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Bile acids regulation of cellular stress responses in liver physiology and diseases

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Abstract

Bile acids are physiological detergents and signalling molecules that are critically implicated in liver health and diseases. Dysregulation of bile acid homeostasis alters cell function and causes cell injury in chronic liver diseases. Therapeutic agents targeting bile acid synthesis, transport and signalling hold great potential for treatment of chronic liver diseases. The broad cellular and physiological impacts of pharmacological manipulations of bile acid metabolism are still incompletely understood. Recent research has discovered new links of bile acid signalling to the regulation of autophagy and lysosome biology, redox homeostasis and endoplasmic reticulum stress. These are well-conserved mechanisms that allow cells to adapt to nutrient and organelle stresses and play critical roles in maintaining cellular integrity and promoting survival. However, dysregulation of these cellular pathways is often observed in chronic liver diseases, which exacerbates cellular dysfunction to contribute to disease pathogenesis. Therefore, identification of these novel links has significantly advanced our knowledge of bile acid biology and physiology, which is needed to understand the contributions of bile acid dysregulation in disease pathogenesis, establish bile acids as diagnostic markers and develop bile acid-based pharmacological interventions. In this review, we will first discuss the roles of bile acid dysregulation in the pathogenesis of chronic liver diseases, and then discuss the recent findings on the crosstalk of bile acid signalling and cellular stress responses. Future investigations are needed to better define the roles of these crosstalks in regulating cellular function and disease processes.

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INTRODUCTION

Bile acids are one of the major constituents of bile that is formed in the liver and released into the small intestine.[1] Bile acids are synthesised exclusively in hepatocytes and secreted into biliary tract, where they form mixed micelles with cholesterol and phospholipids to prevent cholesterol precipitation and non-micellar bile acid damage to the bile duct epithelium.[1] In the small intestine, bile acids, together with phospholipids, form mixed micelles to help emulsify dietary lipids and fat-soluble vitamins to facilitate their absorption. In addition to these classic physiological functions, bile acids also act as signalling molecules by serving as the endogenous ligands of several nuclear receptors and cell surface G protein-coupled receptors.[1] These bile acid-activated receptors are abundantly expressed in the liver and gut that are exposed to high levels of bile acids, and other metabolically active organs and immune cells and regulate various aspects of cellular pathways in normal physiology and diseases, rendering them attractive therapeutic targets.[1] Dysregulation of bile acid homeostasis has been reported in cholestasis where impaired bile flow causes hepatobiliary bile acid toxicity, and other more prevalent chronic liver diseases including metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD). However, the roles and mechanisms of altered bile acid metabolism in MASLD and ALD are less well understood and the causative relationship between bile acid dysregulation and pathogenesis and progression of MASLD and ALD has not been well established. It is perceivable that altered bile acid metabolism in any disease condition can be simultaneously protective adaptation and pathogenic maladaptation. Due to the complex and broad cellular effects of bile acids, drug interventions that manipulate bile acid metabolism and signalling are often associated with therapeutic benefits and undesired treatment effects. While the physiological roles of bile acids in the regulation of lipid, glucose and energy metabolism have been well recognised, recent studies have revealed many new mechanisms linking bile acid signalling to cellular organelle functions, which will also be discussed in this review.

BILE ACID SYNTHESIS AND THE ENTEROHEPATIC CIRCULATION

Hepatocytes synthesise bile acids using cholesterol as the substrate.[1] Bile acid synthesis is a complex process involving many enzymatic reactions and can be classified into two pathways: the classic pathway and the alternative (acidic pathway) (figure 1). In the classic pathway, cholesterol first undergoes 7α hydroxylation mediated by the cholesterol 7α-hydroxylase (CYP7A1), a cytochrome P450 enzyme residing in the endoplasmic reticulum (ER). CYP7A1 is the rate-limiting enzyme in the classic bile acid synthesis pathway and its expression is subjected to bile acid feedback inhibition. In humans and many non-human primates, the classic pathway synthesises two primary bile acids: chenodeoxycholic acid (CDCA) and cholic acid (CA). In the alternative pathway, cholesterol is first hydroxylated at the C-27 position by the mitochondrial enzyme sterol 27-hydroxylase (CYP27A1) to produce 27-hydroxycholesterol. It is believed that the major product of the alternative pathway is CDCA. In both pathways, the bile acid synthesis intermediates undergo side chain shortening to produce 24-carbon bile acid molecules. In humans, the two primary bile acids CDCA and CA account for about 80% of total bile acid pool.

While the bile acid synthesis pathways and enzymes are well conserved in humans and mice, it is also known that in mouse livers CDCA is efficiently converted to muricholic acids (MCA), which make up about half of the total bile acid pool.[2] As a result, mouse bile acid pool contains only trace amount of CDCA.[2] Compared with CDCA, MCAs have an addition of either a 6α-OH or 6β-OH group, which renders them more hydrophilic than CDCA. Because of this, MCAs are also less cytotoxic at higher concentration and poor signalling molecules. In the presence of other hydrophobic bile acids, MCAs even act as a farnesoid X receptor (FXR) antagonist.[3] Although such species difference has been known for decades, the enzyme that mediates the 6-hydroxylation of CDCA to produce MCAs was only identified in 2016 to be cytochrome p450 2C70 (CYP2C70)[4] (figure 1). Mice lacking the *Cyp2c70* gene were largely devoid of endogenous MCAs,[4] suggesting that CYP2C70 is likely the sole C6-hydroxylase of CDCA with little enzyme redundancy in mice.

Newly synthesised bile acids are efficiently conjugated to one of the two amino acids glycine or taurine in hepatocytes. Therefore, unconjugated bile acids usually account for a very small portion of the total bile acids in the biliary tract. In human bile acid pool, the ratio of glycine-conjugates to taurine-conjugates is approximately 3:1. In contrast, mice almost exclusively use taurine to conjugate bile acids, leaving only trace amount of glycine conjugated with likely neglectable physiological significance.[2] The enzymes mediating the bile acid side chain amidation are bile acid-CoA ligase and bile acid coenzyme A:amino acid N-acyltransferase. Conjugation to amino acids reduces the pKa values of bile acids that improve their solubility in the gut lumen.

Bile acids circulate between the liver and intestine in a process called the enterohepatic circulation of bile acids (figure 2). In hepatocytes, the bile salt export pump (BSEP, ABCB11) mediates bile acid secretion into bile canaliculi.[5] In bile, bile acids form micelles with cholesterol and phospholipids, a critical process needed to prevent cholesterol precipitation and free bile acid damage to the bile duct epithelial cells. After release into the small intestine, bile acids are efficiently absorbed mostly in the terminal ileum via the apical sodium-bile acid transporter (ASBT).[6] It is believed that >90% of the bile acids are re-absorbed in the terminal ileum and transported back to the liver via portal circulation. In addition, the hepatocyte basolateral bile acid uptake is mediated by sodium taurocholate co-transporting polypeptide (NTCP)[7] and organic anion transporting polypeptide isoforms.[8] This process is also highly efficient and little bile acids enter the systemic circulation after the liver first-pass under normal physiology.[9] Primarily in the large intestine and to less extent in the terminal ileum, gut bacterial enzymes modify primary bile acids to produce secondary bile acids. In this process, the bacterial bile salt hydrolases (BSH) deconjugate bile acids, which can be further modified by bacterial enzymes with dehydroxylase and epimerase activity. Through these reactions, the primary bile acid CA is converted to deoxycholic acid (DCA) and CDCA is converted to lithocholic acid (LCA) or ursodeoxycholic acid (UDCA).[10] In mice, ω-MCA and other secondary bile acids can be produced from primary α-MCA and β-MCA. Some of the secondary bile acids are passively absorbed in the large intestine, transported to the liver to be conjugated, while the remaining majority are excreted in faeces. Because of this, the large intestine and faecal bile acids are predominantly in unconjugated forms due to efficient deconjugation by bacterial BSHs. DCA is the most abundant secondary bile acid in humans and mice and can account for

about 20% of the total bile acid pool. In contrast, only a small amount of UDCA and LCA is synthesised from CDCA in the gut. LCA is a highly hydrophobic and cytotoxic bile acid and is efficiently metabolised and excreted into faeces.

REGULATION OF BILE ACID SYNTHESIS AND TRANSPORT BY BILE ACID RECEPTORS

Many cellular effects of bile acids are mediated by bile acid-activated nuclear receptors and cell surface receptors. Bile acids were first identified as the endogenous ligands of the nuclear receptor FXR.[11] While hydrophobic primary and secondary bile acids including CDCA, CA, DCA and LCA activate FXR at physiological concentrations with EC50 values ranging ~10–50 μM, the hydrophilic bile acids UDCA and MCAs are poor FXR agonist. Furthermore, MCAs have been shown to antagonise FXR activation in mice.[3] Bile acids, mainly the highly hydrophobic and cytotoxic LCA, have also been shown to activate xenobiotic nuclear receptors, pregnane X receptor and vitamin D receptor, which in turn induce drug metabolism and bile acid detoxification enzymes.[12 13] Takeda G protein coupled receptor (TGR5) is well-characterised cell surface receptor activated by bile acids.[14] While FXR is highly expressed in hepatocytes and enterocytes that are routinely exposed to high concentration of bile acids, TGR5 is expressed in muscle, enterocytes and macrophages but not hepatocytes.[14] As discussed later, bile acid activation of FXR plays a key role in regulating bile acid synthesis and transport in the enterohepatic system. Activation of TGR5 has been shown to promote energy expenditure and insulin sensitisation via various mechanisms,[15 16] and modulate immune functions.[17] Another cell surface bile acid receptor is sphingosine-1 phosphate receptor 2 (S1PR2), which is activated by conjugated bile acids to increase the intracellular lipid mediator S1P signalling.[18] The role of bile acid signalling regulation of nutrient and energy metabolism has been reviewed elsewhere.[1]

Bile acid synthesis is under a tight feedback inhibition by bile acids, which is an important mechanism to maintain bile acid homeostasis under physiology and alleviate bile acid toxicity under pathological conditions. In hepatocytes, increased level of bile acids activates FXR, which induces a repressor small heterodimer partner (SHP) to inhibit CYP7A1 transcription.[19] In intestine enterocytes, increased bile acid concentration induces murine fibroblast growth factor 15 (FGF15), which is secreted into the blood circulation and inhibits CYP7A1 in hepatocytes by activating intracellular ERK signalling.[20] Human FGF19 is the ortholog of murine FGF15 and its expression is induced by FXR in both hepatocytes and enterocytes.[21] By acting as a bile acid sensing receptor in the enterohepatic system, FXR plays a major role in mediating bile acid feedback inhibition of bile acid synthesis.[22] In addition, hepatocyte FXR induces bile acid efflux transporter BSEP and inhibits basolateral bile acid uptake transporter NTCP. In the enterocytes, FXR activation inhibits apical bile acid uptake transporter ASBT and induces basolateral efflux transporter organic solute transporter α (OSTα) and OSTβ.[23 24] Therefore, FXR activation also helps reduce intracellular bile acids by limiting bile acid uptake and promoting bile acid secretion.

BILE ACID HEPATOBILIARY TOXICITY IN CHOLESTASIS

Cholestasis is defined as any pathological condition in which bile flow out of the liver is impaired. Cholestasis can result from mutations of genes encoding canalicular transporters (*ATP8B1, ABCB11* and *ABCB4)*, tight junction protein (*TJP2*) or *NR1H4* (FXR),[25] which are termed progressive familial intrahepatic cholestasis (PFIC). Acquired cholestasis can also result from immune-mediated destruction of small and large bile ducts (primary biliary cholangitis, primary sclerosing cholangitis), drug-induced hepatobiliary toxicity, pregnancy, gallstone, etc. Regardless of the underlying aetiology, the resulting intrahepatic accumulation of bile acids damages hepatocytes and biliary tract and is a major driver of cholestasis progression.

High concentration of hydrophobic bile acid exposure causes hepatocyte necrosis in vitro. Consistently, rodent models of cholestasis and human cholestasis patients show histological characteristics of hepatocellular necrosis. Because of the detergent property of hydrophobic bile acids, high concentration of bile acids typically seen under cholestasis conditions can disrupt plasma membrane integrity via solubilising plasma membrane lipids and impairing membrane protein function.[26] Even without obstruction of bile flow, the detergent property of bile acids needs to be quenched through mixed micelle formation with phospholipids and cholesterol to reduce their direct interaction with bile duct epithelial cells. The importance of this process is best demonstrated in PFIC-3, where defective phospholipid secretion into bile due to *ABCB4* mutation destabilises micelles, resulting in non-micellar bile acid-mediated damage to the bile duct epithelium, cholesterol crystal formation in the bile duct and intrahepatic cholestasis. In addition, high concentrations of bile acids have been shown to cause mitochondria dysfunction and cellular ATP depletion, preceding hepatocyte necrosis.[27]

Bile acids also cause apoptosis in cultured hepatocytes. A few studies showed that the pro-apoptotic effect of hydrophobic bile acids may be initiated via activation of intracellular stress kinases including c-Jun N-terminal kinase (JNK), protein kinase C and the epidermal growth factor receptor, and ligand-independent Fas receptor activation, leading to mitochondrial permeability transition pore opening, cytochrome c release and caspase activation in cultured hepatocytes.[28] The mechanism by which bile acids promote apoptosis is not fully clear. Blocking transporter-mediated conjugated bile acid uptake into hepatocytes also attenuated conjugated bile acids-mediated hepatocyte apoptosis,[29] suggesting that bile acids can initiate apoptotic signalling cascade within cells. Consistent with this model, studies suggested that intracellular bile acids impaired mitochondrial bioenergetics function and membrane potential and promoted mitochondrial reactive oxygen species generation.[30] Other studies showed that bile acids caused mitochondrial membrane depolarisation, mitochondrial permeability transition pore and cytochrome c release, leading to cell death via activation of the intrinsic apoptotic pathway.[31] Activation of S1PR2 leads to intracellular activation of JNK, AKT and ERK signalling, which has been shown to promote cholangiocyte proliferation and implicated in cholangiocarcinoma.[32 33] Bile acid activation of S1PR2 has also been implicated in bile acid-induced hepatocyte apoptosis.[34] TGR5 is not expressed in hepatocytes but is expressed at high levels in cholangiocytes and Kupffer cells in liver. Activation of TGR5 promotes cholangiocyte proliferation and protects against

bile acid hepatotoxicity.[35 36] TGR5 in Kupffer cells also play an anti-inflammatory role in cholestasis.[17] Recently, new evidence suggests that cholestasis and bile acid-induced cell death may also be linked to cellular necroptosis.[37] The underlying mechanisms and potential crosstalk with other types of cell death remain to be delineated.

It should be noted that although different types of cell death markers have all been detected in cholestasis human livers and experimental murine cholestasis livers, direct bile acid toxicity to hepatocytes were mainly demonstrated in cultured hepatocytes. Therefore, it is presumed that high bile acid-mediated hepatocyte cell death may trigger initial liver injury but the relative contribution of direct bile acid-induced hepatocyte death in chronic cholestasis remains unclear. This is mainly because all forms of cholestasis are associated with inflammatory infiltration.[38] Dead or injured hepatocytes release chemokines and damage-associated molecular pattern molecules that propagate inflammation. In response to biliary injury, bile ducts usually undergo hyperplasia, a phenomenon called ductular reaction.[39] There is evidence suggesting that high levels of bile acids cause biliary injury and promote cholangiocyte proliferation.[40] In chronic cholestasis conditions including human primary biliary cholangitis and murine models of cholestasis, some cholangiocytes also exhibited senescence phenotype,[41] which is characterised with cell cycle arrest and loss of cellular proliferative capacity.[42] Senescent cells have been found to commonly be associated with a senescence-associated secretory phenotype, characterised by increased secretion of proinflammatory cytokines and chemokines that modulate the extracellular environment and exacerbate inflammation and biliary injury.[43] S1PR2 is expressed in cholangiocytes and mediates cholangiocyte proliferation in response to conjugated bile acids.[44] Knockout (KO) or pharmacological inhibition of S1PR2 attenuated cholestasis liver injury, suggesting that S1PR2 also mediates bile acid hepatotoxicity in cholestasis.[44 45] Macrophages infiltrated around the portal area are also a major source of hepatic cytokines during cholestasis.[46] Neutrophil infiltration has also been suggested to play important roles in hepatocyte cell death in cholestatic liver injury.[47] These findings suggest that various direct and indirect mechanisms contribute to bile acid-dependent cellular injury in cholestasis, and interventions that target cell death pathways are unlikely to be effective in slowing cholestasis progression without addressing the underlying bile acid toxicity.

BILE ACID HEPATOTOXICITY IN MASLD AND ALD

Altered bile acid metabolism has been reported in patients with MASLD and ALD and experimental models. Compared with cholestasis, the roles of bile acids in the pathogenesis of MASLD and ALD are far from clear. Bile acids signalling activation of FXR and TGR5 have been shown to improve lipid and glucose homeostasis, insulin sensitivity and inflammation.[1] These studies demonstrated key roles of bile acids in maintaining metabolic homeostasis under normal physiology, which serves as the molecular basis for developing FXR and TGR5 agonists for treating MASLD. However, it has been increasingly recognised that patients with MASLD often had elevated circulating bile acids and possibly intrahepatic bile acid retention.[48 49] In bariatric surgery, postoperation elevation of circulating bile acids are generally thought to contribute to the rapid improvement of insulin sensitivity.[50] However, whether elevated circulating bile acids play a beneficial role in slowing disease progression or is merely a marker of liver injury in MASLD or ALD is still not clear.

Histological signs of bile acid-induced hepatobiliary injury have been reported in MASH, and alcohol hepatitis and viral hepatitis.[51 52] It is perceivable that chronic inflammation likely contributes to hepatobiliary dysfunction and rendering hepatocytes and bile duct epithelial cells more susceptible to bile acid toxicity. Other possible molecular mechanisms underlying these hepatic bile acid changes in the MASLD liver are still not well delineated. Particularly, it remains to be determined if increased circulating bile acids could be a result of increased total bile acid pool in the enterohepatic circulation, altered gut bile acid absorption, decreased basolateral bile acid uptake in liver sinusoids or basolateral bile acid efflux due to impaired biliary bile acid secretion in MASLD. Some studies have suggested that hepatic bile acid accumulation may contribute significantly to hepatic inflammation and injury in patients with chronic liver diseases,[48 49 52] which can be supported by the known role of bile acids in inducing cytokine and chemokine expression and stellate cell activation in mice.[46] Because human bile acid pool is more hydrophobic, intrahepatic retention of bile acids may have a more detrimental effect. Therefore, many of the pathogenic mechanisms of bile acid toxicity in cholestasis may also be relevant in MASLD. Consistently, reduction of hepatic bile acid load was thought to contribute to the beneficial effects of the FGF19 analogue in MASLD.[53] A strong reduction of bile acid pool by concomitant inhibition of hepatic bile acid synthesis and intestine bile acid absorption has also been shown to alleviate MASLD, especially liver fibrosis, in mice.[54] In clinical trials, FGF19 analogue has demonstrated beneficial effect but ASBT inhibitor treatment was largely ineffective in human patients with MASLD.[55 56] FGF19 analogue inhibits hepatic de novo bile acid synthesis. ASBT inhibitor blocks intestine bile acid absorption and induces compensatory induction of de novo bile acid synthesis. The effect of these interventions on hepatic bile acid load in human patients is still not known.

Elevated circulating bile acids has also been reported in patients with ALD.[51] Serum bile acid levels positively correlated with ALD severity, suggesting that liver injury may be a potential cause of serum bile acid elevation.[51] However, bile acid pool size was increased in experimental ALD model,[57] which implies that ethanol metabolism in the liver and gut may regulate bile acid metabolism via undetermined mechanisms. Interestingly, Fxr KO mice had higher susceptibility to alcohol-induced liver injury.[58] These findings suggest that either FXR plays a protective role in ALD, or a secondary increase of tissue bile acids in Fxr KO mice synergizes with ethanol toxicity to driver ALD progression. In support of a protective role of FXR activation, studies have shown that FXR activation and FGF19 overexpression improved hepatic steatosis and inflammation in ethanol-fed mice.[51 59] On the other hand, blocking intestine bile acid uptake by ASBT inhibitor also appeared to be beneficial in ethanol-fed mice.[60] These treatments reduce hepatic bile acids. To date, the efficacy of bile acid targeting agents in ALD has not been tested in human clinical trials. Unlike cholestasis, bile acid hepatobiliary toxicity is not the primary cause of pathogenesis in MASLD and ALD, but therapeutics that can reduce hepatic bile acid load may have added beneficial effects in advanced disease stage where the hepatic ability to maintain bile acid homeostasis is impaired.

BILE ACID SIGNALLING CROSSTALK WITH THE AUTOPHAGY-LYSOSOME PATHWAY

Autophagy is a lysosome-dependent cellular degradation pathway[61] (figure 3). In this process, autophagosomes, double membrane vesicles, engulf and transport the cargoes to endosomes/lysosomes via vesicle fusion where the autophagy substrates are degraded by lysosome enzymes. Autophagy is generally considered a cytoprotective mechanism because it mediates the turnover of obsolete proteins and damaged organelles to help maintain cellular integrity. In addition, autophagy is also considered part of the cellular catabolic metabolism by degrading macronutrients.[62] As such, cellular energy status has a major impact on autophagic activity in most cells. Autophagy is induced in response to nutrient deprivation and fasting and repressed on energy excess. It is now known that the mechanistic target of rapamycin (mTOR), which is activated on cellular nutrient abundance and by extracellular nutrient/growth factors, is one of the most potent repressor of autophagy activity.[62] In contrast, AMPK activation on nutrient scarce promotes autophagy in many cell types studied so far.[63]

Impaired autophagy has been reported in many chronic liver diseases including cholestasis[64] and fatty liver.[65] Mice with hepatic autophagy gene *Atg5* or *Atg7* deletion lack hepatic autophagy activity and developed hepatic injury accompanied by elevated bile acids in the liver and blood, ductular reaction and impaired FXR activity,[66] and impaired hepatic autophagy has been suggested to contribute to liver injury in cholestasis.[67] Although the roles and mechanisms of the bile acid and autophagy crosstalk is still incompletely understood, studies in the past few years have shed light on the mechanisms by which bile acid signalling regulates autophagy activity in liver.

It is well known that circulating bile acids and FGF15/19 rapidly increased during the postprandial state in humans and mice.[68 69] It is suggested that postprandial elevation of bile acids synergizes with other endocrine hormones such as insulin to regulate hepatic metabolic switch, including suppression of hepatic glucose production and stimulation of hepatic protein synthesis.[70 71] Consistently, both bile acid-activated FXR and bile acid-induced FGF15/19 have been shown to suppress gluconeogenic gene expression in livers. Interestingly, bile acid-activated FXR has also been shown to repress autophagy genes resulting in reduced cellular autophagy flux.[72] FXR was also reported to induce Rubicon, a repressor of autophagosome maturation.[73] Furthermore, FGF15/19 was reported to inhibit autophagic flux in hepatocytes.[74] The transcription factor EB (TFEB), a member of the basic helix-loop-helix leucine zipper family of transcription factors,[75] has been demonstrated to act as a master inducer of genes involved in autophagy and lysosome biogenesis, and its transcriptional activation is regulated by a cytosol-nucleus shuttling mechanism that is inhibited by mTOR. Activation of mTOR causes phosphorylation of TFEB, which retains TFEB in the cytosol. During fasting or starvation, TFEB is dephosphorylated and subsequently translocate to the nucleus to transcriptionally induce a network of genes to promotes autophagy flux and lysosome biogenesis.[76 77] Consistently, amino acid starvation, which causes mTOR inactivation, causes strong TFEB nuclear translocation. TFEB is also activated under conditions of lysosome stress/impairment, which results

in TFEB activation to promote cellular lysosome biogenesis as an adaptive response. It is known that lysosomes play a key role in cholesterol metabolism and intracellular trafficking. However, disease conditions where cholesterol accumulates in the lysosomes cause lysosome dysfunction. lysosomal cholesterol accumulation has also been shown to activates TFEB, which stimulates lysosome biogenesis and bile acid synthesis to counter cellular cholesterol accumulation.[78] Interestingly, bile acid-induced FGF15/19 also activates mTOR to inhibit TFEB. In mouse model of fatty liver disease, blocking intestine bile acid absorption by bile acid sequestrant treatment has been shown to induce hepatic autophagy,[79] which may play a beneficial role in antagonising hepatic steatosis. Bile acid sequestrant also improves cholestasis liver injury by reducing hepatic bile acid load. The effect of bile acid sequestrant on hepatic autophagy activity in cholestasis models has not been reported. Taken together, new studies have revealed mechanisms by which bile acid-activated cellular pathways inhibit autophagic activity in hepatocytes. From a physiological perspective, the regulation of hepatic autophagy by bile acid and FGF15/19 is consistent with the cellular function of autophagy in maintaining cellular energy homeostasis as part of the cellular catabolic metabolism. However, bile acid suppression of autophagy during cholestasis causes cellular maladaptation in the presence of organelle damage, which contributes to liver injury.

BILE ACID REGULATION OF HEPATIC SULFUR AMINO ACID METABOLISM AND ANTIOXIDANT DEFENSE

Cholestasis liver injury is associated with redox imbalance and elevated oxidative stress. It is also shown that hepatic glutathione synthesis capacity is diminished during chronic cholestasis.[80] Interventions that targeting the glutathione antioxidant defence mechanisms, such as SAMe and N-acetylcysteine supplementation, have been shown to alleviate liver injury.[80 81] These interventions are thought to provide hepatoprotective effect in cholestasis at least in part via enriching hepatic sulfur amino acid cysteine to promote hepatic glutathione synthesis capacity. Recent studies have revealed that bile acid signalling crosstalks with hepatic sulfur amino acid metabolism, which is closely linked to hepatic antioxidant defence mechanism (figure 4). The sulfur amino acids methionine and cysteine support various cellular synthesis pathways including the synthesis of protein, S-adenosyl-methionine (SAMe), glutathione, taurine and sulfate.[82] Via the methionine cycle and transsulfuration pathway, methionine is used to synthesise the universal methyl donor SAMe and further serves as a major source of cellular cysteine synthesis. Cysteine is one of three amino acids used to synthesise the major antioxidant glutathione, and its cellular availability is a major determinant of cellular glutathione synthesis capacity. Although all mammalian cells can synthesise glutathione, sulfur amino acid metabolism is highly active in hepatocytes and many sulfur amino acid metabolising enzymes are expressed at significantly higher levels in hepatocytes than other cell types. Cysteine is prone to oxidation, and at high levels, cysteine may also cause oxidative stress and cytotoxicity in certain cell types.[82] Excess cysteine is incorporated into glutathione, which serves as a cysteine reservoir. In addition, cysteine dioxygenase type-1 (CDO1), which is highly expressed in hepatocytes, catalyses the irreversible conversion of cysteine to cysteine sulfinic acid, which is the major cellular cysteine elimination mechanism. Cysteine sulfinic

acid is further used by cysteine sulfinic acid decarboxylase (CSAD) to synthesise taurine, which is used to conjugate bile acids. Liver uptakes a significant amount of circulating cysteine and express high levels of CDO1, and therefore is a major organ that regulates cysteine catabolism.

The bile acid crosstalk with sulfur amino acid metabolism was first reported in a study where bile acids and FXR were shown to inhibit CSAD that mediates taurine synthesis.[83] [84] This finding suggested that de novo bile acid synthesis and hepatic production of taurine, which is used for bile acid conjugation, was coordinately regulated by bile acids. However, mice lacking CDO1 and therefore taurine synthesis only in liver did not show defective bile acid conjugation due to compensation by extrahepatic sources of taurine.[85] Instead, these mice showed elevated hepatic cysteine and glutathione, presumably due to reduced cysteine catabolism. Another study employing metabolomics approach revealed that mice treated with bile acid sequestrant cholestyramine, which caused a significant reduction of bile acid pool and signalling, showed significant hepatic cysteine and glutathione depletion, which was attributed to induction of hepatic CDO1 expression.[86] This led to the discovery that bile acids and FXR also inhibit hepatic CDO1 expression via a mechanism that depends on SHP induction.[86] Unlike CSAD, which only mediates cysteine sulfinic acid conversion to taurine, CDO1 mediates the first and irreversible catabolism of cysteine. As a result, induction of CDO1 by cholestyramine in mice significantly reduced hepatic cysteine availability and impaired hepatic glutathione synthesis on acetaminophen overdose-induced glutathione depletion,[86] while mice with hepatic CDO1 deletion were less sensitive to acetaminophen hepatotoxicity due to enhanced glutathione synthesis.[87] Given that hepatic taurine synthesis does not seem to be an essential process required to maintain overall taurine homeostasis,[85] bile acid inhibition of hepatic cysteine catabolism may play a physiological role in preserving cellular cysteine availability and directing cysteine to other cellular synthesis pathways such as synthesis of glutathione, protein and coenzyme A.[88] However, because CDO1 and CSAD expression is under bile acid and FXR inhibition to limit the amount of cysteine used to synthesise taurine under basal physiological condition, further inhibition of this pathway by bile acids or FXR agonists probably cannot further enrich hepatic cysteine availability by a significant extent. As such, bile acid suppression of CDO1 and CSAD under cholestasis is not expected to significantly compensate for hepatic glutathione depletion and oxidative stress.[86] Genetic deletion of *Fxr* in mice increased the susceptibility to cholestasis liver injury.[89] FXR mutation in humans caused *PFIC*-5.[25] It remains to be determined if hepatic CDO1 induction under FXR loss of function may contribute to impaired glutathione synthesis to promote oxidative stress that exacerbates cholestasis liver injury.

BILE ACIDS AND ER STRESS IN CHOLESTASIS LIVER INJURY

Impaired ER function can lead to accumulation of unfolded or misfolded proteins, a cellular condition termed ER stress.[90] In response to protein misfolding and ER stress, cells activate unfolded protein response (UPR), which consists of three downstream branches activated by the ER stress sensors inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 and protein kinase RNA-like ER kinase.[90] These ER stress sensors activate cellular adaptation to ER stress by reducing ER protein misfolding and de novo protein synthesis to maintain cellular integrity and survival. However, prolonged unresolved ER stress eventually

leads to cell cycle arrest and apoptosis, which is also mediated in part by the UPR signalling cascade. It has been reported that cholestasis is associated with elevated ER stress markers.[91] Treating hepatocytes with hydrophobic bile acids at high concentrations caused ER stress.[92] The hydrophilic bile acid UDCA has been shown to alleviate chemical induced ER stress in liver cells.[93] UDCA is non-cytotoxic and does not activate known bile acid signalling receptors, and its antagonism of ER stress may be mainly attributed to its chemical chaperon activity.[94] In mice lacking CCAAT/enhancer-binding protein (C/EBP) homologous protein, a key component in ER stress-mediated apoptosis, apoptosis and liver injury were attenuated on bile duct ligation.[95] It was reported that mice lacking XBP1 were more susceptible to bile acid hepatotoxicity due to the impaired ability to attenuate hepatic ER stress.[96] These findings suggest that bile acid-induced ER stress plays a role in hepatocyte injury and death during cholestasis. Bile acids and FXR activation have been shown to activate the hepatic IRE1α/XBP1 branch of the UPR,[97] which mainly activates the adaptive mechanisms to resolve ER stress. In contrast, the FXR-induced repressor SHP has been shown to promote post-translational proteosome degradation of the spliced form of XBP1 (XBP1s) in exocrine pancreas,[98] suggesting that distinct mechanisms may mediate bile acid and FXR regulation of the IRE1α/XBP1 cascade. However, the mechanisms by which high levels of bile acids impair ER function and cause ER stress in hepatocytes are still not fully clear and remain to be further elucidated. Some studies have also reported that ER stress and the UPR signalling pathways regulate bile acid synthesis and metabolism. In models of chemical-induced ER stress, hepatic CYP7A1 expression and de novo bile acid synthesis were both reduced, resulting in reduced hepatic bile acid accumulation in mice.[99] However, liver-specific XBP1 KO mice showed significantly downregulated bile acid synthesis and almost 50% smaller bile acid pool.[100] Decreased bile acid synthesis was not associated with a reduction of CYP7A1 protein. The potential roles of other UPR signalling pathways and components in bile acid regulation have not been well studied. Given that CYP7A1 is an ER resident enzyme, whether a post-translational mechanism links ER stress to inhibition of CYP7A1 enzyme activity remains to be further investigated.

CONCLUSION

Recent research has identified novel crosstalk of bile acid signalling and regulation of cellular stress responses and adaptive mechanisms, which significantly improves our knowledge of the roles of bile acids in liver physiology and disease. In cholestasis, reducing bile acid-mediated hepatobiliary toxicity remains the major treatment goal regardless of underlying aetiology. New evidence suggests that bile acid hepatotoxicity may also contribute to disease progression in MASLD and ALD. Pharmacological interventions that manipulate bile acid signalling also hold promise in treating MASLD, and possibly ALD as well. However, the broad impact elicited by these bile acid-based therapeutics and the underlying molecular and cellular mechanisms are only partially understood, and many conflicting findings yet cannot be explained. Future research directed at dissecting the bile acid action at the cellular and molecular levels will help us obtain a more comprehensive understanding of the bile acid functions, which is needed to determine the contribution of bile acids in disease pathogenesis, establish bile acids as potential diagnostic markers and develop bile acid-based pharmacological interventions.

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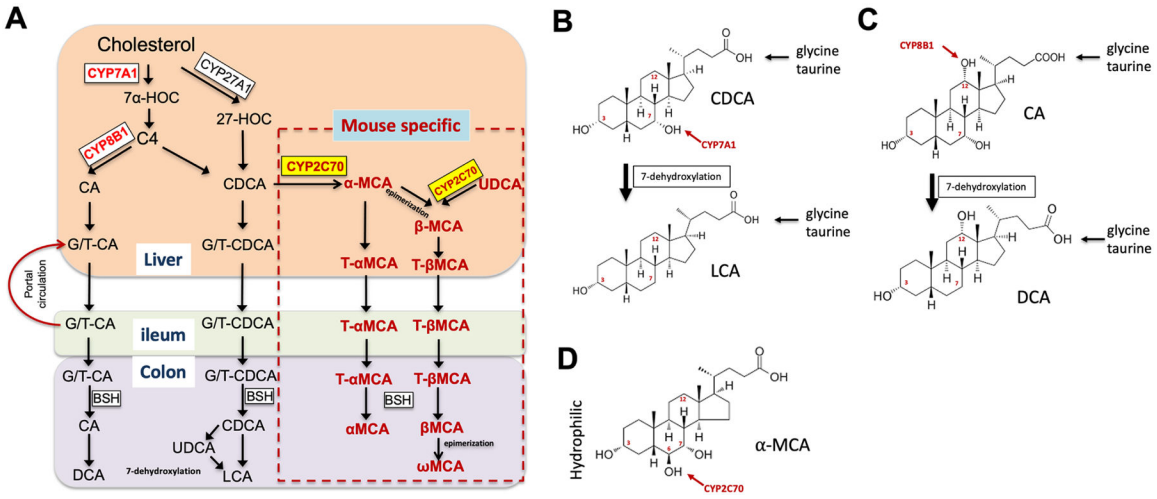

Figure 1.

Species differences in bile acid synthesis. (A) The classic bile acid synthesis pathway: cholesterol 7α-hydroxylase (CYP7A1) converts cholesterol to 7α-hydroxycholesterol (7α-HOC). The sterol 12α-hydroxylase (CYP8B1) converts the intermediate 7α-hydroxy-4 cholesten-3-one (C4) to 7α, 12α-dihydroxy-4-cholesten-3-one, eventually leading to synthesis of cholic acid (CA). C4 can also be eventually converted to chenodeoxycholic acid (CDCA). The mitochondrial sterol 27-hydroxylase (CYP27A1) catalyses the steroid side-chain oxidation of CA and CDCA. The alternative bile acid synthesis pathway: CYP27A1 converts cholesterol to 27-hydroxycholesterol (27-HOC), which mainly leads to the synthesis of CDCA. In mouse liver, CYP2C70 converts CDCA to α-MCA, which can be epimerized to β-MCA. In small and large intestine, bacterial bile salt hydrolase (BSH) deconjugates bile acids. Bacterial 7-dehydroxylase dehydroxylates CA to produce deoxycholic acid (DCA) and CDCA to produce lithocholic acid (LCA). Bacterial enzymes also produce secondary bile acids, including ω-muricholic acid (ω-MCA) and ursodeoxycholic acid (UDCA). (B–D) Structure of primary and secondary bile acids.

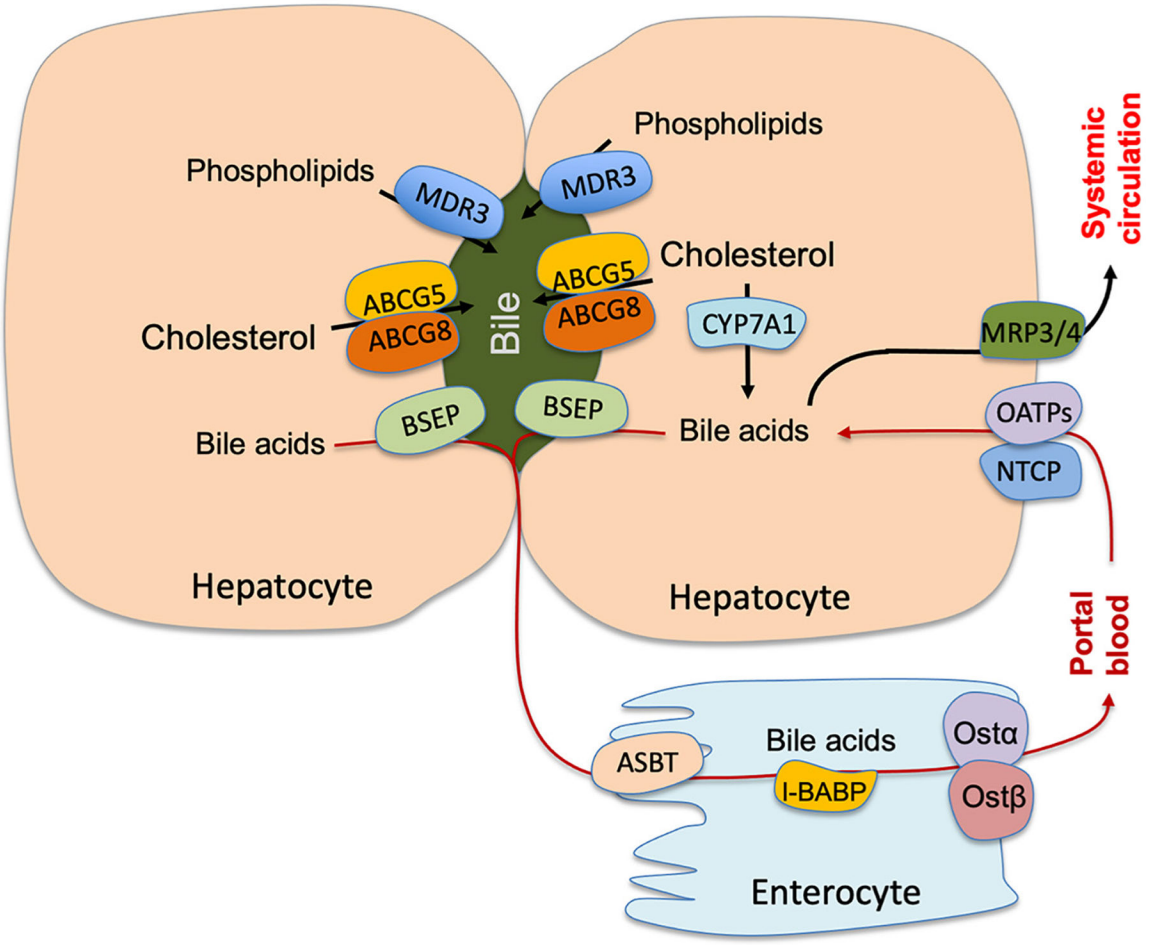

Figure 2.

Bile acid transport in the enterohepatic circulation. In hepatocytes, bile acids are secreted into bile canaliculi by bile salt export pump (BSEP), cholesterol is secreted by ATP binding cassette subfamily G member 5 (ABCG5) and ABCG8 heterodimer and phospholipids are secreted by multidrug resistance-3 (human MDR3, mouse MDR2). In bile, cholesterol, bile acids and phospholipids form mixed micelles. Bile acids are secreted into small intestine lumen, where bile acids facilitate dietary lipid absorption. Bile acids are absorbed in the terminal ileum by apical sodium-dependent bile acid transporter (ASBT). In enterocytes, bile acids bind intestinal bile acid binding protein (I-BABP). At the basolateral side of enterocytes, bile acid efflux is mediated by organic solute transporter α (OSTα) and OSTβ heterodimers. Bile acids are transported in portal blood to the liver where bile acids are taken up by hepatocytes via the Na^+-dependent taurocholate co-transporting polypeptide (NTCP) and organic anion transporting polypeptide (OATP) isoforms. A small amount of bile acids that are not taken up by hepatocytes enter the systemic circulation. Hepatocytes also efflux bile acids across the basolateral membrane via multidrug resistance-associated protein 3 (MRP3) and MRP4. This process is often increased during cholestasis as an adaptive protection against hepatic bile acid accumulation, resulting in significantly increased bile acid concentration in systemic circulation.

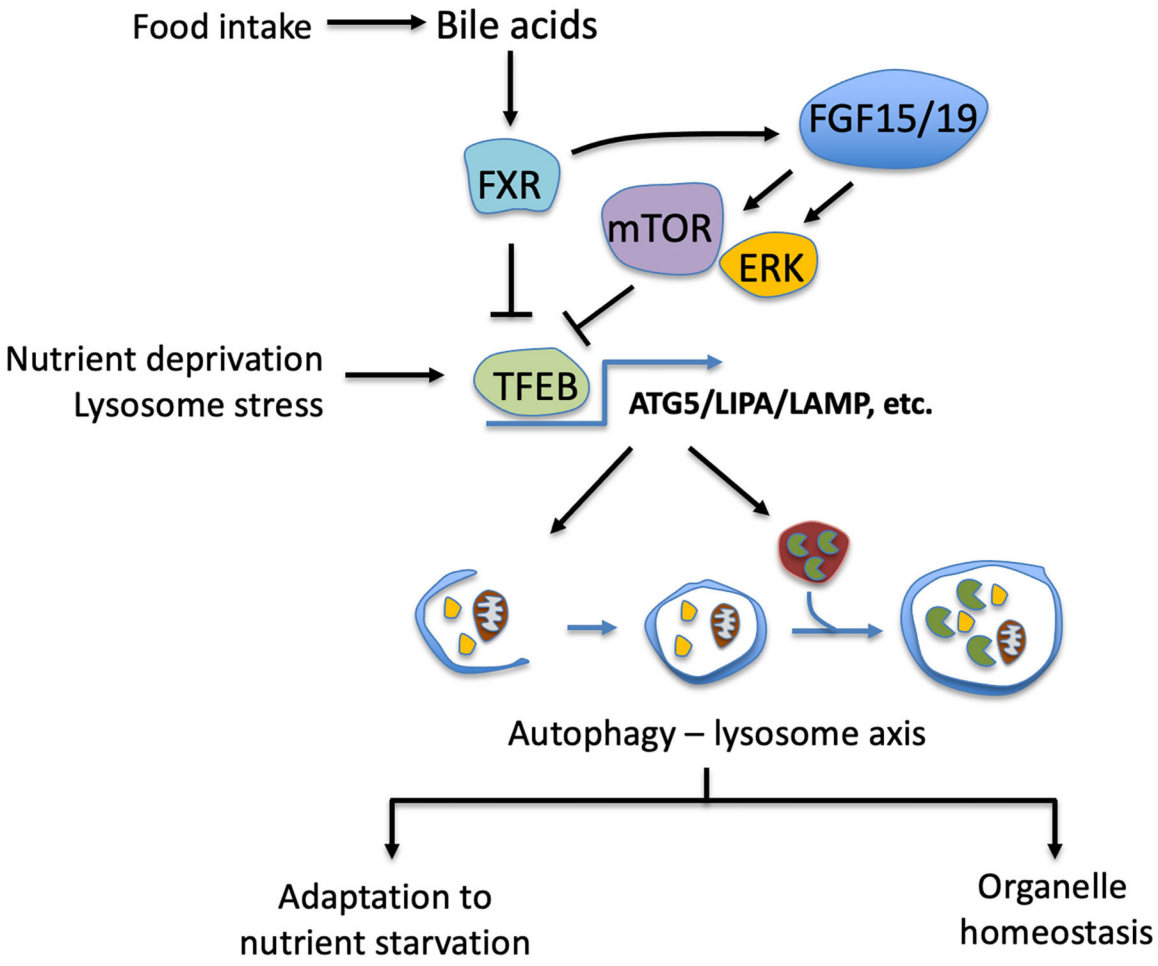

Figure 3.

Bile acid regulation of the autophagy-lysosome axis. Autophagy is a lysosome-dependent cellular degradation pathway that plays a key role in cellular nutrient homeostasis, organelle homeostasis and lipid homeostasis. Transcription factor EB (TFEB) is a nutrient and stress-sensing transcriptional factor that is activated in response to nutrient starvation and lysosome stress. In turn, TFEB induced genes that promote autophagy and lysosome biogenesis. Postprandial circulating bile acids and fibroblast growth factor 15 or 19 (FGF15/19) increase in response to food intake. Bile acids activated hepatic farnesoid X receptor (FXR) represses autophagy genes. In addition, FGF15/19 signalling inhibits TFEB nuclear translocation via activating intracellular mechanistic target of rapamycin (mTOR) and extracellular signal-regulated kinase (ERK) signalling. As a result, bile acids contribute to the postprandial repression of the hepatic autophagy-lysosome axis. In cholestasis, bile acid accumulation may contribute to impaired hepatic autophagy-lysosome axis, which in turn exacerbates cellular dysfunction and injury in hepatocytes.

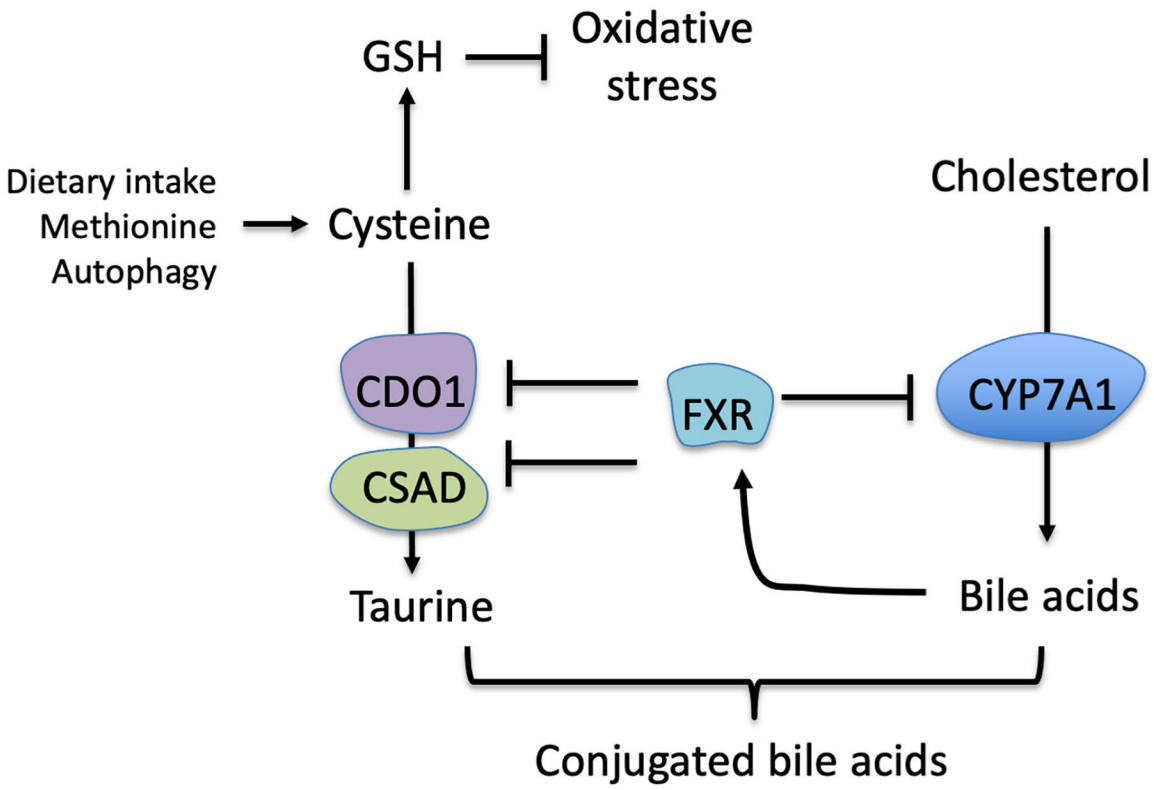

Figure 4.

Bile acid crosstalk with sulfur amino acid metabolism. Liver is the major organ for metabolism of sulfur amino acids (methionine, cysteine, taurine) and expresses high levels of sulfur amino acid synthesis and metabolising enzymes. Dietary intake, methionine (via transsulfuration pathway) and autophagy-mediated protein breakdown are major sources of cellular cysteine. Cysteine is the substrate for synthesis of the antioxidant glutathione (GSH). Cysteine conversion to taurine is a major cysteine elimination pathway and this process is catalysed by cysteine dioxygenase 1 (CDO1) and cysteine sulfinic acid decarboxylase (CSAD). Taurine is used in hepatocytes for bile acid conjugation. Bile acids activate farnesoid X receptor (FXR) to repress the expression of CDO1 and CSAD to inhibit taurine synthesis and at the same time repress cholesterol 7α-hydroxylase (CYP7A1) to inhibit bile acid synthesis. Therefore, FXR coordinates the synthesis of taurine with bile acids synthesis. FXR repression of cysteine catabolism helps preserve cellular cysteine availability for synthesis of GSH, which plays a key role in regulating cellular redox homeostasis and antioxidant defence against cellular oxidative stress.