulate expression of IL-8 cytokine[48]. Our study proved that IL-8 secreted by LCA-stimulated CRC cells, HCT116, could stimulate tube-like formation of endothelial cells. Our findings proved that BAs promote colon tumor progression *via* enhancing angiogenesis activity[49].

Bile acids stimulate ROS production

BAs have been demonstrated to enhance the generation of ROS in different cell lines including CRC cells. This effect is well-known to be the consequence of the activation of plasma membrane enzymes, NAD(P)H oxidases, and phospholipase A2[37] (Figure 2). Otherwise, BAs are proven to strongly stimulate ROS generation in mitochondria (Figure 2) through multiple mechanisms with the involvement of Na^+/K^+-, ATPase, cytochrome P450 monooxygenases, and Ca^{2+} influx modulation[30]. If ROS are produced in excessive and uncontrollable amounts, they may damage various cellular macromolecules such as lipids, proteins, and DNA. Damaged products can result in either cell cycle arrest or induction of transcription, induction of signal transduction pathways, replication errors, or genomic instability, all of which are associated with colon carcinogenesis[50]. Moreover, ROS also regulate key cellular functions such as proliferation, differentiation, growth, and apoptosis through cellular signaling. The most well-known pathways are NF-κB, PI3K/Akt, MAPK, and heat shock proteins[51,52]. Payne proved that DCA induces oxidative stress and activates NF-κB signaling (Figure 3), which is associated with the development of apoptosis resistance and contributes to genomic instability and the initiation of cancer[53]. In addition to cancer initiation, ROS generation is proven to play an important role in all phases of carcinogenesis including initiation, promotion, and progression[54].

Signals involved in bile acid-induced colorectal cancer

The EGFR pathway, central to proliferative signaling by many CRC-causing factors[55], was also demonstrated to be the central signaling for BA action associated with CRC progression. Over-activation of this pathway in tumor cells is associated with tumor cell proliferation, survival, angiogenesis, invasion, and metastasis. This signaling expression itself may be a prognostic factor for many epithelial tumors including CRC[56]. PI3K and MAPK are two dominant downstream signaling cascades of EGFR activation (Figure 3).

Our study indicated that LCA stimulates all of three MAPK pathways including p38, JNK, and Erk1/2[45,49]. MAPK activation was demonstrated to be involved in the regulation of expression of many oncogenic genes such as mucinex 2 (MUC2)[57], uPAR[45], and IL-8[49], and is implicated in CRC progression *via* enhancing cancer cell invasion and angiogenesis activity. Interestingly, we revealed that Erk1/2 signaling stimulated by LCA results in the inhibition of STAT3 signaling for final IL-8 expression up-regulation in CRC cell lines[49] (Figure 3). STAT3 signaling is still described as an oncogenic signaling that promotes tumorigenesis and metastasis. However, recently, several studies found that STAT3 signaling has anti-tumor effects in CRC[58,59]. Our findings provide additional proof supporting the contradictory role of STAT3 in CRC development by the negative regulation of IL-8 cytokine production in CRC cells.

In a study by Parsons *et al*[60], phosphoinositide-3'-kinase (PI3K)/Akt signaling regulating apoptosis and cell proliferation was determined to be mutated in 40% of CRC cases. This signaling was also related to post-signaling of EGFR. PI3K/Akt was proven to be activated by conjugated BA and deoxycholyltaurine and mediated for CRC cell survival and proliferation. Moreover, conjugated BAs also inhibit programmed cell death by multiple PI3K/Akt-mediated mechanisms including phosphorylation of glycogen synthase kinase 3, and NF-κB activation[40]. PI3K/Akt was also reported to activate transcription factor NF-κB (Figure 3) and then induced MUC2 expression, whose abnormal synthesis and secretion is related to diverse biological properties of CRC cells including cell-cell interactions, cell-substratum interactions, differentiation, proliferation, invasion, and metastasis[53,57].

NF-κB is a redox-associated transcription factor that is involved in the activation of survival pathways. NF-κB protects cells against apoptosis and is constitutively elevated in many different types of cancers. NF-κB enhances tumor progression, in part through the activation of inducible nitric oxide synthase and Cox-2 and the release of proliferative and anti-apoptotic cytokines. BA-induced NF-κB is reported in CRC cell lines *via* Akt activation[40,57] or mitochondrial oxidative stress[53] (Figure 3). The activation of these transcription factors increases resistance of CRC to stress-induced apoptosis as well as chemotherapy and radiation.

Cox-2/Prostaglandin E2 (PGE_2) is one of the signaling events that potentially influences the development of CRC. Levels of Cox-2 are elevated in a majority of colorectal carcinomas, and aberrant expression of Cox-2 leads to an increase in PGE_2. Cox-2/PGE_2 signaling through the EP_4 receptor activates the Ras/MAPK/ERK pathway, which through the CREB transcription factor increases the expression of the pro-survival B-cell lymphoma 2 (Bcl-2) protein. Bcl-2 suppresses p53-induced apoptosis thereby promoting tumorigenesis. Additionally, PGE_2 signaling through both EP_2 and EP_4 receptors coupled to $G\alpha_s$ is known to stimulate cAMP production, which can stimulate tumor growth by suppressing apoptosis. BAs increase the synthesis of PGE_2 *via* Cox-2 enzyme induction[61] and signaling

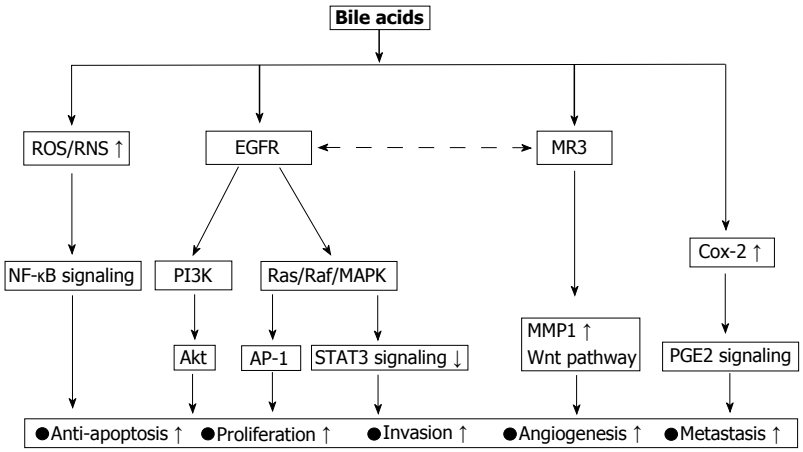

Figure 3 Oncogenic signaling network activated by bile acids. The epidermal growth factor receptor (EGFR) pathway is central signaling for bile acid (BA) action associated with colorectal cancer (CRC) progression. Over-activation of this pathway in tumor cells is associated with tumor cell proliferation, survival, angiogenesis, invasion, and metastasis. PI3K and Ras/Raf/MAPK are two dominant downstream signaling cascades of EGFR activation. Muscarinic cholinergic receptor 3 (MR3) is another actor that mainly contribute to CRC initiation and progression mediated by BAs. This action of CR3 requires cross-talk with EGFR transactivation. MR3 activation stimulates MMP1 expression, which promotes CRC invasion and mediates for BA-induced CSCs in the colonic epithelial population *via* Wnt pathway. NF-κB is also one of major signaling activated by BAs. This signaling is activated by oxidative stress and as downstream of PI3K signaling. It protects cells against apoptosis and enhances cell proliferation. Cox-2/PGE2 is one of the signaling events of BAs action, BAs increase the synthesis of PGE2 *via* Cox-2 enzyme induction. This signaling increases the expression of Bcl-2, that then suppresses p53-induced apoptosis thereby promoting tumorigenesis. Additionally, PGE2 signaling is known to stimulate cAMP production, which can stimulate tumor growth by suppressing apoptosis. ROS: Reactive oxygen species; RNS: Reactive nitrogen species, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K: Phosphatidylinositol-4,5-bisphosphate 3-kinase; EGFR: Epidermal growth factor receptor; MAPK: Mitogen activated protein kinase; AP-1: Activator protein 1; STAT3: Signal transducer and activator of transcription 3; Cox-2: Cyclooxygenase 2; PGE2: Prostaglandin E2; MR3: Muscarinic cholinergic receptor 3.

mediated by calcium concentration and protein kinase C[62] (Figure 3).

Muscarinic receptor (MR), specifically MR3, was documented to be activated by BAs that mainly contribute to CRC cell proliferation promotion[41,63,64]. As discussed above, this action of BAs requires cross-talk between CR3 and EGFR transactivation, and post-signaling Erk1/2[41]. MRs activation also stimulates matrix metalloprotease (MMP) 1 expression, which promotes CRC invasion[65] (Figure 3). Otherwise, MR3 is mediated for BA-induced CSCs in the colonic epithelial population *via* Wnt/β-catenin signaling that leads to increased levels of c-Myc, a gene regulating cell stemness[35] (Figure 2).

Genes involved in the colon carcinogenesis mechanism of bile acids

LCA and DCA decreased the expression of human leukocyte antigen (HLA) class Ⅰ antigens on the surface of colon cancer cells but not in liver cells. Loss of HLA antigen expression helps tumor cells to escapes immune surveillance. Therefore, this is considered to be one of the mechanisms whereby BAs promote tumor development[66] (Figure 4).

DCA was proven to suppress accumulation of p53 protein as well as p53 transactivation and impaired the p53 response of the cells to DNA damaging agents. The p53 level was documented to be suppressed by DCA in human colon tumor cell line HCT116. This inhibition was mediated by stimulating the process of proteasome-mediated degradation of p53 and in part by ERK signaling[33].

Invasion is the initiation stage of cancer metastasis, and it is the most serious state in cancer development, resulting in the death of most patients with cancer. MMPs are important components of cell invasion capable of degrading a range of extracellular matrix proteins, allowing cancer cells to migrate and invade. The secretion of MMPs is linked to increased cellular invasion and in tumors, increased capacity for metastasis. BAs were proven to induce the production of MMPs including MMP1 and MMP2 proteins that in turn enhance invasiveness of CRC cells[65,67]. Otherwise, in normal human colonic epithelial cells, DCA and LCA were revealed to induce a marked rise in MMP1, MMP3, and MMP10 mRNA expression[35]. Along with MMP proteins, uPAR and its antagonist, uPA, also play a major role in cell invasiveness regulation. Particularly, uPA interacts with specific membrane receptor uPAR and converts the proenzyme plasminogen to plasmin, which is capable of degrading extracellular matrix directly or indirectly through the activation of MMPs. It was demonstrated that secondary BAs up-regulated the expression of uPAR and then enhanced the invasiveness of human colon cancer[44,45]. Moreover, BA-induced uPAR was also mediated for BA-enhanced cell proliferation. This means that uPAR not only modulates cell invasiveness but also cell proliferation (Figure 4).

Cyclin D1, which regulates cells to the proliferative stage of the cell cycle, plays a key role in tumorigenesis. A study by Pai *et al*[44] showed that DCA stimulates the expression of cyclin D1 *via* the β-catenin pathway and promotes CRC growth. In addition, Cheng *et al*[64] discovered that conjugated BAs (deoxycholyltaurine) induced the expression of MMP-7 that is mediated for EGFR transactivation and finally enhanced CRC proliferation (Figure 4).

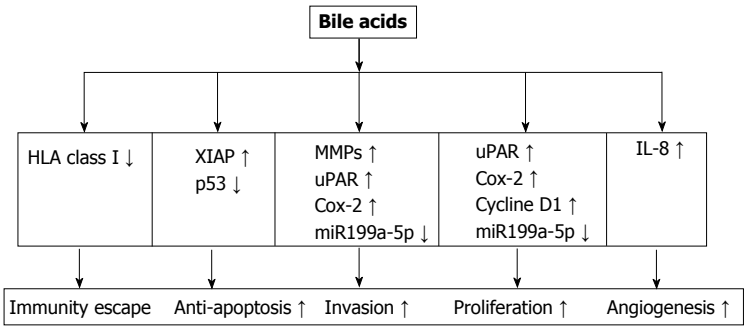

Figure 4 Bile acids regulate gene expression towards tumor development. Bile acids (BAs) decrease the expression of human leukocyte antigen class Ⅰ antigens on the surface of colorectal cancer cells, helping cancer cells escape from immune surveillance. They enhance the apoptosis resistance ability of cancer cells *via* up-regulating XIAP expression, and degrading p53 protein. BAs stimulates cancer proliferation and invasion *via* their effect on a series of oncogenes including MMPs, uPAR, Cox-2, Cycline D1, and miR199a-5p. By inducing IL-8 expression, BAs enhance angiogenesis activity for tumor growth and metastasis. HLA: Human leukocyte antigen; MMP: Matrix metalloproteinase; UPAR: Urokinase receptor; Cox: Cyclooxygenase; IL-8: Interleukin-8; VEGF: Vascular endothelial growth factor, XIAP: X-linked inhibitor of apoptosis protein.

Cox-2 is a rate-limiting enzyme for the generation of prostaglandins, small lipid messengers participating in pain, inflammation, and colorectal carcinogenesis. It was proven to be a major regulator implicating CRC. However, how Cox-2 signaling affects colonic carcinogenesis at the cellular level is still not clear. Substantial studies demonstrated that Cox-2 expression is up-regulated *via* PKC signaling by both primary and secondary BAs[68-71]. This induction promotes CRC progression through enhancing the proliferation and invasiveness of CRC cells[70].

IL-8 is an inflammatory cytokine that exerts potent angiogenic stimuli on endothelial cells through interaction with its cognate receptors, CXCR1 and CXCR2. It was proven to be up-regulated by secondary BAs and in turn stimulate CRC cell angiogenesis[49]. Otherwise, this cytokine induction is also mediated by MMP-2 expression and increased invasion of CRC cells[48,72].

Bile acids regulate microRNAs

MicroRNAs (miRNA) are small noncoding, single-stranded RNAs that bind to the 3-UTR region of protein-coding mRNAs, leading to mRNA cleavage or translational repression of their respective targets. Single miRNAs can target multiple genes, thereby regulating several signaling molecules or pathways. Thus, aberrant expression of miRNAs maintains the disease state through the regulation of multiple genes.

Recently, miRNA is getting increased attention because of its involvement in cancer progression. It is known to be involved in the initiation, development, and progression of cancers. They are indicated as useful biomarkers for cancer diagnosis and prognosis as well as therapeutic tools.

An increasing amount of evidence links miRNA deregulation to carcinogenesis in several human tumors including CRC. In a recent study, Wang *et al*[73] proved a different profile of miRNA expression in colon adenocarcinoma compared with normal adjacent tissue. They observed global miRNA up-regulation in tumors in which eight miRNAs (hasmir-141, -19a, -20a 19b-1, 19b-2, 16, 590, and -335) were closely associated with the carcinogenesis of colon adenocarcinoma.

Even though there are no studies in CRC cells, studies in liver and pancreatic cells revealed that the miRNA expression profile was significantly modified under the effect of BAs[74,75]. Particularly, UDCA[76] and taurolithocholic acid[75] were proven to stimulate oncogenic miRNA miR21 in liver and pancreatic cells.

DCA was demonstrated to inhibit miR-199a-5p, a tumor suppressor in CRCs, and in turn target tumor-promoting protein CAC1 and cell cycle-regulating protein CDK2. Inhibition of miR-199a-5p leads to the induction of tumor cell growth, migration, and invasion as well as tumor formation in the mouse model[77] (Figure 4).

BILE ACIDS AS THERAPEUTIC TARGETS FOR COLORECTAL CANCER

BAs have been clearly proven to be implicated in CRC initiation and progression. So, targeting BAs is a promising therapeutic method for CRC prevention and treatment (Table 1).

FXR is well-known as a major player regulating BA synthesis *via* SHP and FGF19 up-regulation that in turn inhibits major BA synthesizing enzyme, CYP7A1. So, FXR is considered an intestinal tumor suppressor. A series of studies on the mice model, xenograft model, and human showed that diminished FXR expression is associated with increased risk of CRC as well as advanced CRC stage[78-80]. So, FXR signaling is a potential target for blocking the BA effect on CRC promotion. GW4064, an FXR agonist, was proven to attenuate CRC cell proliferation by down-regulating EGFR (Tyr845) phosphorylation and ERK activation[81]. Desnoyers *et al*[82] developed an anti-FGF-19 monoclonal antibody that selectively blocks the interaction of FGF-19 with FGFR4. This antibody could abolish FGF-19-mediated activity *in vitro* and inhibit growth of colon tumor xenografts *in vivo*.

UDCA is converted from the primary BA, CDCA, along with LCA. However, contrary to the toxic of hydrophobic BAs, UDCA is a hydrophilic BA and exhibits a chemopreventive effect against CRC[83-85]. This BA

Table 1 Therapeutic agents developed against colorectal cancer targeting bile acids

Therapeutic agents	Type	Mechanism	Development phase	References
UDCA	Hydrophilic BA	Secondary BAs reduction	Clinical	[96-99]
Diosgenin	Phytochemical	BAs re-absorption prevention	Preclinical	[104-106]
Cetuximab	EGFR antibody	EGFR signaling blocking	Clinical	[101]
Panitumumab	EGFR antibody	EGFR signaling blocking	Clinical	[102]
GW4064	FXR agonist	BAs synthesis inhibition	Preclinical	[81]
Anti-FGF-19	Monoclonal Ab	BAs synthesis inhibition	Preclinical	[82]
HS-1030	UDCA derivatives		Preclinical	[100]
HS-1183	UDCA derivatives		Preclinical	[100]
HS-1199	CDCA derivatives		Preclinical	[100]
HS-1200	CDCA derivatives		Preclinical	[100]
LCA-TMA$_1$	LCA derivatives	Apoptosis induction	Preclinical	[107]
LCA-PIP1	LCA derivatives	Apoptosis induction	Preclinical	[108]

UDCA: Ursodeoxycholic acid; LCA: Lithocholic acid; EGFR: Epidermal growth factor receptor; BA: Bile acid; FGF-19: Fibroblast growth factor 19; TMA: Trimethylammonium; PIP: Piperidine.

is able to inhibit BA synthesis in liver[86], alter the composition of colonic BAs, and reduce the concentration of the toxic secondary BAs in blood[87,88] and stool[89]. It protects against CRC *via* multiple mechanisms including CRC stem-like cell formation inhibition, CRC cell proliferation inhibition[90], reduction of colorectal mucosal proliferation[91], increased MHC antigen for tumor surveillance enhancement[92], Cox-2 expression inhibition[93], and inhibiting oncogenic signaling stimulated by toxic BAs[94,95]. In humans, many clinical studies were conducted to check UDCA efficacy in CRC prevention and treatment. The results showed that UDCA application reduces CRC risk in patients with primary sclerosing cholangitis and ulcerative colitis[96], patients with chronic liver diseases[97], and patients with primary biliary cirrhosis[98] and reduces the CRC recurrence in patients after colorectal tumor removal[99].

Based on UDCA properties, other synthetic derivatives of UDCA were synthesized to enhance the UDCA effect in CRC prevention and treatment. Otherwise, derivatives of primary BAs also were synthesized for the purpose of seeking a potential CRC treatment method. Park *et al*[100] synthesized two UDCA derivatives, HS-1030 and HS-1183, and two CDCA derivatives, HS-1199 and HS-1200. These synthetic compounds were proven to inhibit cell proliferation and induce apoptosis in CRC cells.

EGFR is a major receptor mediating BA toxicity and promoting CRC development (Figure 4). So, blocking EGFR signaling is an efficacious strategy to block carcinogenic properties of BAs on colorectal cells. Cetuximab and panitumumab, both monoclonal antibodies against EGFR, are currently in clinical trials for CRC treatment therapy[101,102].

Diosgenin, a natural steroid saponin, is a precursor of various synthetic steroidal drugs that are extensively used in the pharmaceutical industry. This phytochemical demonstrates a beneficial role against metabolic diseases, inflammation, and cancer. This compound is proven to bind to BAs and thereby limit bile salt re-absorption in the gut, consequently protecting colonic epithelial cells from BA toxicity[103]. Several studies revealed that diosgenin could induce apoptosis in CRC cell lines, HCT116 and HT29[104,105]. In a mice model, diosgenin uptake also inhibited aberrant crypt foci formation induced by azoxymethane[106].

As discussed above, in addition to having carcinogenic properties, BAs at high concentrations are strong apoptosis stimulators. Therefore, a strategy that introduces cationic charge to BAs to evaluate their apoptotic activity is being performed to develop new CRC drugs. Singh *et al*[107] conjugated trimethylammonium to the hydroxyl group of LCA, CDCA, DCA, and CA and revealed a synthetic compound, LCA-TMA$_1$, with high apoptosis induction efficacy in CRC cells. In another study, this group successfully synthesized a compound with a 10-times higher toxicity, LCA-PIP$_1$, by conjugating piperidine with LCA. This compound showed greater activation of apoptosis compared to LCA. A single dose of LCA-PIP$_1$ was enough to reduce the tumor burden by 75% in a tumor xenograft model[108].

CONCLUSION

The evidence reviewed here indicates that BAs play a key role in CRC development. There still exist many points need to be cleared in the carcinogenesis mechanism of BAs in CRC development, but this evidence suggests that controlling BA synthesis and composition, and targeting oncogenic signals stimulated by BAs are efficacious strategies for CRC prevention and treatment. Moreover, synthesizing BA derivatives to evaluate apoptotic activity is also a very promising approach for developing highly efficacious CRC drug treatments.

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