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REVIEW

The role of bile acids in carcinogenesis

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Abstract

Bile acids are soluble derivatives of cholesterol produced in the liver that subsequently undergo bacterial transformation yielding a diverse array of metabolites. The bulk of bile acid synthesis takes place in the liver yielding primary bile acids; however, other tissues have also the capacity to generate bile acids (e.g. ovaries). Hepatic bile acids are then transported to bile and are subsequently released into the intestines. In the large intestine, a fraction of primary bile acids is converted to secondary bile acids by gut bacteria. The majority of the intestinal bile acids undergo reuptake and return to the liver. A small fraction of secondary and primary bile acids remains in the circulation and exert receptor-mediated and pure chemical effects (e.g. acidic bile in oesophageal cancer) on cancer cells. In this review, we assess how changes to bile acid biosynthesis, bile acid flux and local bile acid concentration modulate the behavior of different cancers. Here, we present in-depth the involvement of bile acids in oesophageal, gastric, hepatocellular, pancreatic, colorectal, breast, prostate, ovarian cancer. Previous studies often used bile acids in supraphysiological concentration, sometimes in concentrations 1000 times higher than the highest reported tissue or serum concentrations likely eliciting unspecific effects, a practice that we advocate against in this review. Furthermore, we show that, although bile acids were classically considered as pro-carcinogenic agents (e.g. oesophageal cancer), the dogma that switch, as lower concentrations of bile acids that correspond to their serum or tissue reference concentration possess anticancer activity in a subset of cancers. Differences in the response of cancers to bile acids lie in the differential expression of bile acid receptors between cancers (e.g. FXR vs. TGR5). UDCA, a bile acid that is sold as a generic medication against cholestasis or biliary surge, and its conjugates were identified with almost purely anticancer features suggesting a possibility for drug repurposing. Taken together, bile acids were considered as tumor inducers or tumor promoter molecules; nevertheless, in certain cancers, like breast cancer, bile acids in their reference concentrations may act as tumor suppressors suggesting a Janus-faced nature of bile acids in carcinogenesis.

Keywords Bile acid · Primary bile acid · Secondary bile acid · Bile acid biosynthesis · Bile acid receptors · Bile acid transporters · Microbiome · CA · CDCA · DCA · LCA · UDCA · Carcinogenesis · TGR5 · S1PR2 · Muscarinic receptor CHRM2 · Muscarinic receptor CHRM3 · FXR · PXR · CAR · VDR · LXR · SHP · Oesophageal carcinoma · Gastric cancer · Hepatocellular carcinoma · Pancreatic adenocarcinoma · Colorectal carcinoma · Breast cancer · Prostate cancer · Ovarian cancer · Epithelial–mesenchymal transition · Oxidative stress · Warburg metabolism

Abbreviations

AKT	Serine/threonine kinase 1
AMPK	AMP-activated protein kinase
AP-1	Activator protein-1
APE1	Apurinic/apyrimidinic endodeoxyribonuclease 1
ATG5	Autophagy related 5
BA	Bile acids
Bai	Bile acid inducible operon
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2
BE	Barrett's esophagus

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Beclin-1/BECN1	Coiled-coil myosin-like BCL2-interacting protein
BIRC7/Livin	Baculoviral IAP repeat-containing protein 7
BSEP/ABCB11	ATP-dependent cassette transporter
BSH	Bile salt hydrolases
BRCA1	Breast cancer type 1 susceptibility protein
CA	Cholic acid
cAMP	Cyclic adenosine monophosphate
CAR/NR1H3	Constitutive androstane receptor
CDCA	Chenodeoxycholic acid
CDX1/2	Caudal type homeobox 1/2
C/EBPα	CCAAT/enhancer-binding protein alpha
CHRM2/3	Muscarinic receptor 2/3
c-Myc	Myc-related translation/localization regulatory factor
COX2	Cyclooxygenase-2
CRC	Colorectal carcinoma
CREB	CAMP response element-binding protein
CSC	Cancer stem cells
CYP	Cytochrome P450
CYP7A1	Cholesterol 7α-hydroxylase
CYP7B1	25-Hydroxycholesterol 7α-hydroxylase
CYP8B1	Sterol 12α-hydroxylase
CYP27A1	Sterol 27-hydroxylase
CYP3A4	Cytochrome P450 family 3 subfamily
DC	Deoxycholate
DCA	Deoxycholic acid
Dlc1	Deleted in Liver Cancer 1
DNA-PK	DNA-dependent protein kinase
DR5	Death receptor 5
EAC	Oesophageal adenocarcinoma
EGF	Epidermal growth factor
EGFR	Epithelial growth factor receptor
EMT	Epithelial–mesenchymal transition
EPHA2	EPH Receptor A2
ER	Estrogen receptor
ERK	Extracellular signal-regulated kinase
FAK/PTK2	Focal adhesion kinase
FAS	Fas Cell Surface Death Receptor
FGF19	Fibroblast growth factor 19
FGF15	Fibroblast growth factor 15
FGFR4	Fibroblast growth factor receptor 4
FLK1/KDR	Fetal liver kinase 1/Kinase Insert Domain receptor
FXR/ NR1H4	Farnesoid X receptor
FXREs	FXR response elements
GADD153	Growth arrest- and DNA damage-inducible gene 153
GBC	Gallbladder cancer
GERD	Gastroesophageal reflux disease
GCA	Glycocholic acid
GCDCA	Glycochenodeoxycholic acid
GCDA	Glycochenodeoxycholate acid
GCDC	Glycochenodeoxycholate
GDC	Glycodeoxycholate
GDCA	Glycodeoxycholic acid
GLCA	Glycolithocholic acid
GPBAR1/TGR5	G-protein-coupled bile acid receptor/Takeda-G-protein-receptor-5
GUDCA	Glycoursodeoxycholic acid
HCC	Hepatocellular carcinoma
HDCA	Hyodeoxycholic acid
HER2	Human epidermal growth factor receptor 2
HNF4α	Hepatocyte nuclear factor-4α
HSC	Hepatic stellate cells
I-BABP	Intestinal BA-binding protein
IGFBP2	Insulin-like growth factor binding protein 2
IKKβ/IKBKB	Inhibitor Of Nuclear Factor Kappa B Kinase Subunit Beta
IL1	Interleukin 1
IL6	Interleukin 6
IL8/CXCL8	Interleukin 8
iNOS	Inducible nitric oxide synthase
JAK2	Janus kinase 2
JNK	C-Jun N-terminal kinase
JUN	Jun Proto-Oncogene AP-1 Transcription Factor Subunit
KLF4	Kruppel Like Factor 4
LBD	Ligand-binding domain
LCA	Lithocholic acid
LCT	Lithocholyltaurine
LOD	Limit of detection

LRH-1/NR5A2	Liver receptor homolog-1
LXRα/β/NR1H3-2	Liver X receptor
mAChR	Muscarinic acetylcholine receptor
MAPK/MEK	Mitogen-activated protein kinase
MCA	Muricholic acid
MCL1	Induced myeloid leukemia cell differentiation protein
MDM2	Mouse double minute 2
MDM4	Double Minute 4
MDR1/ ABCB1	Multidrug resistance protein 1
MMP2	Matrix metalloproteinase 2
MMP9	Matrix metalloproteinase 9
MRP2/ABCC2	Multidrug resistance-associated protein 2
MRP3/ABCC3	Multidrug resistance-associated protein 3
MRP4/ABCC4	Multidrug resistance-associated protein 4
MSK1/RPS6KA5	Nuclear mitogen- and stress-activated protein kinase 1
mTOR	Mammalian target of rapamycin
mTORC1	Mammalian target of rapamycin complex 1
MUC2	Mucin 2
MUC4	Mucin 4
MUTYH	MutY DNA Glycosylase
MYC	Myc proto-oncogene protein
NB	Neuroblastoma
NDRG2	N-Myc downstream regulated gene 2
ND	Not detected
NF-κB	Nuclear factor κappa-light-chain-enhancer of activated B cells
NOX5	NADPH Oxidase 5
NR	Nuclear receptor
NRF2/NFE2L2	Nuclear factor erythroid 2-related factor 2
NR4A1/Nur77/TR3/NGFIB	Nuclear receptor subfamily 4 group A member 1
NSCLC	Non-small cell lung cancer
NTCP/SLC10A1	Sodium/taurocholate cotransporting polypeptide
OATP1A2/SLCO1A2	Solute carrier organic anion transporter family member 1A2
OATP1B/SLCO1B	Solute carrier organic anion transporter family
OATP2	Organic anion-transporting polypeptide
OCT4/POU5F1	Octamer-binding transcription factor
OGG1	8-Oxoguanine DNA glycosylase
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1 alpha
PGE2	Prostaglandin E2
PI3K	Phosphatidylinositol 3-kinase
PKA	Protein kinase A
PKC	Protein kinase C
PLA2	Phospholipase A2
Prx2	Peroxiredoxin II
PXR/ NR1H2	Pregnane X receptor
PTEN	Phosphatase and tensin homolog
p38/MAPK14	P38 MAP kinase
Rac1	Rac family small GTPase 1
Raf1	Proto-oncogene, serine/threonine kinase
RhoA	Ras homolog family member A
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RXR	Retinoid X receptor
S1PR2	Sphingosine-1-phosphate receptor 2
SHP/ NR5O2	Small heterodimer partner
SLC10A1/NTCP	Solute carrier family 10
SLC10A2/ASBT	Sodium-dependent bile acid transporter
SLC51A/B or OSTα/β	Solute carrier family members
SRC-1/NC0A1	Steroid receptor coactivator 1
Smac	Second mitochondria-derived activator of caspase
SOCS3	Suppressor of cytokine signaling 3
SphK2	Sphingosine kinase 2
SRC-1/NC0A1	Steroid receptor coactivator 1
SREBF	Sterol regulatory element-binding factor
STAT3	Signal transducer and activator of transcription 3
SULT	Sulfotransferase
TCA	Taurocholic acid
TCDC	Taurochenodeoxycholate
TCDCA	Taurochenodeoxycholic acid

TDC	Taurodeoxycholate
TDCA	Taurodeoxycholic acid
TERT	Telomerase Reverse Transcriptase
TGF-β1	Transforming growth factor β-1
TLC	Taurolithocholate
TLCA	Taurolithocholic acid
TLR4	Toll-Like Receptor 4
TSC1	TSC Complex Subunit 1
TUDCA	Tauroursodeoxycholic acid
UCP2	Uncoupling protein-2
UDCA	Ursodeoxycholic acid
UGT	UDP-glucuronosyl-transferase
UGT2B4	Uridine 5′-diphosphate-glucuronosyltransferase 2B4
uPAR/PLAUR	Urokinase-type plasminogen activator receptor
VDR/NR1H1	Vitamin D receptor
VEGF	Vascular endothelial growth factor
WNT	Wingless-type MMTV integration site family

Background

Bile acids (BAs) belong to cholesterol-derived sterols. Due to the side chain carboxyl group and hydroxylation of their steroid ring they are more polar than cholesterol. They have an amphipatic character for which they are known as natural detergents. Majority of cholesterol is excreted by bile acids that are prone to enterohepatic circulation between the gallbladder and the liver. Cholesterol absorption in the intestine and cholesterol secretion into the bile both require bile salts, which are, together with enterohepatic circulation of BAs, crucial for balancing the plasma cholesterol level [1].

BAs are also signaling molecules. They deorphanized the farnesoid X nuclear receptor (FXR) which is now known as a ligand-inducible transcription factor responsive to BAs [2]. It is important to note that BAs are metabolized in a similar manner as xenobiotics, contributing to the cross-talk between the endogenous and xenobiotic metabolism in the liver through nuclear receptors Pregnane X receptor (PXR), constitutive androstane receptor (CAR) and others [3]. While their synthesis takes place exclusively in the liver, the homeostasis and excretion involve multiple organs and compartments in the body. After discovering their signaling role, BAs have been considered as pro-carcinogenic molecules [4–6]. However, recent studies have provided evidence that in certain cancers, BAs can have antineoplastic features (e.g. breast cancer [7–11]). This novel, context-dependent, dualistic finding prompted us to thoroughly assess the involvement of BAs in carcinogenesis and cancer progression.

Bile acid biosynthesis

The excess of free cholesterol is toxic to cells and needs to be excreted, primarily through conversion to more polar BAs. The introduction of a hydroxyl group in cholesterol reduces the half-life and directs the oxidized molecule to excretion [12]. BA synthesis is thus the main cholesterol detoxification pathway where multiple cytochrome P450 (CYP) enzymes are involved in the classical or alternative pathways (Fig. 1). The two major primary BAs in humans are cholic acid (CA) and chenodeoxycholic acid (CDCA). They are synthesized in the liver and secreted into the gallbladder as glycine or taurine conjugates [13]. The BA composition in mice substantially differs from the humans which has to be taken into account when using mouse as a model for BA related diseases. The mouse *Cyp2c70* metabolizes CDCA to more hydrophilic primary muricholic acids (MCAs) [14].

The first enzyme of the classical BA synthesis pathway is cholesterol 7α-hydroxylase (CYP7A1), leading to 7α-cholesterol in a rate-limiting reaction step, followed by several enzymatic conversions. This enzyme is prone to the negative feedback regulation by BAs and FXR [2]. Sterol 12α-hydroxylase (CYP8B1) lies at the branching point that leads to CA. Sterol 27-hydroxylase (CYP27A1) is needed for both CA and CDCA. In the alternative pathway, cholesterol is first metabolized by CYP27A1 to form 27-hydroxycholesterol that is a substrate for 25-hydroxycholesterol 7α-hydroxylase (CYP7B1) and later other enzymes [15]. The alternative pathway leads majorly to CDCA. The ratio of CA to CDCA is determined by the expression level of CYP8B1, which transforms a di-hydroxylated BA to tri-hydroxylated BA. The alternative pathway is estimated to account for about 10% of cholesterol conversion [16]. Of importance, there are major differences in individual BA synthesis genes in mouse and in humans which may be due also to different biological roles of human and mouse BA species (reviewed in [15]).

Bacterial metabolism of bile acids, production of secondary bile acids

Hepatocytes secrete BAs to the bile canaliculi. By fusing with each other bile canaliculi form bile ducts, which eventually form the hepatic duct that runs to the gallbladder. The gallbladder empties to the duodenum upon feeding and, hence, releases BAs to the gastrointestinal tract. Primary BAs emulsify dietary fats and activate pancreatic

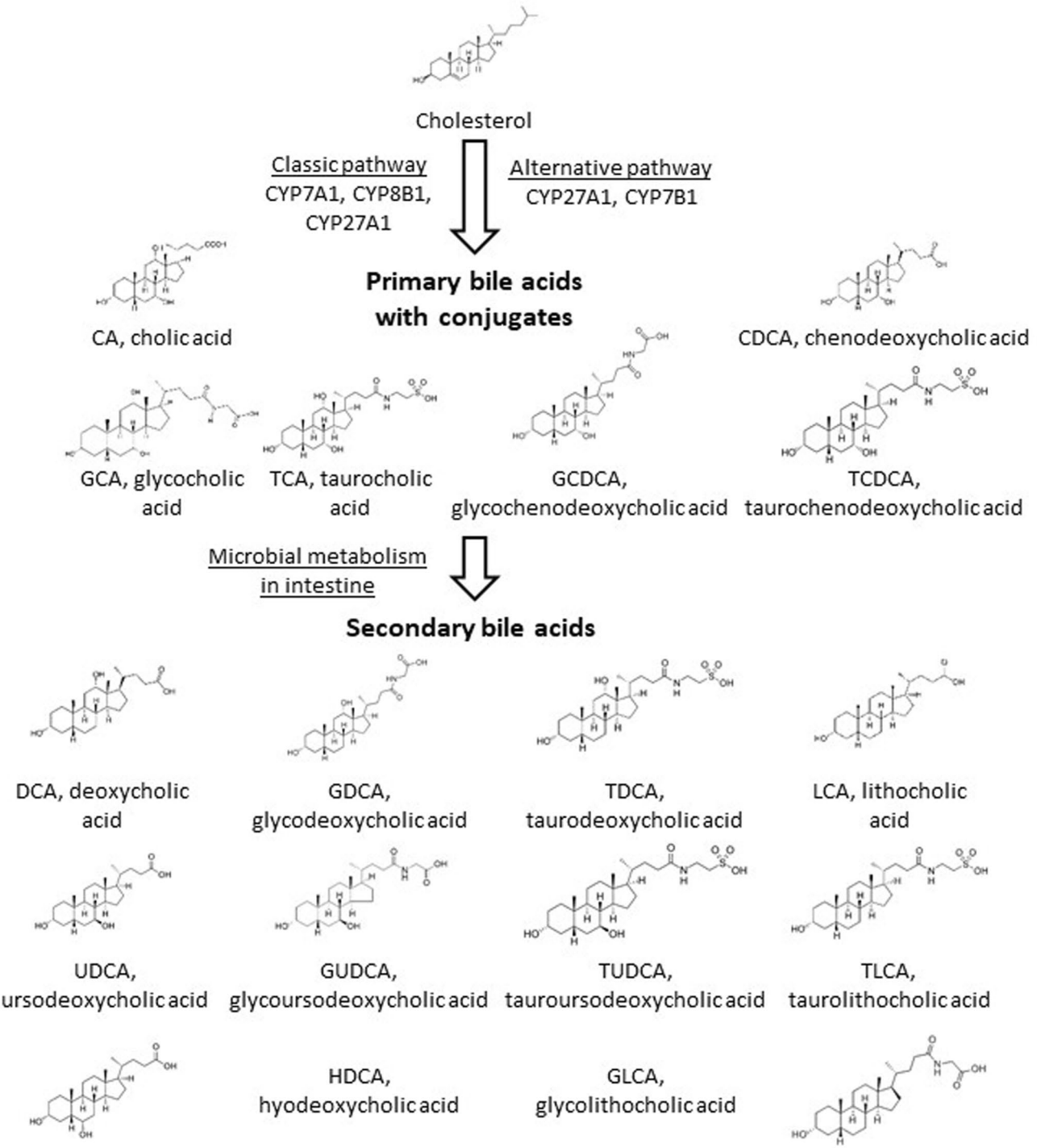

Fig. 1 Scheme of the classical and alternative bile acids in humans. Only enzymes of the CYP family are listed while the pathway involves enzymes of other protein families. CA and DCA are conjugated and further metabolized in the intestine

lipases in the small bowel. BAs are then reabsorbed through the enterocytes and get to the liver for reuptake and reuse through the portal circulation. This circle is termed the enterohepatic circulation of BAs. A fraction of the reabsorbed BAs enter the systemic circulation (total BA concentration in the serum is < 5 μM in a healthy individual) and exert hormone-like effects [7, 17–20]. The reference concentrations of the serum, tissue and fecal bile acids are in Tables 1, 2, 3.

Table 1 Reference serum bile acid levels

	Cohort size, reference	*n* = 40 [303]		*n* = 8 [304]		*n* = 30 [305]		*n* = 28 [306]		n = 56 (pooled) serum [7]
		Mean	± SEM	Mean	± SD	Mean	± SEM	Mean	± SEM	Mean
Primary bile acids	CA	181.5	83.1	440	651	162.05	40.19	153.68	159.64	287
	GCA	233.0	56.0	85	55	42.55	13.72	72.86	93.69	301
	TCA	179.7	47.0	14	12	2.04	0.63	18.56	29.4	71
	CDCA	256.8	56.3	380	410	1160.64	299.60	654.78	660.43	563
	GCDCA	771.5	111.9	450	210	975.59	205.81	649.19	648.55	931
	TCDCA	120.2	21.8	69	56	7.51	1.74	54.28	69.18	137
Secondary bile acids	DCA	386.7	66.0	320	120	593.27	141.09	402.76	350.11	701
	GDCA	246.2	42.5	104	44	190.78	44.32	156.39	149.88	415
	TDCA	44.9	11.8	21	18	44.06	8.86	24.62	22.68	61
	LCA	12.8	1.8			9.74	1.51	94.95	57.21	31
	GLCA	16.3	4.1	17	20			25.26	15.82	25
	TLCA	23.4	3.6	0,33	0,52	0.46	0.07	22.82	19.29	
	UDCA	137.6	25.1	43	27	208.35	32.94	130.83	114.96	147
	GUDCA			76	40	60.92	9.76	128.04	178.12	330
	TUDCA	5.0	1.1	2,7	2,7	1.41	0.30	6.24	5.63	

All concentrations are in nM

CA Cholic acid, *CDCA* Chenodeoxycholic acid, *DCA* Deoxycholic acid, *GCA* Glycocholic acid, *GCDCA* Glycochenodeoxycholic acid, *GDCA* Glycodeoxycholic acid, *GLCA* Glycolithocholic acid, *GUDCA* Glycoursodeoxycholic acid, *LCA* lithocholic acid, *TCA* Taurocholic acid, *TCDCA* Taurochenodeoxycholic acid, *TDCA* Taurodeoxycholic acid, *TLCA* Taurolithocholic acid, *TUDCA* Tauroursodeoxycholic acid, *UDCA* ursodeoxycholic acid

Table 2 Reference fecal bile acid levels

	Cohort size, Reference	*n* = 97 [307]		*n* = 28 [308]		*n* = 15 [309]
		Mean µg/mg	± SD	Median nmol/g	Q1; Q3	Median ng/mg of dry feces
Primary bile acids	CA	56.16	255.46	20.19	5.03;1304.28	0.23
	GCA	199.35	317.56	2.23	1.39;3.55	
	TCA	4.14	7.82	0.72	0.46;2.11	
	CDCA	29.65	102.48	57.16	13.76;1639.92	0.23
	GCDCA			5.17	2.56;10.51	
	TCDCA	3.35	10.5	1.41	0.37;3.58	
Secondary bile acids	DCA			2159.78	1676.03;3094.08	2.6
	GDCA	110.41	167.88	2.67	1.44;6.83	
	TDCA	4.84	12.5	1.75	0.86;6.63	
	LCA	548.75	336.88	2339.24	1737.09;2782.40	3.1
	GLCA	0.18	0.18	0.91	0.41;1.28	
	TLCA	0.94	4.46	1.03	0.36;2.80	
	UDCA			17.21	8.76;33.48	0.1
	GUDCA	0.81	3.88	0.65	0.38;0.87	
	TUDCA			0.37	0.07;1.23	

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Table 3 Reference tissue bile acid levels

		Gastric juice (μM)		Breast cyst fluid (μM)	Adipose tissue (ng/g)		Liver tissue (nmol/g)		Liver tissue (nmol/g)	
		n = 10 [310]		n = 12 [261]	n = 24 [311]		n = 6 [312]		n = 10 [313]	
		Mean	± SEM	Min–Max	Median	Min–Max	Mean	± SEM	Mean	± SEM
Primary bile acids	CA	2.38	1.09	3–119 (n = 1, ND)	˂LOD	0–11.4	21.1	13.0	30.4	5.9
	GCA	0.74	0.65		7.5	2.6–33.6				
	TCA	0.87	0.1		12.5	4.9–106.9				
	CDCA	0.03	0.04	4–305	˂LOD	˂LOD	31.0	16.0	29.8	5.4
	GCDCA	0.55	0.5		15.9	2.2–67.3				
	TCDCA	0.57	0.08		2.6	1.0–3.5				
Secondary bile acids	DCA	3.78	0.6	17–160 (n = 1, ND)	9.4	0–60.6	6.2	2.3	2.0	0.7
	GDCA	0.39	0.2		14.9	4.8–45.3				
	TDCA	5.22	0.02		4.2	1.6–6.0				
	LCA	0.12	0.02	9–23 (n = 6, ND)	˂LOD	˂LOD	1.5	0.2	0.7	0.3
	GLCA	0.12	0.007		8.1	2.9–19.0				
	TLCA	0.86	0.01		˂LOD	˂LOD				
	UDCA	0.02	0.02		˂LOD	˂LOD	2.0	0.8	1.5	0.6
	GUDCA	0.24	0.08		2.0	0–15.9				
	TUDCA	3.58	0.002		0.8	0.3–1.9				

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BAs are very powerful surfactants [21]; therefore, bacteria, mostly in the large bowel, need to protect themselves against being disintegrated by BAs. For example, lipopolysaccharides serve as membrane components in Gram-negative bacteria to passively ward off external toxins or BAs [22]. In addition to that, bacteria have a more sophisticated enzymatic system to cope with BAs termed BA conversion [23].

The hydroxyl groups and the tauryl or glycyl conjugate on BAs are crucial elements of the molecular structure of BAs for their strong surfactant properties. Therefore, the removal, modification or substitution of these molecular elements diminishes the potentially toxic features of primary BAs and renders them largely apolar. The dehydroxylated primary BAs are called secondary BAs and the main site for converting primary BAs to secondary BAs is the large bowel [24]. Secondary BAs can be resorbed to the portal circulation and are transported to the liver, where, however, hydroxylation and conjugation needs to be restored for reuse. The main secondary BAs in humans are lithocholic acid (LCA), deoxycholic acid (DCA) and to a lesser extent, ursodeoxycholic acid (UDCA) [24, 25].

Bile salt hydrolases (BSHs) are responsible for the deconjugation of BAs, namely the removal of glycine or taurine by breaking the C24 *N*-acyl bond. Glycine and taurine can be fed into the metabolism of bacteria to be used as an energy source [23]. BSH activity is common among the bacteria inhabiting the small and the large intestines [23]; both aerobic [26] and anaerobic bacteria can deconjugate bile salts [27]. Namely, among the Gram-positive bacteria BSH was identified in *Clostridium* [27–30], *Enterococcus* [27, 31], *Bifidobacterium* [27, 32, 33], *Lactobacillus* [34, 35], *Streptococcus* [36], *Eubacterium* [37] and *Listeria*, among Gram-negative bacteria in *Bacteroides* [30, 38, 39], while among archea *Methanobrevibacter smithii* and *Methanosphera stadmanae* [40].

The substituents on the gonane core of BAs can be also modified, the term "secondary BA" typically stands for the removal of 7α or 7β-hydroxyl groups from primary BAs. *Clostridiales* and *Eubacteria* were shown to play a major role in dehydroxylation [23, 41–45], although other genre or species were also implicated (e.g. *Bacteroidetes*, *Escherichia)* [7, 38, 44, 46, 47]. Although BA deconjugation and dehydroxylation are different processes, they may be linked through regulatory circuits [30]. Other reactions of BAs involve oxidation, and epimerization that can be linked to intestinal *Firmicutes* (*Clostridium*, *Eubacterium*, and *Ruminococcus*), *Bacteroides* and *Escherichia* [23, 36, 37, 41, 42, 44, 45, 48]. Bacterial enzymes involved in secondary BA production are assembled in the BA inducible

(bai) operon [24]. Collectively, BA transformation renders secondary BAs hydrophobic and BAs loose their ability to act as detergents or toxins to bacteria. Moreover, these changes are vital in fine-tuning the affinity of BAs to BA receptors.

Interactions between BAs and gut microbiota are bidirectional. Microbiota can transform primary BAs and, hence, modulate the composition of the BA pool [49, 50]. Inversely, BAs can influence the composition of the microbiome as well [51–56] and facilitate bacterial translocation to tissues [57], further underlining that notion BAs act as potent drivers of the early intestinal microbiota maturation [58]. Oncobiosis (dysbiosis associated with cancers) [59] can alter the secondary BA pool that may contribute to carcinogenic effects [4, 5, 7, 18]. It is of note that several other non-BA bacterial metabolites are known that play role in carcinogenesis [60–64].

Bile acid transporters

The enterohepatic circulation of BAs depends on BA transporters in the gastrointestinal system. Almost 90% of BAs are involved in circulation due to efficient active transport [65]. Different uptake and efflux BAs transporters are present in the hepatic and intestinal cells (Fig. 2). After BAs are synthesized in the liver they are transported into the bile mainly by the ATP-dependent cassette transporter (BSEP) [65], but also minor transporters, the multidrug resistance-associated protein 2 (MRP2, ABCC2) and the multidrug resistance protein 1 (MDR1, ABCB1) [65]. From the intestinal lumen, BAs are uptaken into the intestinal cells by the major apical sodium-dependent bile acid transporter (SLC10A2, ASBT), which transports BAs also across the canalicular membrane in cholangiocytes and renal tubule apical membrane from glomerular filtrate [66]. BAs are then effluxed into the portal circulation by two Solute Carrier

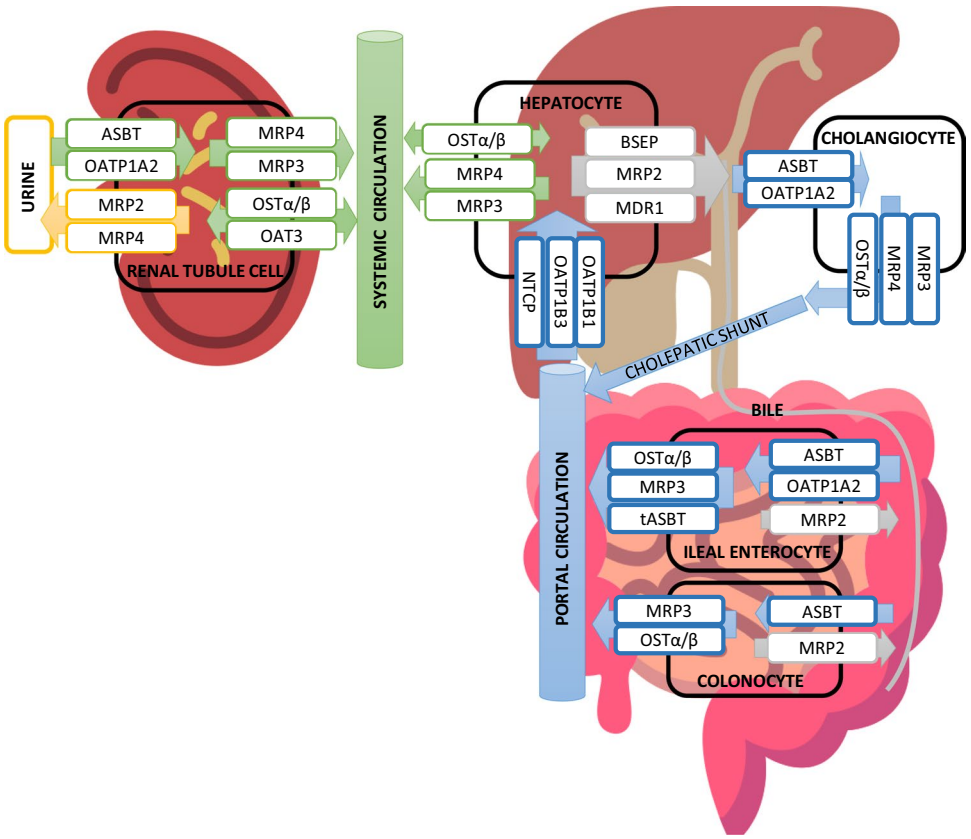

Fig. 2 A scheme of enterohepatic and systemic circulation of bile acids and the transporters in different human cells. Transporters are coloured according to which part of the circulation they belong to. Blue are efflux and influx transporters, which transport BAs in portal circulation. Grey are efflux transporters, which contribute to bile export into bile and faeces. Green are transporters, which are responsible for BA transport into the systemic circulation. Yellow are transporters involved in the efflux of BAs into urine. *ASBT/SLC10A2* sodium-dependent bile acid transporter, *BSEP/ABCB11* ATP-dependent cassette transporter, *MRP2/ABCC2* multidrug resistance-associated protein 2, *MRP3/ABCC3* multidrug resistance-associated protein 3, *MRP4/ABCC4* multidrug resistance-associated protein 4, *OATP1A2/SLCO1A2* Solute Carrier Organic Anion Transporter Family Member 1A2, *OATP1B/SLCO1B* Solute Carrier Organic Anion Transporter Family, *SLC51A/B or OSTα/β* Solute Carrier Family members, *SLC10A2/ASBT* sodium-dependent bile acid transporter

Family members, SLC51A or OSTα and SLC51B or OSTβ. The bile acids are then taken back up into hepatocytes by the major transporter the solute carrier family 10 (SLC10A1, NTCP), [65].

BAs can enter the systemic circulation via export across the hepatic sinusoidal membrane by OSTα/OSTβ, the multidrug resistance-associated protein 3 (MRP3, ABCC3) and the multidrug resistance-associated protein 4 (MRP4, ABCC4) [67]. The MRP transporters have a role in reducing hepatic BA concentration in cholestatic conditions. MRP3 and MRP4 are also present in cholangiocytes, where they efflux BAs to portal circulation and are part of the cholehepatic shunt together with ASBT [66]. Several transporters are expressed in the kidney, where they participate in BA elimination via urine (Fig. 2) [66, 68, 69]. The Solute Carrier Organic Anion Transporter Family, OATP1B1 or SLCO1B1 and OATP1B3 or SLCO1B3 contribute to the systemic clearance of BAs via liver [70]. Other cells also express BA transporters and can, therefore, uptake BAs from the systemic circulation [68, 69, 71].

Bile acids as signaling molecules

In addition to their role in digestion, BAs act as signaling molecules. BAs can activate membrane receptors (Fig. 3), such as G protein-coupled bile acid receptor 1 (GPBAR1, also known as TGR5), sphingosine-1-phosphate receptor 2 (S1PR2), muscarinic receptors (CHRM2 and CHRM3) and nuclear receptors (NRs), such as farnesoid X receptor (FXR, NR1H4), PXR (NR1H2), vitamin D receptor (VDR, NR1H1), CAR (NR1H3) and liver X receptor (LXR, NR1H2-3). Each BA can interact with more than one receptor. Receptors are differentially activated by BAs. For example, FXR is activated by CDCA > DCA > LCA > CA [72], while TGR5 is activated by LCA > DCA > CDCA > CA [73, 74], respectively. VDR and PXR are mainly activated by LCA. BAs mediate immune responses [75], gastrointestinal mucosal barrier function, gestation [76], carcinogenesis [11, 18, 56] and metabolic diseases [20]. The activation of BA receptors may lead to the induction of signaling pathways involved in the regulation of several physiological functions, such as glucose, lipid and energy metabolism, as well as, in cancers. Below, we review the mode of action of BA receptors and highlight those receptor-mediated functions that have a key role in regulating the behavior of cancer cells.

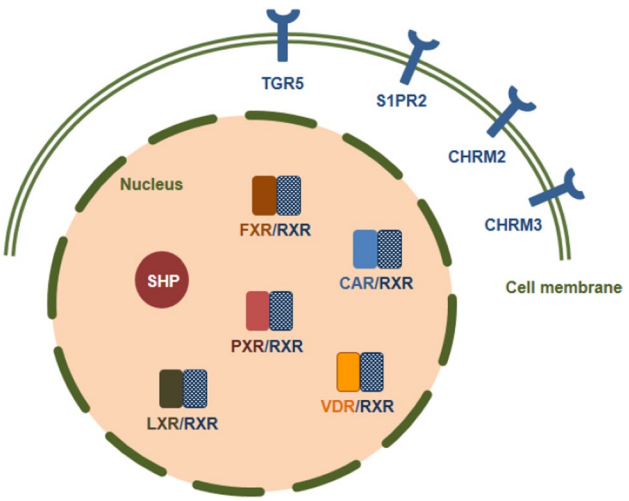

Fig. 3 The subcellular localization of bile acid receptors. *TGR5* G protein-coupled bile acid receptor 1, *S1PR2* Sphingosine-1-phosphate receptor 2, *CHRM2* Muscarinic receptor-2, *CHRM3* Muscarinic receptor-3, *FXR* Farnesoid X receptor, *PXR* Pregnane X receptor, *CAR* Constitutive androstane receptor, *VDR* Vitamin D receptor, *SHP* Small heterodimer partner

Cell membrane receptors

G protein-coupled bile acid receptor 1 (GPBAR1, TGR5)

TGR5 is a member of the G protein-coupled receptor superfamily, highly expressed in the epithelium of the gallbladder [77], the intestine [74], the brown adipose tissue and the skeletal muscle [20], as well as in the brain [78]. TGR5 is also expressed in human monocytes/macrophages [73]. TGR5 is not expressed by hepatocytes, while Kupffer cells and liver sinusoidal cells can express the receptor [79].

Secondary BAs LCA and DCA are the most potent, natural ligands for TGR5, but the receptor also responds to CDCA and CA [73, 74] and a set of artificial ligands [80–84] (Table 4). Ligand binding to the TGR5 receptor triggers activation of adenylate cyclase leading to the production of cAMP [73, 74, 85] and the downstream activation of extracellular signal-regulated kinase 1/2 (ERK1/2), protein kinase A (PKA), protein kinase B (AKT), mammalian target of rapamycin complex 1 (mTORC1) and Rho kinase [86–89]. TGR5 activation leads to metabolic changes characterized by energy expenditure and β-oxidation [20, 90]. BA-dependent induction of TGR5 has immunomodulating effects. Most studies point to TGR5-dependent immunosuppression [73, 79, 91–94] partly due to the suppression of the Toll-Like Receptor 4—Nuclear factor-κB (TLR4–NF-κB) pathway [91, 93, 94]. In line with that, in a murine model of breast cancer, LCA treatment induced the proportions of tumor-infiltrating lymphocytes through TGR5 [7].

Sphingosine-1-phosphate receptor 2 (S1PR2)

Conjugated BAs activate S1PR2 [95–97] that upregulates the expression of sphingosine kinase 2 (SphK2), which in turn enhances the level of sphingosine-1-phosphate in the nucleus. Elevated nuclear sphingosine-1-phosphate inhibits the function

Table 4 Bile acid receptors, their ligands and connected cancers

Receptor	Bile acid ligands	Connected cancers
GPBAR1 (TGR5)	TLCA, LCA, DCA, CDCA, CA	Breast cancer Pancreatic cancer Gastric cancer Colon cancer Oesophageal adenocarcinoma
S1PR2	GCA, TCA, GCDCA, TCDCA, GDCA, TDCA	Cholangiocarcinoma Oesophageal adenocarcinoma
CHRM2, CHRM3	LCT, TLCA	Colon cancer Cholangiocarcinoma
FXR	CDCA, DCA, LCA, CA	Colon cancer Hepatocellular carcinoma Breast cancer Oesophageal adenocarcinoma
PXR	LCA, 3-keto-LCA, CDCA, DCA, CA	Colon cancer Oesophageal adenocarcinoma
CAR	LCA	Breast cancer
VDR	LCA	Colon cancer
LXR α/β	HDCA	Ovarian cancer
SHP	DCA	Hepatocellular carcinoma Breast cancer Gastric cancer

CA Cholic acid, *CAR* Constititive androstane receptor, *CDCA* Chenodeoxycholic acid; CHRM2/M3, Muscarinic receptor 2 and 3, *DCA* Deoxycholic acid, *FXR* Farnesoid X receptor, *GCA* Glycocholic acid, *GCDCA* Glycochenodeoxycholic acid, *GDCA* Glycodeoxycholic acid, *HDCA* hyodeoxycholic acid, *LCA* Lithocholic acid, *LCT* Lithocholyltaurine, *LXR* Liver X receptor, *PXR* Pregnane X receptor, *S1PR2* Sphingosine-1-phosphate receptor 2, *SHP* Small heterodimer partner, *TCA* Taurocholic acid, *TCDCA* Taurochenodeoxycholic acid, *TDCA* Taurodeoxycholic acid, *TGR5/GPBAR1* G protein- coupled bile acid receptor 1, *TLCA* Taurolithocholic acid, *VDR* Vitamin D receptor

of histone deacetylases resulting in the upregulation of genes encoding nuclear receptors and enzymes involved in lipid and glucose metabolism [98] Similar to TGR5, ligand binding to S1PR2 can activate different downstream signaling pathways, such as ERK, AKT and/or c-Jun N-terminal kinase (JNK1/2) [96, 97, 99, 100]. Glycochenodeoxycholic acid (GCDCA) can trigger apoptosis in hepatocytes through activating S1PR2 [101]. S1PR2 is highly expressed in macrophages [102] and has widespread immunological roles [100, 102, 103].

Muscarinic receptors (CHRM2 and CHRM3)

Taurine conjugated BAs can activate muscarinic receptors, the cholinergic receptor muscarinic 2 and 3 (CHRM2 and CHRM3). CHRMs are overexpressed in colon cancer cells and stimulate cell proliferation and invasion [104, 105]. Taurolithocholic acid (TLCA) induces cholangiocarcinoma cell growth via muscarinic acetylcholine receptor and EGFR (epithelial growth factor receptor)/ERK1/2 signaling [106].

Nuclear receptors

Farnesoid X receptor (FXR, NR1H4)

FXR is a member of the nuclear hormone receptor superfamily. There are two FXR genes, encoding FXRα and FXRβ of which only FXRα is expressed, FXRβ is present as a non-expressed pseudogene in humans. The FXR receptor heterodimerizes with retinoid X receptor (RXR) and binds to FXR response elements (FXREs) within the regulatory regions of its target genes [107]. BAs are physiological ligands for FXR (with decreasing affinity: CDCA, DCA, LCA, CA) [72]. FXR is expressed mainly in the liver, intestine, kidney and adrenal glands [107].

FXRα controls BA synthesis, transport and detoxification. The activation of FXR receptor by BAs reduces the expression of *Cyp7a1* and *Cyp8b1*, key enzymes of BA biosynthesis pathway. In the liver, FXRα induces the transcription of its target gene encoding small heterodimer partner

(SHP, NR5O2), an orphan nuclear hormone receptor (see in detail later) that lacks a DNA binding domain and acts as a transcriptional repressor [108]. SHP inhibits the expression of *Cyp7a1* through the inhibition of the interaction with liver receptor homolog-1 (LRH-1, NR5A2) [109]. In addition to LRH-1, SHP also prevents the function of hepatocyte nuclear factor-4α (HNF4α), a positive regulator of *Cyp7a1* and *Cyp8b1* [110]. In the intestine, FXRα induces the expression of fibroblast growth factor 19 (FGF19) in humans and its mouse homolog fibroblast growth factor 15 (FGF15). The secreted growth factor via portal blood reaches the liver where it binds to its receptor, fibroblast growth factor receptor 4 (FGFR4) and induces JNK and ERK pathways and causes repression of *Cyp7a1*, thus reducing BA synthesis [111]. In addition to *Cyp7a1*, *Cyp8b1* is also repressed by FXRα via SHP-dependent mechanism involving HNF4α [110].

FXRα is also a key regulator of BA transport by influencing the expression of BA transporters. FXRα activation suppresses BA reuptake to hepatocytes through repressing the expression of *NTCP* via SHP dependent mechanism [112]. At the same time, FXRα facilitates the efflux of BAs from hepatocytes into bile by enhancing the expression of *BSEP* and into the systemic circulation via *OSTα/β* transporter [113]. FXR also upregulates MRP2, which promotes BA secretion into the gallbladder. Finally, FXRα activates the expression of intestinal BA-binding protein (I-BABP) in the ileum which promotes transport of BAs from enterocytes into portal blood [114] whereas limits enterocyte uptake of BAs by reducing *ASBT* expression. FXRα increases the expression of enzymes involved in the detoxification of BAs, such as cholesterol 25-hydroxylase or cytochrome P450 family 3 subfamily A4 (CYP3A4) [115], dehydroepiandrosterone-sulfotransferase (SULT) 2a1 [116] and uridine 5′-diphosphate-glucuronosyltransferase 2B4 (UGT2B4) [117]. Many studies have reported the relationship between FXR and inflammation. NF-kB activation suppressed FXR-mediated gene expression, indicating that there is a negative crosstalk between the FXR and NF-kB signaling [118].

Pregnane X receptor (PXR, NR1I2)

In humans, PXR is mainly expressed in the liver and intestine [119]. Among BAs, the most potent ligand of PXR is LCA, and the oxidized, 3-keto form of LCA. PXR acts as a xenobiotic sensor and regulates the expression of genes involved in the detoxification and metabolism of BAs [120]. Upon ligand binding, PXR binds to the promoter of its target gene as a heterodimer with RXR. Activation of PXR induces the uptake of xenobiotics, their modification by phase I enzymes (CYPs, including CYP3A, CYP2B, CYP2C), conjugation by phase II enzymes, such as glutathione S-transferases, UDP-glucuronosyl-transferases (UGTs) and sulfotransferases, and finally elimination by phase III drug transporters including MDR1, MRP2 and organic anion-transporting polypeptide (OATP2) [120]. The activation of PXR prevents cholesterol gallstone disease by regulating BA biosynthesis and transport [121] and protects the liver against LCA-induced toxicity [122–125]. PXR activation disrupts the interaction between HNF4α and peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α, PPARGC1A), which is required for the activation of CYP7A1 gene expression, thus reducing the expression of *CYP7A1* and inhibiting the synthesis of BAs [126]. PXR activation is anti-inflammatory [127–129]. PXR activation facilitates lipogenesis, suppressing β-oxidation and ketogenesis and gluconeogenesis [130–132]. Furthermore, PXR through HNF4 and PGC-1α modulates the expression of *CYP7A1* [133].

Constitutive androstane receptor (CAR, NR1I3)

CAR is the closest relative to the PXR and is expressed primarily in the liver. First studies identified that CAR has constitutive transcriptional activity in the absence of its ligand [134]. Later, it was reported that the constitutive transcriptional activity of CAR is reversed by androstane metabolites, which are inverse agonists [135]. CAR can be activated by direct ligand binding and indirect activation [136]. In the absence of ligand binding, CAR forms a heterodimer with RXR and transactivates its target genes [137]. CAR recruits coactivators in the nucleus, such as steroid receptor coactivator 1 (SRC-1, NC0A1) and PGC-1 [138]. Similar to PXR, CAR controls the expression of drug-metabolizing enzymes and transporters, thereby supporting the detoxification of xenobiotics [120, 139]. In contrast to PXR, it remains unclear whether BAs can function as natural ligands for CAR; nevertheless, there are reports underscoring the involvement of CAR in BA signaling [11].

Vitamin D receptor (VDR, NR1I1)

In humans, VDR is highly expressed in the kidney, intestine, bone as well as in hepatocytes but expressed at low levels in other tissues [140–142]. LCA is a potent endogenous VDR ligand [143, 144]; hence, VDR can act as an intestinal BA sensor. VDR activation induces expression of *CYP3A* that metabolizes LCA [143, 145]. In addition, VDR induces the expression of *SULT2A1*, *MRP3* and *ASBT* to stimulate BA sulfonation, excretion and transport [146–148]. The activated VDR plays a role in the inhibition of BA synthesis via suppression of *CYP7A1*, thus protecting liver cells during cholestasis [140].

VDR can function as a nuclear receptor and a membrane-bounded receptor. Upon ligand binding, VDR translocates into the nucleus, where it binds to DNA response elements

as a heterodimer with RXR to mediate gene transcription. Plasma membrane-associated VDR receptor activates several signaling cascades to inhibit *CYP7A1* transcription [142, 149]. It has been shown that the activation of membrane VDR signaling by LCA in the liver activates MEK1/2ERK1/2 pathway, which stimulates nuclear VDR/RXRα heterodimer recruitment of corepressors to inhibit *CYP7A1* gene transcription [150]. In biliary epithelial cells, bile salts (CDCA, UDCA) stimulate the expression of cathelicidin, an antimicrobial peptide, via VDR and FXR to control innate immunity [151]. The possible role of VDR in regulating immunity and the role of VDR in different cancer cells and diseases is reviewed in detail elsewhere [152].

Liver X receptor (LXR, NR1H2-3)

LXRs are activated by naturally occurring cholesterol metabolites such as oxysterols and bind to DNA as heterodimers with the RXR [153]. LXRα (NR1H3) and LXRβ (NR1H2) share a high structural homology [154]. LXRβ is ubiquitously expressed, while LXRα is primarily expressed in the liver, the adipose tissue, the intestine and macrophages. Upon ligand activation LXRs regulate gene expression via binding to LXR response elements in the promoter regions of the target genes. LXRα promotes the conversion of cholesterol into BAs through the induction of CYP7A1 expression in the liver. LXRs enhance the efflux of cholesterol from cells [155] and have an anti-inflammatory response in the adipose tissue and macrophages [156]. Hyodeoxycholic acid (HDCA), a naturally occurring secondary BA generated by bacterial C-6 hydroxylation of LCA, is a weak LXRα agonist [157].

Small heterodimer partner (SHP, NR5O2)

SHP is a unique nuclear receptor that contains a ligand-binding domain but lacks the conserved DNA-binding domain. SHP acts as a transcriptional corepressor regulating different metabolic processes, including lipid, glucose, energy homeostasis and BA synthesis via interaction with multiple transcription factors and nuclear receptors (reviewed in [158]). BAs or FGF19 signaling enhances posttranslational modifications of SHP, which modulates the regulatory function of SHP protein [159, 160]. SHP acts as an inhibitory regulator in Hedgehog/Gli signaling pathway [161].

Effects of bile acids in cancers

The role of BAs was implicated in a wide variety of neoplasias (Fig. 4, Tables 5, 6, 7). When assessing the effects of BAs, one has to keep in mind that the concentrations applied in the experiments need to correspond to the reference concentrations in serum or the compartment in question (e.g. parts of the gastrointestinal tract). However, several reports are using substantially higher concentrations than the reference. These studies need to be considered as ones using "therapeutic" concentrations. In the forthcoming chapters, we will review those neoplasias where BAs were implicated in pathogenesis.

Oesophageal carcinoma

The development of Barrett's esophagus (BE) and its progression to oesophageal adenocarcinoma (EAC) are linked to gastroesophageal reflux disease (GERD). Conjugated BAs, mainly taurocholic acid (TCA) and glycocholic acid (GCA) are the main BA constituents in GERD refluxate [162]. Conjugated BA levels in the refluxate from patients with advanced BE or EAC are significantly higher than from patients with benign BE [163]. Conjugated BAs, as TCA or taurodeoxycholic acid (TDCA), promote EAC progression [164, 165] (Table 7). Unconjugated BAs, including DCA and CDCA, induce oxidative stress, DNA damage and inflammation contributing to EAC carcinogenesis, while UDCA protects against DCA-induced injury (Tables 5 and 7).

Apparently, numerous BA receptors as TGR5, S1PR2, FXR and VDR are activated in EAC cells in response to BAs in the refluxate [164–167]. In good agreement with that, the inhibition of the FXR receptor suppresses tumor cell viability in vitro and reduced tumor formation in nude mouse xenografts [168]. Furthermore, TGR5 is highly expressed in the EAC and precancerous lesions and is associated with worse overall survival [169] suggesting that these observations can be translated to the human situation.

Acidic bile acids bring about oxidative stress, TDCA can induce NADPH Oxidase 5 (NOX5) through TGR5 [164]. Furthermore, bile acids can induce inflammation through FXR activation [170] and the EGFR–STAT3 (signal transducer and activator of transcription 3)—Apurinic/Apyrimidinic Endodeoxyribonuclease 1 (APE1) pathway [171]. Acidic bile salts can also induce epithelial–mesenchymal transition (EMT) through vascular endothelial growth factor (VEGF) signaling in Barrett's cells [172]. Interestingly, the activation of the EGFR-DNA-PKs (DNA-dependent protein kinase) pathway by insulin-like growth factor binding protein 2 (IGFBP2) protects EAC cells against acidic bile salt-induced DNA damage [173].

Gastric cancer

Carcinogenesis in gastric cancer is a sequential process that includes chronic superficial gastritis, intestinal metaplasia (IM), atrophic gastritis, intramucosal carcinoma, dysplasia and invasive neoplasia [174]. IM is considered a risk factor for gastric tumorigenesis. The concentrations of

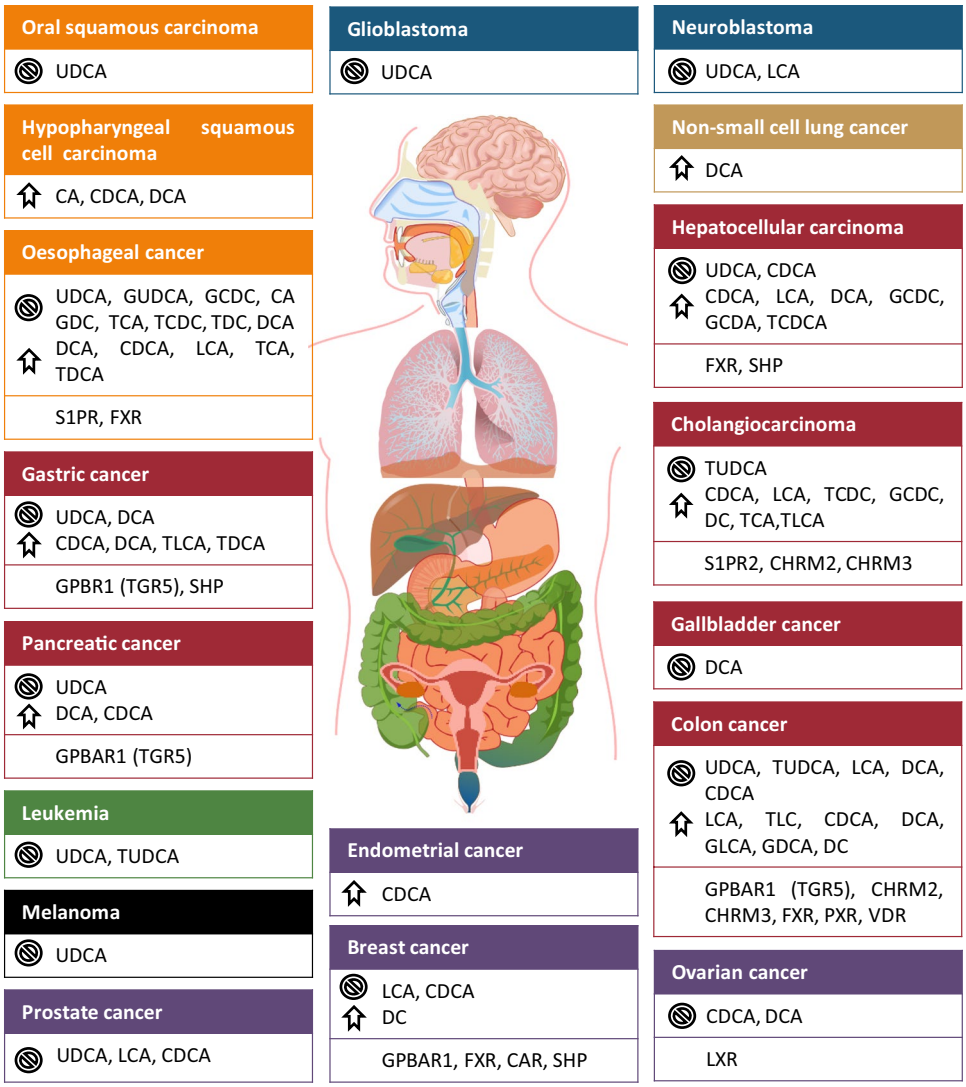

Fig. 4 Different roles of bile acids and bile acids receptors in a wide variety of cancers. Some BAs have opposite effects, which depend on the cell line, BA concentration and other treatment conditions. The crossed circle symbol marks the tumor suppressor effects and the arrow marks the tumor promoter effects. *CA* Cholic acid, *CAR* Constitutive androstane receptor, *CDCA* Chenodeoxycholic acid, *CHRM2/M3* Muscarinic receptor 2 and 3, *DC* Deoxycholate, *DCA* Deoxycholic acid, *FXR* Farnesoid X receptor, *GCDA* Glycochenodeoxycholate acid, *GCDC* Glycochenodeoxycholate, *GDC* Glycodeoxycholate, *GDCA* Glycodeoxycholic acid, *GLCA* Glycolithocholic acid, *GUDCA* Glycoursodeoxycholic acid, *LCA* Lithocholic acid, *PXR* Pregnane X receptor, *S1PR2* Sphingosine-1-phosphate receptor 2, *SHP* Small heterodimer partner, *TCA* Taurocholic acid, *TCDC* Taurochenodeoxycholate, *TCDCA* Taurochenodeoxycholic acid, *TDC* Taurodeoxycholate, *TDCA* Taurodeoxycholic acid, *TGR5/GPBAR1* G protein-coupled bile acid receptor 1, *TLC* Taurolithocholate, *TLCA* Taurolithocholic acid, *TUDCA* Tauroursodeoxycholic acid, *UDCA* Ursodeoxycholic acid, *VDR* Vitamin D receptor

BAs in gastric juice positively correlate with the degree of intestinal metaplasia [175] and BAs serve a critical multi-pronged role in the induction of intestinal metaplasia. BAs can enhance caudal-related homeobox family 2 (CDX2) and mucin 2 (MUC2) expression via FXR/NF-κB signaling [176, 177] and cyclooxygenase-2 (COX-2) expression via induction of SHP [178], all promoting gastric intestinal metaplasia. Acidic bile salts can induce telomerase activity in a c-Myc-dependent fashion [179, 180], while DCA can induce the metaplastic phenotype of gastric cancer cells [181] (see Tables 6 and 7). TGR5 is a key factor in BA-induced gastric metaplasia via HNF4α [181], EGFR and mitogen-activated protein kinase (MAPK) [182] activation and promotes EMT in gastric carcinoma cells [183]. TGR5 is overexpressed in gastrointestinal adenocarcinomas, and moderate to strong TGR5 staining is associated with decreased patient survival [184]. Nevertheless, there anticarcinogenic effects of bile acids in gastric cancer, as UDCA (Table 5) or DCA in supraphysiological concentrations [185, 186] or 23(S)-mCDCA [187].

Hepatocellular carcinoma (HCC)

Several studies have shown that more hydrophobic BAs as LCA, DCA and CDCA, are the main promoters of liver cancer and can contribute to the development of HCC (see in Table 7) [188–192]. Nevertheless, CDCA (> 100 µM) [193, 194], UDCA and Tauroursodeoxycholic acid (TUDCA) inhibit HCC cell growth and induce apoptosis [195–199] (see in Tables 5 and 6). Deregulation of BA homeostasis marked by the expression of hepatic BA transporters (BSEP, OSTα/β, MRP2, MDR2-3, NTCP) is diminished leading to increased hepatic BA sequestration and inflammation and reduced FXR signaling [200–203] in liver cirrhosis and non-alcoholic steatohepatitis that are risk factors for the development of HCC. In good agreement with that, metabolomics identified long-term elevated serum BAs in HCC patients

Table 5 Tumor suppressive effects of UDCA, TUDCA and GUDCA in cancers

Cancer type	Cell models	Concentration	Effects	Ref
Glioblastoma	A172, LN229	400–800 μM	UDCA inhibits cell viability, induces ROS production and endoplasmic reticulum stress, synergizes with proteasome inhibitor Bortezomib	[314]
Neuroblastoma	SH-SY5Y	100 μM	TUDCA protects against mitochondrial damage, cell death and ROS generation via mitophagy	[315]
Pancreatic cancer	HPAC, Capan1	0.2 mM	UDCA reduces intracellular ROS level and *Prx2* expression, as well as suppresses EMT and stem cell formation	[227]
Prostate cancer	DU145	0–200 μg/ml	UDCA inhibits cell growth and induces apoptosis via extrinsic and intrinsic pathways	[274]
Melanoma	M14, A375	0–300 μg/ml	UDCA inhibits cell proliferation and induces apoptosis via ROS-triggered mitochondrial-associated pathway	[316]
Hepatocellular carcinoma (HCC)	Huh-BAT, HepG2	750 μM	UDCA has a synergistic effect on the antitumor activity of sorafenib in HCC cells via activation of ERK and dephosphorylation of STAT3	[195]
	HepG2, BEL7402	0.1–1 mM	UDCA inhibits proliferation and induces apoptosis of HCC cell lines by blocking cell cycle and regulating the expression of *Bax/Bcl-2* genes. UDCA suppresses growth of BEL7402 cells in vivo	[196] [317]
	HepG2	0.25–1 mM	UDCA induces apoptosis via regulating of *Bax to Bcl-2* ratio, the expressions of *Smac* and *Livin*, and caspase-3 expression and activity	[197]
	Huh-Bat, SNU761, SNU475	200 μM	UDCA suppresses cell growth and induces DLC1 tumor suppressor protein expression by inhibiting proteasomal DLC1 degradation in an ubiquitin-independent manner	[198]
	HepG2, SK-Hep1, SNU-423, Hep3B	100 μM	UDCA switches oxaliplatin-induced necrosis to apoptosis via inhibition of ROS production and activation of the p53-caspase 8 pathway	[199]
Oral Squamous Carcinoma	HSC-3	100–400 μg/ml	UDCA induces apoptosis via caspase activation	[318]
Leukemia	T leukemia cell line (Jurkat cell)	100 μg/ml	TUDCA and UDCA induce a delay in cell cycle progression	[319]
Gastric cancer	MKN-74	200 μM	UDCA suppresses chenodeoxycholic acid-induced PGE2 production and tumor invasiveness without affecting the *COX-2* expression	[320]
	SNU601, SNU638	0.25–1 mM	UDCA induces apoptosis, which is mediated by lipid raft-dependent death receptor 5 (DR5) expression and activation	[321]
	SNU601	0.6–1 mM	UDCA induces apoptosis via MEK(MAPK)/ERK pathway. DCA-mediated ERK activation exerts an antiapoptotic activity in this cell line	[322]
	SNU601	0.5–1 mM	UDCA induces apoptosis via CD95/Fas death receptor, downregulates ATG5 level and prevents autophagic pathway	[323]

Table 5 (continued)

Cancer type	Cell models	Concentration	Effects	Ref
Oesophageal cancer / Barett's esophagus	BAR-T, BAR-10 T	125–250 μM	UDCA increases antioxidant expression and prevents DCA-induced DNA damage and NF-κB activation	[324]
	SKGT-4, OE33	300 μM	UDCA inhibits DCA-induced NF-κB, AP-1 activation and *COX-2* upregulation	[325]
	BE CP-A	0.1–0.2 mM	GUDCA has cytoprotective role by inhibiting oxidative stress	[326]
Colon cancer	HCT116	500 μM	UDCA inhibits DCA-induced apoptosis via modulation of EGFR/Raf-1/ERK signaling	[246]
	HCT116	500 μM	UDCA suppresses DCA-induced apoptosis by stimulating AKT-dependent survival signaling	[327]
	HCT116	500 μM	UDCA protects colon cancer cells from apoptosis induced by DCA by inhibiting apoptosome formation independently of the survival signals mediated by the PI3K, MAPK, or cAMP pathways	[328]
	HCT116	400 μM	UDCA inhibits cell proliferation by suppressing the expression of c-Myc protein and cell cycle regulatory molecules	[329]
	HT29, HCT116	0.2 mM	UDCA inhibits cell proliferation by regulating ROS production, induces activation of ERK1/2, and inhibits formation of colon cancer stem-like cell	[244]
	HCT116	300 μM	UDCA inhibits interleukin β1 and blocks DCA-induced NF-κB and AP-1 activation	[330]
	HT-29	250 μM	UDCA suppresses cell growth, which is enhanced in the presence of caveolin; UDCA promotes endocytosis and degradation of EGFR receptor	[331]
	HCT116, COLO 205	50 μg/ml	TUDCA suppresses NF-κB signaling and ameliorates colitis-associated tumorigenesis	[332]
Cholangiocarcinoma	Mz-ChA-1	0.2–200 μM	TUDCA inhibits cell growth via a signal-transduction pathway involving MAPK p42/44 and PKCα	[333]

AKT AKT Serine/Threonine Kinase 1, *AP-1* activator protein-1, *ATG5* Autophagy Related 5, *BIRC7/Livin* baculoviral IAP repeat-containing protein 7, *Bax* Bcl-2-associated X protein, *Bcl-2* B-cell lymphoma 2, *cAMP* Cyclic adenosine monophosphate, *c-Myc* Myc-Related translation/localization regulatory factor, *COX2* cyclooxygenase-2, *DCA* Deoxycholic acid, *Dlc1* Deleted in Liver Cancer 1, *DR5* death receptor 5, *EGFR* epithelial growth factor receptor, *EMT* epithelial–mesenchymal transition, *ERK* extracellular signal-regulated kinase, *FAS/CD95* Fas Cell Surface Death Receptor, *GUDCA* Glycoursodeoxycholic acid, *HCC* hepatocellular carcinoma, *MAPK* mitogen-activated protein kinase, *NF-κB* nuclear factor κappa-light-chain-enhancer of activated B cells, *PGE2* prostaglandin E2, *PI3K* Phosphatidylinositol 3-kinase, *PKCα* protein kinase C α, *Prx2* peroxiredoxin II, *RAF1* Raf-1 Proto-Oncogene, Serine/Threonine Kinase, *ROS* reactive oxygen species, *Smac* second mitochondria-derived activator of caspase, *STAT3* signal transducer and activator of transcription 3, *TUDCA* Tauroursodeoxycholic acid, *UDCA* Ursodeoxycholic acid

[204] and children (< 5 years of age) with bile salt export pump deficiency developed HCC [205].

FXR activity is a major inhibitor of HCC carcinogenesis. Whole-body FXR-deficient mice spontaneously develop liver tumors [206, 207] in which the activation of the Wnt/β-catenin signaling pathway and oxidative stress were identified as the major drivers [208–210]. Nevertheless, liver-specific FXR deficiency in mice does not induce spontaneous liver tumorigenesis, but may only serve as a tumor initiator [211]. Due to their amphipathic nature, BAs can disrupt the plasma membrane and activate protein kinase C (PKC) and phospholipase A2 (PLA2) inducing the p38-MAPK-p53-NFκB pathway [212, 213]. Inflammation can suppress FXR activity that contributes to bile acid accumulation and carcinogenesis [185, 193, 194, 214].

Interestingly, senescence-associated secretory phenotype has crucial role in promoting obesity-associated HCC development in mice. Administration of high-fat diet to mice induces alterations in the gut microbiota and increases the levels of DCA. Increased DCA level promotes SASP

Table 6 Antitumor effects of bile acids other than UDCA in cancers

Cancer types	Cell lines	Concentration of bile acids	Effects of bile acids	Refs.
Breast cancer	MCF7, MDA-MB-231	LCA (50–200 μM)	LCA induces *TGR5* expression and exhibits anti-proliferative and pro-apoptotic effects. LCA inhibits lipogenesis and reduces *ERα* expression in MCF7 cells	[10]
	MCF7, 4T1	LCA (0.3 μM)	LCA inhibits cell proliferation, EMT transition, VEGF production and induces antitumor immune response and elicits changes in metabolism through TGR5 receptor	[7]
	MCF7, 4T1	LCA (0.3 μM)	LCA induces NRF2/NFE2L2 dependent oxidative/nitrosative stress via TGR5/CAR receptors	[11]
	MCF7	CDCA (50 μM)	CDCA activates FXR receptor and inhibites Tamoxifen-resistant breast cancer cells proliferation and EGF-induced growth through downregulation of *HER2* expression	[268]
	MCF7, MDA-MB-231	CDCA (30 μM)	CDCA induces cell death via activation of FXR	[334]
Colon cancer / Colorectal carcinoma	Caco-2, HT29C19A	LCA (20 μM)	LCA activates VDR to block inflammatory signals in colon cells	[335]
	HCT116	LCA (150–400 μM)	LCA activates p53 and promotes apoptosis by its bindig to MDM4 and MDM2, key negative regulators of p53	[336]
	HCT116	DCA, CDCA (500 μM)	DCA and CDCA induce apoptosis	[337]
	HCT116	DCA (200–250 μM)	DCA induces apoptosis via AP-1 and C/EBP mediated GADD153 expression	[338]
	HCT116	DCA (0.05–0.3 mM)	DCA in physiologically relevant dose inhibits cell growth and induces apoptosis	[242]
Gallbladder cancer (GBC)	NOZ, GBC-SD, EGH1	DCA (50–200 μM)	DCA functions as a tumor suppressive factor in GBC by interfering with miR-92b-3p maturation	[339]
Gastric cancer	SGC7901	DCA (0.1–0.3 mM)	DCA induces apoptosis via the mitochondrial-dependent pathway	[186]
	BGC-823	DCA (0.3 mM)	DCA inhibits the growth of gastric cancer cells via p53 mediated pathway	[185]
	SNU-216, MKN45	DCA (200 μM)	DCA induces *MUC2* expression and inhibits tumor invasion and migration	[340]
Hepatocellular carcinoma (HCC)	HEPG2, L02	CDCA (10–50 μM)	CDCA reduces the expression of inflammation mediators, inhibits STAT3 phophorylation and increases expression of *SOCS3* via FXR	[193]
	HepG2, Huh7, mouse hepatoma Hepa 1–6	CDCA (50–100 μM)	CDCA induces tumor suppressor N-Myc downstream regulated gene 2 (NDRG2) expression through FXR receptor	[194]
Neuroblastoma (NB)	SK-n-MCIXC, BE(2)-m17, SK-n-SH, Lan-1	LCA (100 μM)	LCA selectively kills the NB cell lines while sparing normal neuronal cells. LCA triggers intrinsic and extrinsic pathways of apoptosis	[8]

Table 6 (continued)

Cancer types	Cell lines	Concentration of bile acids	Effects of bile acids	Refs.
Ovarian cancer	OVCAR3	CDCA, DCA (10 µM)	CDCA and DCA upregulate *BRCA1* and downregulate *ER1* gene expression, which are important implications for disease penetrance and chemoprevention strategies in carriers of *BRCA1* mutations	[281]
	A2780	CDCA, DCA (200–400 mM)	CDCA and DCA have significant cytotoxic activity via induction of apoptosis	[279]
Prostate cancer	LNCaP, PC-3	LCA (25–75 µM)	LCA inhibits the proliferation of cancer cells and induces apoptosis	[273]
	PC-3, DU145	LCA (3–50 µM)	LCA decreases cell viability, induces apoptosis as well as induces endoplasmic reticulum stress, autophagy and mitochondrial dysfunction	[9]
	LNCaP, DU145	CDCA (50 µM)	Activation of FXR by CDCA inhibits cell proliferation and lipid accumulation via SREBF pathway	[270]
	LNCaP	CDCA (5 µM)	FXR activation by CDCA inhibits cell growth via upregulation of PTEN	[271]

AP-1 activator protein-1, *BRCA1* breast cancer type 1 susceptibility protein, *CA* Cholic acid, *CAR* constitutive androstane receptor, *CDCA* Chenodeoxycholic acid, *C/EBP* CCAAT/enhancer-binding protein beta, *DCA* Deoxycholic acid, *EGF* epidermal growth factor, *EMT* epithelial–mesenchymal transition, *ER* estrogen receptor, *FXR* Farnesoid X receptor, *GADD153* growth arrest- and DNA damage-inducible gene 153, *GBC* Gallbladder cancer, *GCDC* Glycochenodeoxycholate, *GDC* Glycodeoxycholate, *HER2* human epidermal growth factor receptor 2, *LCA* Lithocholic acid, *MDM2* Mouse double minute 2, *MDM4* Double Minute 4, *MUC2* mucin 2, *NB* Neuroblastoma, *NDRG2* N-Myc downstream regulated gene 2, *NRF2* nuclear factor erythroid 2-related factor 2, *NFE2L2* PTEN, phosphatase and tensin homolog, *SOCS3* suppressor of cytokine signaling 3, *SREBF* sterol regulatory element-binding factor, *STAT3* signal transducer and activator of transcription 3, *TCA* Taurocholic acid, *TCDC* Taurochenodeoxycholate, *TDC* Taurodeoxycholate, *TGR5* G protein-coupled bile acid receptor 1, *VEGF* vascular endothelial growth factor, *VDR* vitamin D receptor

phenotype in hepatic stellate cells (HSCs), which in turn secretes various tumor-promoting factors in the liver, thus facilitating HCC development in mice exposed to chemical carcinogen [6]. SHP has a pleiotropic role in HCC, regulates cell proliferation [215], apoptosis [216], epigenetic changes [217] and inflammation [200, 218], which are associated with the antitumor role of SHP in the development of liver cancer.

Pancreatic adenocarcinoma

BAs are involved in the induction and development of pancreatic adenocarcinoma at multiple stages. Gallstone formation can block bile flow and, therefore, can induce and sustain pancreatitis [219], a risk factor for pancreatic adenocarcinoma [220–222]. In fact, several BA species showed a drastic increase in pancreatic adenocarcinoma patients [223]. Treatment of pre-malignant pancreas ductal cells with bile induced carcinogenic transformation [224, 225]. In pancreatic adenocarcinoma cells BAs decrease susceptibility to apoptosis, boost cell cycle progression, the expression of inflammatory mediators and cellular movement, and, in high concentrations, may perturb biomembranes (Table 7) [220, 226]. UDCA, similar to its previously discussed beneficial properties, prevents EMT in pancreatic adenocarcinoma cell lines and, therefore, has antineoplastic properties (Table 5) [227].

Colorectal carcinoma (CRC)

The western diet has tumor promoting activity associated with elevated concentrations of colonic BA (mainly LCA and DCA) and increased fecal BA levels, as detected in samples from CRC patients [228]. In animals, a high-fat diet stimulates bile discharge and results in elevated BA levels in the colon [229]. Moreover, cholecystectomy, through prolonging BA exposure of the intestinal mucosa, has been suggested as a risk factor for the development of CRC [230].

BAs induce genetic instability marked by genomic instability and DNA damage via oxidative stress, defects in mitotic checkpoints, cell cycle arrest, improper chromosome alignment and multipolar division [231, 232]. Genomic instability caused by BAs is coupled with apoptosis resistance due to the degradation of p53 and the inhibition of caspase-3 activity [233]. Furthermore, secondary BAs perturb cell membranes and modulate signaling cascades [234, 235].

Table 7 Tumor promoter effects of bile acids in cancers

Cancer types	Cell lines	Concentration of bile acids	Effects of bile acids	Refs.
Breast cancer	4T1	DC (100 μM)	DC promotes survival of breast cancer cells by elevating *FLK-1* (KDR) and decreasing ceramide-mediated apoptosis of breast cancer progenitor cells	[341]
Cholangiocarcinoma	THLE-3	CDCA (100 μM) LCA (100 μM)	CDCA and LCA induce *Snail* and reduce E-cadherin expression and facilitate invasion and migration	[188]
	KMBC	TCDC, DC, GCDC (200 μM)	BAs participate in progression of cholangiosarcoma by activating EGFR and inducing *COX-2* expression via MAPK cascade	[342]
	human: HuCCT1, CCLP1, SG231, rat: BDE1, BDEspTDE$_{H10}$	TCA (100 μM)	TCA promotes cholangiosarcoma cell invasion via activation of S1PR2. TCA induces invasive growth of cells, upregulate *COX2* expression and PGE2 production through S1PR2 receptor	[96] [95]
	RMCCA-1	TLCA	TLCA induces cell growth through muscarinic acetylcholine receptor (mAChR) and EGFR/ERK1/2 signaling pathways	[106]
Colon cancer / Colorectal carcinoma	HT29, SW620	LCA (30 μM)	LCA induces expression of urokinase-type plasminogen activator receptor (uPAR) and enhances cell invasiveness via ERK1/2 and AP-1 pathway	[343]
	H508, SNU-C4	LCT (300 μM)	LCT interacts with M3 muscarinic receptor and increases cell growth	[105]
	HCT-8/E11, SRC transformed PCmsrc cells	LCA, CDCA, DCA (10 μM)	BAs stimulate cellular invasion, which was dependent on several signaling pathways, such as RhoA, Rac1, PI3K, PKC, MAPK, COX2 and FXR receptor	[344]
	Normal human colonic epithelial cells (HCoEpiC)	LCA, DCA (100 μM)	BAs promote colon cancer by inducing cancer stemness in colonic epithelial cells via modulating CHRM3 and Wnt/β-catenin signaling	[238]
	CaCo-2	LCA (26.6 μM)	LCA increases cell invasion through promoting matrix metalloproteinase 2 (MMP-2) secretion	[345]
	HCT116, HT29	LCA (20 μM), DCA (150 μM)	BAs promote colon carcinogenesis via regulation of Nur77-mediated cell proliferation and apoptosis	[190]
	HCT116	LCA (30 μM)	LCA induces IL-8 expression by activating Erk1/2 MAPK and suppressing STAT3 Metformin inhibits LCA induced IL-8 upregulation in HCT116 cells by suppressing ROS production and NF-kB activity	[346] [347]

Table 7 (continued)

Cancer types	Cell lines	Concentration of bile acids	Effects of bile acids	Refs.
	SNU-C4, H508	GLCA, GDCA, (50–300 μM), DCA (300–1000 μM)	BAs induce colon cancer cell proliferation which is CHRM3-dependent and is mediated by transactivation of EGFR	[348]
	HCT116	DC (0.3–0.5 mM)	DC induces mitochondrial oxidative stress and activates NF-kB in cancer cells through multiple mechanisms involving NAD(P)H oxidase, Na^+ /K^+ -ATPase, CYP, Ca^{2+} and the terminal mitochondrial respiratory complex IV	[349]
	HT-29	DCA (250 μM)	DCA promotes colorectal tumorigenesis through activation of EGFR-MAPK pathway and induction of calcium signaling	[350]
	HT-29, Caco-2, HCA7, HCT116	DCA (300 μM)	DCA activates COX-2 signaling and mediates proliferation and invasiveness of colorectal epithelial cancer cells	[351]
	HCT-116, HCA-7	DCA (300 μM)	DCA activates EGFR, MAPK and STAT3 signaling and induces tumorigenicity. DCA-induced activation of cellular signaling is mediated by the TGR5	[226]
	SW480, LoVo	DCA (5–50 μM)	DCA activates β-catenin signaling and promotes colon cancer cell growth and invasiveness	[352]
	HCT116, DLD-1, SW620	DCA (100–200 μM)	DCA induces upregulation of *EPHA2* in colon cancer cells, which is due to activation of ERK 1/2 cascade, and is p53-independent	[353]
	Caco-2	DCA (20 μM)	DCA stimulates colon cancer-cell migration via PKC	[354]
	Caco-2, HT-29	DC < 20 μM > 100 μM	Low-dose (< 20 μM) DC stimulates colon cancer cell proliferation, while high dose (> 100 μM) induces apoptosis in colon cancer cells	[355]
	HCT116	DCA (250 μM)	DCA stimulates pro-apoptotic and anti-apoptotic signaling pathways; sensitivity to DCA induces apoptosis can be modulated by the ERK/MAP kinase	[356]
	HCT116	DCA (200 μM)	DCA suppresses p53 by stimulating proteasome-mediated degradation of p53. DCA suppression of p53 is mediated by stimulating the ERK signaling pathway	[357]

Table 7 (continued)

Cancer types	Cell lines	Concentration of bile acids	Effects of bile acids	Refs.
	HM3	DCA (200 μM)	DCA upregulates *MUC2* transcription via multiple pathways involving activation of EGFR/PKC/Ras/Raf-1/MEK1/ERK/CREB, PI3/Akt/IKKB/NF-κB and p38/MSK1/CREB while DCA induced *MUC2* transcription is inhibited by JNK/c-Jun/AP-1 pathway	[358]
	HT-29	DCA (50–500 μM)	DCA induces oxidative stress and upregulates Thioredoxin reductase (TR) mRNA	[359]
	HT-29	DCA (50–200 μM)	DCA activates anti-apoptotic effect of NF-κB and induces IL-8 expression	[360]
	murine model	/	DCA and tauro-β-muricholic acid have major role in promoting cancer stem cell proliferation	[361]
Endometrial cancer	Ishikawa	CDCA (5 μM)	CDCA enhances cyclin D1 expression and promotes cancer cell proliferation through TGR5-dependent CREB signaling activation	[362]
Gastric cancer	Normal human gastric epithelial cell: GES-1	CDCA, DCA (200 μM)	BAs upregulate *CDX2* and *MUC2* expression via activation of FXR/NF-κB signaling pathway	[176]
	Normal human gastric epithelial cell: GES-1 gastric carcinoma cell lines (AGS, MKN45, BGC823, AZ521, N87, KATO III, SGC7901)	DCA (200 μM)	DCA activates TGR5-ERK1/2 pathway following induction of *HNF4α* expression, which further promotes metaplasia markers expression through direct regulation of KLF4 and CDX2	[181]
	AGS	DCA (50 μM)	DCA activates ERK1/2, MAPK and causes a TGR5-dependent trans-phosphorylation of the EGFR	[182]
	MKN74, MKN45	TLCA, TDCA (100 μM)	Activation of TGR5 by BAs promotes EMT process	[183]
	MKN45, AGS	DCA (100 μM)	DCA enhances *COX-2* expression via CDX1 and SHP	[178]
	MKN28, MGC803, SGC7901	DCA, CDCA (100 μM)	BAs under acidic conditions increase *TERT* expression by activation of c-MYC transcription	[179]

Table 7 (continued)

Cancer types	Cell lines	Concentration of bile acids	Effects of bile acids	Refs.
Hepatocellular carcinoma (HCC)	HuH-7, Hep3B	CDCA (100 μM)	CDCA induces EMT phenotypes in HCC cells via FXR	[189]
	Huh7, Hep3B and mouse primary hepatocytes (MPH)	LCA (20 μM), DCA (150 μM)	BAs promote liver carcinogenesis via regulation of Nur77-mediated cell proliferation and apoptosis	[190]
	Huh-BAT, SNU-761, SNU-475	DCA (100 μM)	DCA induces ER stress accelerated apoptosis in NTCP-positive HCC cells under hypoxic conditions, while DCA induces COX-2-dependent *IL-8* overexpression in NTCP-negative human HCC cells mediated by NFκB	[191]
	SMMC7721, Huh7	GCDC (200 μM)	GCDC promotes HCC invasion and migration by AMPK/mTOR dependent autophagy activation	[363]
	HepG2, BeL-7402, Huh7	GCDA (100 μM)	GCDA contributes to the development of HCC and chemoresistance by inducing MCL1 phosphorylation at T163 via ERK1/2, which stabilizes MCL1 protein to enhance its antiapoptotic function	[364]
	HepG2, Bel7402, QGY7703, SMMC7721, Huh7	GCDA (100 μM)	GCDA induces survival and chemoresistance of liver cancer cells through activation of BCL-2 by phosphorylation	[365]
	LX2, Huh7	DCA (20–80 μM)	DCA causes HSC senescence by modulating malignant behavior of HCC	[192]
	HepG2	TCDCA (100 μM)	TCDCA promotes liver cancer via down-regulation of the expression of tumor suppressor gene CEBPα	[366]
	Hep3B	LCA, CDCA (100 μM)	BAs increase cancer invasiveness in human hepatocellular carcinoma and cholangiocarcinoma through repressing E-cadherin and inducing Snail expression	[188]
Hypopharyngeal squamous cell carcinoma	FaDu cells	CA (100 μM), CDCA (100 μM), DCA (100 μM), LCA (20 μM)	BAs induce EMT markers *TGFβ1* and *MMP-9* in vitro	[367]
Non-small cell lung cancer (NSCLC)	H1975, H1299, PC-9, A549	DCA (20–40 μM)	DCA increases cell migration and invasion through a TGR5-dependent way. TGR5 promotes NSCLC cell proliferaton and migration via JAK2/STAT3 pathway	[368]
Oesophageal adenocarcinoma (EAC) / Barett's esophagus	HET-1A	DCA (300 μM), CDCA (300 μM), LCA (25 μM)	BAs activate the unfolded protein response and induce Golgi fragmentation via a src-kinase dependant mechanism contributing to cancer progression in the oesophagus	[369]

Table 7 (continued)

Cancer types	Cell lines	Concentration of bile acids	Effects of bile acids	Refs.
	SEG-1, BE3 CPC-A, CPC-C	CDCA (100–300 μM)	CDCA induces activation of IKKβ/TSC1/mTOR pathway leading to enhanced EAC cell proliferation	[370]
	OE-33, SK-GT-4	CDCA (100 μM)	CDCA stimulates the development of human esophageal cancer by promoting angiogenesis via the COX2 pathway	[371]
	HET-1A, QH	DCA (100–300 μM)	DCA promotes development of gastroesophageal reflux disease and Barrett's oesophagus by modulating integrin-α_v trafficking	[372]
	OE19, OE33	DCA (100, 300 μM)	DCA inhibits Notch signaling pathway with induction of *CDX2* gene expression contributing to the formation of Barrett's oesophagus	[373]
	OE19	DCA (300 μM)	DCA shows carcinogenic effects via upregulation of *COX2*, *CDX2* and downregulation of DNA repair enzymes (*MUTYH, OGG1*)	[374]
	OE-19, OE-33	TCA (100 μM)	TCA promotes invasive growth of EAC cells via S1PR2	[165]
	OE19	DCA (50–300 μM)	DCA promotes the progression of EAC by inducing inflammation	[375]
	HET-1A, CP-A, CP-C, OE33	DCA (0.2 mM)	DCA increases *Beclin-1/BECN1* expression and autophagy but chronic exposure to BAs leads to decreased *Beclin-1/BECN1* expression and autophagy resistance	[376]
	BAR-T	DCA (250 μM)	DCA induces ROS/RNS production, which causes genotoxic injury, and simultaneously induces activation of the NF-κB pathway, which enables cells with DNA damage to resist apoptosis	[377]a
	OE33, KYSE-30	DCA (100–200 μM)	DCA is genotoxic to oesophageal cells at neutral and acid pH through the induction of ROS	[378]
		DCA ≥ 100 μM	DCA induces DNA damage and NF-kB activation (at doses of 100 uM and higher in oesophageal OE33 cells)	[379]
	SEG-1, SKGT-4, CP-A	CDCA, DCA (100 μM, 200 μM)	BAs induce CREB and AP-1-dependent *COX2* expression in Barrett's oesophagus and EAC through ROS-mediated activation of PI3K/AKT and ERK1/2	[380]

Table 7 (continued)

Cancer types	Cell lines	Concentration of bile acids	Effects of bile acids	Refs.
	Het-1A, SEG-1, HKESC-1, HKESC-2	DCA (100–1000 μM)	DCA upregulates both intestinal differentiation factor *CDX2* and goblet cell-specific gene *MUC2* in normal esophageal and cancer cell lines suggesting the involvement of DCA in the pathogenesis of Barrett esophagus	[381]
	SEG-1 cells	DCA (50–300 μM)	DCA induces *MUC2* overexpression by activation of NF-kB transcription through a process involving PKC-dependent but not PKA, independent of activation of MAP kinase	[382]
	SKGT-4	DCA (300 μM)	DCA induces *COX2* expression via Erk1/2, p38-MAPK and AP-1-dependent mechanisms	[383]
	OE33 cells	DCA (250 μM)	DCA promotes the expression of *KLF4* and *OCT4* via IL-6/STAT3 signaling pathway. DCA has a malignancy-inducing effect on the transformation of EAC stem cells	[384]
	BAR-T, OA, FLO	TDCA (10^{-11} M)	TDCA induces cell proliferation through the upregulation of *NOX5*-S expression and ROS production mediated by activation of the TGR5 receptor	[164]
	OE33, FLO-1, Esc2	DCA (100 μM)	DCA enhances the aggressive phenotype of EAC cells with concomitant metabolic changes occurring via downregulation of *UCP2*	[385]

Table 7 (continued)

Cancer types	Cell lines	Concentration of bile acids	Effects of bile acids	Refs.
Pancreatic cancer	T3M4, HPAF, Capan-1	DCA, CDCA (5–100 μM)	BAs increase the tumorigenic potential of pancreatic cancer cells by inducing FXR/FAK/c-Jun axis to upregulate *MUC4* expression	[386]
	BxPC-3, AsPC-1, Capan-2	DCA (300 μM)	DCA activates EGFR, MAPK and STAT3 signaling and induces tumorigenicity. DCA-induced activation of cellular signaling is mediated by the TGR5	[226]

AKT Serine/Threonine Kinase 1, *AMPK* AMP-activated protein kinase, *AP-1* activator protein-1, *BA* bile acid, *Bcl-2* B-cell lymphoma 2, *Beclin-1/BECN1* Coiled-Coil Myosin-Like BCL2-Interacting Protein, *CDCA* chenodeoxycholic acid, *CDX1* Caudal Type Homeobox, *CDX2* Caudal Type Homeobox 2, *CEBPα* CCAAT/enhancer-binding protein alpha, *CHRM3* Muscarinic Acetylcholine Receptor M3, *COX2* cyclooxygenase-2, *CREB* cAMP response element-binding protein, *DC* Deoxycholate, *DCA* Deoxycholic acid, *EAC* Oesophageal adenocarcinoma, *EGFR* epithelial growth factor receptor, *EMT* epithelial-mesenchymal transition, *EPHA2* EPH Receptor A2, *ERK* extracellular signal-regulated kinase, *FAK/PTK2* focal adhesion kinase, *FLK1/KDR* Fetal liver kinase 1/Kinase Insert Domain receptor, *FXR* farnesoid X receptor, *GCDA* Glycochenodeoxycholate acid, *GCDC* Glycochenodeoxycholate, *GDCA* Glycodeoxycholic acid, *GLCA* Glycolithocholic acid, *HCC* hepatocellular carcinoma, *HNF4α* hepatocyte nuclear factor-4α, *HSC* hepatic stellate cells, *IKKβ/IKBKB* Inhibitor Of Nuclear Factor Kappa B Kinase Subunit Beta, *IL1* interleukin 1, *IL6* interleukin 6, *IL8/CXCL8* interleukin 8, *JAK2* Janus kinase 2, *JNK* c-Jun N-terminal kinase, *JUN* Jun Proto-oncogene, AP-1 Transcription Factor Subunit, *KLF4* Kruppel Like Factor 4, *LCA* Lithocholic acid, *LCT* Lithocholyltaurine, *mAChR* muscarinic acetylcholine receptor, *MAPK/MEK* mitogen-activated protein kinase, *MCL1* Induced myeloid leukemia cell differentiation protein, *MMP2* matrix metalloproteinase 2, *MMP9* matrix metalloproteinase-9, *MSK1/RPS6KA5* Nuclear Mitogen- And Stress-Activated Protein Kinase 1, *mTOR* mammalian/mechanistic target of Rapamycin, *MUC2* Mucin 2, *MUC4* Mucin 4, *MUTYH* MutY DNA Glycosylase, *MYC* Myc Proto-Oncogene Protein, *NF-κB* nuclear factor κB, *NOX5* NADPH Oxidase 5, *NR4A1/Nur77/TR3/NGFIB* Nuclear receptor subfamily 4 group A member 1, *NSCLC* non-small cell lung cancer, *NTCP/SLC10A1* sodium/taurocholate cotransporting polypeptide, *OCT4/POU5F1* Octamer-Binding Transcription Factor, *OGG1* 8-Oxoguanine DNA Glycosylase, *p38/MAPK14* p38 MAP Kinase, *PGE2* prostaglandin E2, *PI3K* Phosphatidylinositol 3-kinase, *PKA* protein kinase A, *PKC* protein kinase C, *Rac1* Rac Family Small GTPase 1, *Raf1* Proto-Oncogene, Serine/Threonine Kinase, *RhoA* Ras Homolog Family Member A, *RNS* reactive nitrogen species, *ROS* reactive oxygen species, *S1PR2* sphingosine 1-phosphate receptor 2, *SHP* Small heterodimer partner, *STAT* signal transducer and activator of transcription, *TCA* Taurocholic acid, *TCDC* Taurochenodeoxycholate, *TCDCA* Taurochenodeoxycholic acid, *TDCA* Taurodeoxycholic acid, *TERT* Telomerase Reverse Transcriptase, *TGF-β1* Transforming growth factor β-1, *TGR5/GPBAR1* G-protein-coupled bile acid receptor/Takeda-G-protein-receptor-5, *TLCA* Taurolithocholic acid, *TSC1* TSC Complex Subunit 1, *TXNRD1* Thioredoxin reductase 1, *UCP2* uncoupling protein-2, *uPAR/PLAUR* urokinase-type plasminogen activator receptor, *WNT* wingless-type MMTV integration site family

These all lead to colonic cell hyperproliferation, survival and invasion [236, 237].

The disruptive effect of BAs on colon epithelium evokes a compensatory cell renewal mechanism by inducing colonic epithelial cells to become cancer stem cells (CSCs) through β-catenin signaling (Table 7) [238]. In the CRC rodent model, both LCA and DCA have tumor promoter role on colonic crypt cells in the early stages of colon carcinogenesis [239]; however, it is important to note that BAs are suggested as tumor promoters, but not as mutagenic agents, since they can not induce tumor formation without a carcinogen/mutagen or a genetic alteration [240, 241]. It should be noted that DCA in low concentrations (0.05–0.3 mM) inhibit colonic cell proliferation via cell cycle block and apoptosis pathways (Table 6) [242].

UDCA can reduce the concentration of toxic BA in stool and blood [243] and has shown to protect against CRC by inhibiting CSC and CRC cell formation and proliferation [244, 245], oncogenic signaling pathways [246], as well as, inducing tumor surveillance [247] (Table 5). Moreover, UDCA can reduces CRC recurrence [248], as well as the risk to develop CRC in patients with pre-cancerous conditions, as colitis [249] or primary biliary cirrhosis [250].

Sustained inflammation was implicated in the pathogenesis of colorectal cancer due to barrier breach, and bacterial translocation leading to inflammation and neoplastic transformation of colonic epithelial cells [251–253]. TGR5 activation by UDCA and LCA may also exert anti-inflammatory responses through TLR4 activation or by reducing pro-inflammatory cytokine production in the colon that can decrease the frequency of developing CRC [254]. BAs can change the gut microbial community [255, 256], suggesting that BAs may also interfere with bacterial translocation.

Breast cancer

The BAs in the breast are of gut origin [257, 258]. Hepatic production of BA is reduced in breast cancer patients as marked by decreasing levels of serum and fecal BAs [7, 259]. Furthermore, bacterial conversion of BAs to secondary BAs is also suppressed, which is the most dominant in in situ and stage I patients [7]. The serum bile acid composition of breast cancer and benign breast disease patients is different; specifically, breast cancer patients had higher serum chenodeoxycholic acid levels and lower dihydroxy tauro-conjugated BA (Tdi-1) and sulfated dihydroxy glyco-conjugated bile acids (Gdi-S-1) [260]. Total fecal bile acid levels are lower in breast cancer patients as compared to controls [259]. LCA concentrations in the breast can be higher than the serum levels [261] (Table 6). Reports showed increased DCA levels in the serum [262] and the breast cyst fluid [263] of breast cancer patients.

LCA is an inhibitor of breast cancer cell proliferation (Table 6) [7, 258, 264]. However, the reports on DCA and UDCA are contradictory [7, 258, 262–264] in physiological concentrations, LCA tunes cancer cell metabolism towards a more oxidative state (through AMP-activated protein kinase (AMPK), PGC-1β and NRF1/NFE2L1) and induces mild oxidative stress through reducing NRF2 (nuclear factor erythroid 2-related factor 2, NFE2L2) expression and inducing Inducible nitric oxide synthase (iNOS) that reverts EMT, reduces VEGF expression, induces antitumor immunity and changes to cancer metabolism that culminates in reduced metastasis formation [7, 11]. In supraphysiological concentrations (> 1 μM) LCA inhibits fatty acid biosynthesis [10] and induces cell death [8–10, 265, 266]. LCA does not exert antiproliferative effects in its tissue reference concentrations on non-transformed primary fibroblasts [7]. LCA exerts its antineoplastic effects through the TGR5 [7] (Table 6).

CDCA in supraphysiological concentrations induces MDRs through FXR [265] and modulates estrogen and progesterone receptor-mediated gene transcription [267]. Furthermore, CDCA inhibits tamoxifen-resistant breast cancer cell proliferation through the activation of the FXR receptor [268] (Table 6). In contrast to that, a report by Journe and colleagues [269] showed that FXR activation has a positive correlation with estrogen receptor expression and luminal characteristics, as well as supported cancer cell proliferation.

Prostate cancer

Among the BAs LCA, UDCA and CDCA exerted antiproliferative effects in prostate cancer. Activation of FXR by CDCA inhibits proliferation of prostate cancer cells, reduces lipid anabolism via inhibiting Sterol Regulatory Element Binding Transcription Factor 1 (SREBF1) [270] and induces the expression of the tumor suppressor phosphatase and tensin homolog (PTEN) [271] (Table 6). Interestingly, FXR signaling also controls androgen metabolism in prostate cancer cells, its activation reduces the expression of UDP-glucuronosyltransferase (UGT) 2B15 and UGT2B17 within cells and causes a reduction of androgen glucuronidation [272]. Similar to CDCA, LCA has antiproliferative effects in prostate cancer and induces apoptosis, endoplasmic reticulum stress, autophagy and mitochondrial dysfunction [9, 273] (see Table 6). UDCA induces death receptor-mediated apoptosis in human prostate cancer cells [274] (Table 5).

Ovarian cancer

In the serum of ovarian cancer patients, 3b-hydroxy-5-cholenoic acid, GUDCA, DCA and TCDCA levels decreased [275, 276]; importantly, taurochenodeoxycholic acid levels decreased in early-stage epithelial ovarian cancer [276]. Zhou and colleagues have shown that sulfolithocholylglycine

and TCA showed changes in the serum of ovarian cancer patients [277]. Changes to the BA pool are so characteristic that Guan and colleagues suggested [278] a set of 12 BAs, including glycolithocholic acid, to be used as markers to separate healthy controls from ovarian cancer patients.

The available studies assessed the effects of BAs at supra-physiological concentrations. These concentrations of BAs are cytotoxic and induce apoptosis likely due to changes to membrane damage [279, 280] that is unlikely at physiological concentrations of BAs [7]. DCA can modulate the expression of breast cancer type 1 susceptibility protein (BRCA1) and the estrogen receptor and, through these, can control drug sensitivity of ovarian cancer cells (Table 6) [281]. Furthermore, cholylglycinate interferes with the transport of cisplatin [282] and TCDC sensitizes ovarian carcinoma cells to doxorubicin and Mitomycin [280].

LXR [283–285], PXR [286], VDR [287–296] or CAR [297, 298] activation was shown to exert protective features against ovarian cancer, similar to BA-elicited effects suggesting that BAs may have a more profound role in protecting against ovarian cancer. These protective effects involved the suppression of proliferation [283, 284, 286], invasion [291], EMT [288], de novo fatty acid biosynthesis [295], the proportions of the cancer stem cell population [289], and the improvement of the efficacy of chemotherapy [285, 297, 298] culminating in better patient survival [292, 293]. Conflicting with these observation on report provided evidence that under certain conditions PXR may support proliferation [299]. BAs can influence the expression and the activity of multiple PARP enzymes [300]; therefore, it is likely that BAs could modulate the efficacy of PARP inhibition that is a novel modality in the chemotherapy of ovarian cancer.

Conclusions

Primary and secondary BAs are long-standing players in carcinogenesis. Although these molecules were considered as initiators of neoplasias, recent advances have shown that the pro- or anticarcinogenic activity of BAs varies among neoplasias [301], most probably due to differences in the expression of BA receptors, transporters and cell-specific differences in the outcome of receptor activation. Key pathways activated in neoplasias by BAs are regulated by nuclear receptors, FXR, CAR, SHP, PXR, LXR and VDR and other membrane receptors such as S1PR2, TGR5, CHRM2 and CHRM3. They activate numerous downstream signaling pathways such as EGFR, STAT3, MAPK, HNF4α, NF-κB, TLR4, SOCS3 and β-catenin just to name some. Furthermore, BAs regulate all aspects of tumor development and progression, the EMT, invasion, metabolism, apoptosis, proliferation, senescence, immune environment and response to chemotherapy.

The effect of BAs on neoplasias also depends on the concentrations used in the studies. While in certain models BAs in low concentration have anti-cancer effects, in superphysiological concentrations BAs have pro-cancer effects. This phenomenon is related to their amphipathic structure and the activation of additional off-target pathways not tiggered at physiological concentration. At high concentrations, BAs may perturb membranes and activate signaling pathways that sense disturbance of membranes, such as PLA2 and PKC. At high concentrations, they are also toxic and activate the detoxifying pathways, which regulate the activity of transporters of steroid hormones and chemotherapeutics. Therefore, we would urge the community to carry out studies where the concentrations of BAs correspond to the reference concentrations established for the tissue or, as a proxy, to the serum reference concentrations. As a continuation of that, in the case of UDCA the therapeutic serum concentrations can also be used as a guide. These data are summarized in Table 1. Such studies would be invaluable to understand the (patho)physiological roles of BAs and would give a good frame for the therapeutic applicability.

Along the same lines, it is apparent that BAs can be considered as possible treatment options in certain cancers. Foremost, UDCA, that is a therapeutically available drug, has beneficial effects in multiple neoplasias (e.g. [227, 248, 302], Table 5) pointing towards the possibility for repurposing UDCA. The picture for other BAs is hazier due to frequent contradictions making it hard to outline applicability. However, before the application of BAs in neoplasias we would need to decipher the cross-talk between BAs and drug metabolism, the effect on drug efficacy and drug availability, and discover the possible adverse effects of BAs, that is currently largely missing. Moreover, it is tempting to consider the manipulation of the intestinal microbiome to affect the levels of selected secondary bile acids in humans. Finally, the modulators of BA receptors should be considered as therapeutic options as well. Given the emerging evidence on the potential anti-cancer effects of BAs, further studies are vital in order to develop novel therapeutic strategies using BAs.

Search strategy and selection criteria

References to this review were identified through the prior knowledge of the authors that was complemented by systematic search of PubMed by using the combinations “Prostate cancer AND (bile acid)”, “Gastric cancer AND (bile acid)”, “Hepatocellular carcinoma AND (bile acid)”, “Oesophageal cancer AND (bile acid)”, “(bile acid) receptors AND cancer”, “(bile acid) receptors AND prostate cancer”, “(bile acid) receptors AND gastric cancer”, “(bile acid) receptors AND hepatocellular carcinoma”, “(bile acid) receptors

AND oesophageal cancer", "(bile acid) AND ABC AND transporter", "(bile acid) AND SLC AND transporter", "(bile acid) AND SLCO AND transporter", "(bile acid) AND transport AND review", "Farnesoid X receptor (FXR) AND the cancer types assessed in the study", "Pregnane X receptor (PXR) AND the cancer types assessed in the study", "Constitutive androstane receptor (CAR) AND the cancer types assessed in the study", "Vitamin D receptor (VDR) AND the cancer types assessed in the study" "Liver X receptor (LXR) AND the cancer types assessed in the study", "Small heterodimer partner (SHP) AND the cancer types assessed in the study". Articles published in English were included with no restriction on publication date. All references were checked at Pub Peer, two papers were flagged ([215] and [156]), but when reviewing the reports we decided that the issues raised do not impact on the main message and kept the references.

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Declarations

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