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Bile acid transporters in health and disease

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Abstract

In recent years the discovery of a number of major transporter proteins expressed in the liver and intestine specifically involved in bile acid transport has led to improved understanding of bile acid homeostasis and the enterohepatic circulation. Na^+-dependent bile acid uptake from portal blood into the liver is mediated primarily by the Na^+ taurocholate co-transporting polypeptide (NTCP), while secretion across the canalicular membrane into bile is carried out by the Bile salt export pump (BSEP). In the ileum, absorption of bile acids from the lumen into epithelial cells is mediated by the Apical Na^+ bile salt transporter (ASBT), whereas exit into portal blood across the basolateral membrane is mediated by the Organic solute transporter α/ β ($OST\alpha/\beta$) heterodimer. Regulation of transporter gene expression and function occurs at several different levels: In the nucleus, members of the nuclear receptor superfamily, regulated by bile acids and other ligands are primarily involved in controlling gene expression, while cell signaling events directly affect transporter function, and subcellular localization. Polymorphisms, dysfunction, and impaired adaptive responses of several of the bile acid transporters, e.g. BSEP and ASBT, results in liver and intestinal disease. Bile acid transporters are now understood to play central roles in driving bile flow, as well as adaptation to various pathological conditions, with complex regulation of activity and function in the nucleus, cytoplasm, and membrane.

Introduction on enterohepatic circulation and bile acid transport in normal physiology

The liver plays an essential role in removing endogenous and xenobiotic compounds from the body. Normal hepatobiliary secretion and enterohepatic circulation are required for the elimination of endogenous compounds such as cholesterol and bilirubin and their metabolites from the body, as well as the maintenance of lipid and bile acid homeostasis. In addition it provides the body's primary means of eliminating toxic compounds such as drugs, carcinogens and potentially toxic metabolites of endogenous compounds (i.e., endobiotics). These xenobiotics and endobiotics, including bile acids, are taken up by the liver from portal blood and secreted into bile by distinct transport proteins with individualized substrate specificities and capacities located at the sinusoidal and canalicular membranes. At physiological pH, taurine and glycine conjugated bile acids exist in anionic form and are unable to cross membranes by diffusion, and thus, are completely dependent upon membrane transport proteins to enter or exit the hepatocyte. Moreover, since bile acids are the main solute in bile, their transport across the canalicular membrane provides the primary driving force for bile formation (Hofmann 1999; Hofmann 2007). In addition, bile acid secretion into bile occurs against a concentration gradient with very high concentration of bile acids in bile, requiring an active transport system. Thus, the creation, maintenance and regulation of bile formation rests

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mainly upon the functional competency of membrane transporters, with a central reliance upon the transport of bile acids.

After secretion into bile, bile acids, cholesterol and phospholipids are stored in the gallbladder as mixed micelles. Food entering the duodenum triggers the release of hormones that cause the gallbladder to contract, and delivery of bile from the gallbladder into the duodenum to mix with food and pancreatic juices. In the intestine, bile acids are essential for facilitation of absorption of lipids and cholesterol and lipid-soluble vitamins by incorporation into mixed micelles.

Within the intestinal lumen, a portion of the pool of primary bile acids is modified by intestinal bacteria into secondary bile acids, mainly by single or dual dehydroxylation reactions of the steroid nucleus. Deconjugation of the side chain linkage to taurine or glycine can also occur. Although some bile acids can be passively absorbed in the jejunum, most of the reabsorption, both primary and secondary, takes place in the terminal ileum where they are transported into these enterocytes, and then secreted into portal blood to return to the liver. In this first pass, 75-90% of bile acids are taken up by hepatocytes, completing one round of enterohepatic circulation (Hofmann 1999; Hofmann 2007). Bile acids make several rounds per day and in each tour, a small amount of bile acids is lost in the feces, which is replaced by neosynthesis in the liver via a complex negative feedback loop (see accompanying review by Graham et al in this issue).

Over the past 5-10 years, much has been learned about the mechanisms of bile acid transport and homeostasis, mainly due to the identification and cloning of membrane transporter genes, and by new findings about the means of regulating their expression in health and disease. Interestingly, the layers of regulation extend from the nucleus, to cell signaling, to membrane transporter protein modification, all woven together in ways that modulate bile acid flux, with a strong overriding regulatory drive to maintain safe intracellular levels of bile acids. Many bile acid transporters have been discovered that are principally involved in maintaining the flow of the enterohepatic circulation, including transporters of the MRP (ABCC) and OATP (SLCO) families (see respective Chapters in this issue by Drs. Ishikawa and Hagenbuch). In this review, we will focus upon the function and regulation of the four main bile acid transporters: Bile Salt Export Pump (Bsep), Sodium Taurocholate Co-Transporting Polypeptide (Ntcp), Apical Sodium Bile salt Transporter (Asbt) and the heterodimeric Organic Solute Transporter α and β (Ostα/β) (Figure 1).

2. Specific roles for NTCP, BSEP, ASBT, and OST α/β in bile acid transport

Bile acids in portal blood coming from the intestine are bound to albumin (Meier 1995) and released by conformational changes in albumin upon contact with the basolateral membrane (Horie et al. 1988; Meier 1995; Trauner and Boyer 2003). The majority of conjugated bile acids are taken up from portal/sinusoidal blood by hepatocytes via high-affinity, sodium dependent transport, mediated by the Sodium Taurocholate Co-Transporting Polypeptide NTCP (official nomenclature: SLC10A1) as well as by a subset of the family of organic anion transporters (OATP/SCLO) that mediate sodium independent uptake of amphipatic organic compounds including conjugated and unconjugated bile acids, (see review in this issue by Hagenbuch for a more detailed discussion of the OATP family, as well as references (Hagenbuch and Meier 2004; Kullak-Ublick et al. 2004; Meier and Stieger 2002). The relative proportion of Na^+-dependent vs. Na^+-independent uptake mechanisms is not fully defined, but the majority appears Na^+-dependent with differences among species. In humans, it has been estimated that approximately >80% of conjugated bile acid uptake and <50% of unconjugated bile acids takes place via Na^+-dependent mechanisms (Kullak-Ublick et al. 2004; Meier and Stieger 2002). In addition, there may be a potential role for the enzyme microsomal epoxide hydrolase (mEH)

in hepatic Na^+-dependent bile acid uptake (von Dippe et al. 1996; von Dippe et al. 2003) although this is controversial and its role is not fully defined. In transfected HepG2 cells mEH mediated uptake of bile acids (von Dippe et al. 2003.). A mutation in mEH has been found in a patient with hypercholanemia (Zhu et al. 2003) with normal levels of NTCP, but *mEH-/-* mice have normal bile acid homeostasis (Miyata et al. 1999). However these mice may not have a major phenotype, since it appears that glycoconjugated bile acids are the preferred substrates for mEH and most bile acids in mice are taurine conjugated. The ultimate contribution of mEH to Na^+- dependent bile acid uptake is unknown.

Early studies using purified basolateral plasma membrane vesicles, isolated hepatocytes and perfused liver (Meier 1995) (Anwer and Hegner 1978) (Van Dyke et al. 1982), indicated that bile acid uptake is dependent upon both a Na^+-gradient and an electrogenic mechanism (Bear et al. 1987); (Weinman et al. 1998). The high affinity uptake for conjugated bile acids such as taurocholate is driven by an inward Na^+ gradient which is maintained by the activity of a Na^+/K^+ ATPase (Meier and Stieger 2002) (Trauner and Boyer 2003). The responsible transporter, NTCP was cloned from rat liver RNA by expression cloning (Hagenbuch et al. 1990; Hagenbuch et al. 1991). Furthermore, these authors showed that Na^+-dependent bile acid transport was dependent upon full expression of Ntcp RNA (Hagenbuch et al. 1996). In a Xenopus Oocytes expression system, Na^+-dependent bile acid uptake driven by expression of total rat liver RNA was inhibited by 95% after injecting Ntcp antisense RNA. The expression cloning of rat Ntcp was a landmark event in transporter research—it was the first hepatobiliary transporter gene cloned and ushered in the current era of molecular analysis of transporter biology. Ntcp is exclusively expressed in the liver at the basolateral membrane of hepatocytes (Hagenbuch and Dawson 2004) (Ananthanarayanan et al. 1994; Geyer et al. 2006) however appears present in rat pancreatic acinar cells, where it may be involved in clearing bile acids from pancreatic ducts (Kim et al. 2002).

Once taken up by the hepatocyte, the intracellular transport of bile acids is poorly understood, but appears to involve several proteins, including: Liver Fatty Acid Binding Protein, oxysterol binding proteins, glutathione transferases and hydroxysteroid dehydratases (Agellon and Torchia 2000).

Upon reaching the canalicular membrane, conjugated bile acids from the enterohepatic circulation join with newly synthesized bile acids for secretion into bile. Transport of bile acids across the canalicular membrane is the critical rate-limiting step of the enterohepatic circulation, as well as the main generator of bile flow. Secretion of bile acids into bile occurs against a steep concentration gradient: the concentration of bile acids in the canalicular lumen is 100-1000 fold higher than that found in the cytoplasm. (Meier and Stieger 2002; Trauner and Boyer 2003). Bile acid secretion is ATP-dependent and the majority is mediated by the bile salt export pump, Bsep (Abcb11/Spgp). In 1995, Childs et al (Childs et al. 1995) cloned a liver-enriched p-glycoprotein (pgp) gene, originally called sister of pgp (spgp), that was subsequently shown to mediate ATP-dependent bile acid transport (Childs et al. 1995; Childs et al. 1998; Gerloff et al. 1998) (Byrne et al. 2002) (Noe et al. 2002). This gene product was renamed to Bsep and is exclusively expressed in liver, at the apical membrane of hepatocytes (Gerloff et al. 1998).

Bile produced by the liver enters the intestine in the duodenum after being stored in the gall bladder, where further concentration of contents occurs. A small proportion of conjugated bile acids entering the intestinal lumen are deconjugated by the intestinal bacteria rendering them uncharged and with increased pKA. Reabsorption of these bile acids can take place by passive diffusion throughout the whole intestine (Krag and Phillips 1974; McClintock and Shiau 1983; Wilson and Treanor 1975) (Alrefai and Gill 2007) (Hagenbuch and Meier 2004; Hofmann 1999; Hofmann 2007). Alternatively bile acids may be dehydroxylated by the

intestinal bacteria which increases the hydrophobicity and facilitates crossing the membrane passively. However this means of reabsorption represents only small part of the total bile acid uptake in intestine. The majority of the reabsorbed bile acids are conjugated and taken up in the terminal ileum (McClintock and Shiau 1983) via a highly efficient sodium dependent mechanism mediated by the apical sodium bile acid transporter Asbt (Slc10a2) (Wong et al. 1994). This transporter is expressed on the apical membrane of ileal intestinal epithelial cells. Asbt is also expressed in cholangiocytes and renal proximal tubular cells (Alpini et al. 1997; Christie et al. 1996; Lazaridis et al. 1997; Wong et al. 1994). In cholangiocytes Asbt may be involved in reabsorption of bile acids from bile, facilitating the “cholehepatic shunting” pathway. The exact physiological relevance of this shunt is not clear, but this pathway may play a role in the modification of bile in the bile ductules and may become more important under cholestatic conditions, providing a mechanism to attenuate high levels of intracellular bile acids, or help improve bile flow within the liver. Within the intestinal epithelia bile acids are transported by the intestinal bile acid binding protein IBABP (Crossman et al. 1994; Gong et al. 1994), after which the bile acids are secreted by several transport proteins including roles for Ostα and Ostβ. This heterodimeric transporter has been identified only recently as a solute transporter in skate liver (Wang et al. 2001). Soon afterwards the human and rodent homologs were identified (Seward et al. 2003). Human OSTα and OSTβ are expressed in a variety of tissues with the highest levels in liver, small intestine, colon, kidney, adrenal gland, testes, and ovary and lower levels in heart, lung, brain, pituitary, thyroid gland, uterus, prostate, mammary gland, and fat (Seward et al. 2003). In mouse, Ostα and Ostβ mRNAs were also abundantly expressed in the small intestine and kidney, but in contrast to human, the genes were expressed at very low levels in the liver (Dawson et al. 2005). At the protein level, localization was found at the basolateral membrane of ileal enterocytes, cholangiocytes and hepatocytes (Ballatori et al. 2005; Dawson et al. 2005; Seward et al. 2003). Ostα and Ostβ can only function as heterodimers, secreting bile acids back into the circulation, both in the intestine and in hepatocytes. Their role in the intestine is of importance under physiological circumstances, whereas in the hepatocytes they seem of more importance during cholestasis, when upregulation serves to protect the hepatocytes against high intracellular bile acids.

3. Substrate specificity

NTCP

NTCP mediates hepatic uptake of conjugated and unconjugated bile acids in a 1:2 stoichiometry with Na^+ (Hagenbuch and Meier 1996) (Weinman 1997). It has the highest affinity for conjugated di- and trihydroxy bile acids (Meier et al. 1997), which is similar between human, mouse and rat NTCP/Ntcp, although human NTCP has a higher affinity for taurocholate (Hagenbuch and Meier 1994). In addition transport of estrogen conjugates such as estrone-3-sulfate (Craddock et al. 1998), as well as bromosulphothalein (BSP), DHEA’s and thyroid hormones (Meier et al. 1997) has been shown. Other studies showed that drugs covalently bound to taurocholate (Kullak-Ublick et al. 1997) and chenodeoxycholate-3-sulfate and taurolithocholate-3-sulfate are also substrates for NTCP, at least *in vitro* (Hata et al. 2003).(Geyer et al. 2006; Hagenbuch and Meier 1996; Pauli-Magnus and Meier 2006; Pauli-Magnus et al. 2005)

BSEP

Bsep mediates the excretion of mainly monovalent conjugated bile acids and has also been shown to have a low affinity for transporting certain drugs (Childs et al. 1998; Lecureur et al. 2000), but the physiological relevance for this is not clear. Bsep of all species has a poor affinity for unconjugated bile acids, with high affinity for conjugated bile acids in this order: taurochenodeoxycholate (TCDCA) over taurocholate (TCA) > taurodeoxycholate (TDCA) > glycocholate (GCA) (Byrne et al. 2002) (Gerloff et al. 1998; Noe et al. 2002) (Green et al.

2000) (Oude Elferink et al. 2006; Stieger et al. 2007; Suchy and Ananthanarayanan 2006). The poor affinity of BSEP for unconjugated bile acids is best exemplified in the patients who have a defect in bile acid conjugation, but when in the presence of normal BSEP protein, secrete very little unconjugated bile acids into bile (Carlton et al. 2003).

ASBT

Human ASBT transports both conjugated and unconjugated bile acids with preference for conjugated bile acids (both taurine and glycine) (Geyer et al. 2006) (Craddock et al. 1998; Hagenbuch and Meier 2004). Asbt has a higher affinity for dihydroxy bile acids which are more hydrophobic (such as CDCA and DCA) over trihydroxy bile acids like CA and TCA and GCA (Craddock et al. 1998). These same researchers reported a lower affinity for TDCA than for TCA. Bile acid transport by Asbt is, similar to Ntcp, sodium-dependent and electrogenic with 2:1 Na^+/BA coupling stoichiometry (Weinman et al. 1998). The two genes are phylogenetically related, with similar membrane spanning structures (see below) and intron-exon organization (Cohn et al. 1995; Wong et al. 1994).

OSTα/β

The transport mediated by the heterodimeric transporter OSTα/β was found to be Na^+-independent and saturable (Wang et al. 2001) (Seward et al. 2003). Transport by Ostα/β is via a facilitated diffusion mechanism, and therefore, in contrast to the other bile acid transporters in this review, can mediate either efflux or uptake of the substrates, depending on the electrochemical gradient (Ballatori et al. 2005). Substrates include the bile acid taurocholate as well as digoxin, DHEAs estrone-3-sulfate, prostaglandin E2 (Seward et al. 2003; Wang et al. 2001), as studied in Xenopus Oocytes expressing Ostα/β.

4. BA transporter gene and protein structure

NTCP

The human NTCP gene is located on chromosome14q24 and encodes for a 349 amino acid protein with an apparent mass of 56 kDa (Hagenbuch and Meier 1994). The Rat *Ntcp* gene is located on chromosome 6q24 and encodes for a 363 amino acid protein and has an apparent mass of 51kDa (Kullak-Ublick et al. 2000; Meier and Stieger 2002). It is N-glycosylated at two sites at amino acids N5 and N11 (Hagenbuch 1997). The mouse *Ntcp* gene is located on chromosome 12q D1 (Cohn et al. 1995), and similar to the rat Ntcp protein, mouse Ntcp is a 362 amino acid protein but exists in 2 isoforms, Ntcp1 and Ntcp2, differing in the C-terminal sequence (Cattori et al. 1999). Ntcp2 is produced by alternative splicing resulting in a truncated protein of 317 amino acids (Cattori et al. 1999) and is expressed at a much lower level than Ntcp1. Although both isoforms are albe to mediate taurocholate transport when expressed in oocytes (Cattori et al. 1999), the physiological relevance of the Ntcp2 isoform is not yet clear.

Initial studies suggested that NTCP had a predicted topology of either seven or nine transmembrane domains with the N-terminus extracellular and the C-terminal intracellular (Hagenbuch and Meier 1994; Hallen et al. 2002) (Mareninova et al. 2005). Earlier experimental data supported a model with nine transmembrane spanning, or seven transmembrane and two membrane-associated domains, (Hallen et al. 2002). However later data indicated that most likely NTCP has 7 transmembrane domains with two segments either forming a large extracellular loop, or are associated with the membrane (Mareninova et al. 2005).

BSEP

The Human BSEP gene maps to chromosome 2q24 (Childs et al. 1998) and results in a protein of 1321 amino acids and a molecular mass of 150–170 kDa (Byrne et al. 2002). Rat Bsep is 1321 amino acid protein of approximately 160 kD with 12 putative membrane spanning

domains and four potential N-like glycosylation sites (Childs et al. 1998; Gerloff et al. 1998). Mouse Bsep is localized to a region on mouse chromosome 2 (Green et al. 2000). Mouse Bsep protein contains several phosphorylation sites appearing to be involved in regulation of bile salt transport function (see below) (Noe et al. 2001). Bsep is a member of the ATP-binding cassette (ABC) superfamily of transporters and consists of 12 transmembrane spanning domains determining the substrate specificity and two typical and highly conserved intracellular nucleotide-binding domains with Walker A and B motifs required for binding and hydrolysis of ATP (Meier and Stieger 2002) (Trauner and Boyer 2003). There is no evidence of BSEP splicing isoforms.

ASBT

The human ASBT gene is found on chromosome 13q33 (Wong et al. 1996) and on 16q12 and 8A1 for rat and mouse Asbt respectively, ASBT is a 48-kDa glycoprotein consisting of 348 amino acids. It shares characteristics with NTCP with respect to amino acid identity (35%) and membrane topology. Similar to NTCP, ASBT is a transmembrane protein containing an extracellular N-terminus and a cytoplasmic C-terminus. As for NTCP, the number of predicted ASBT transmembrane domains is either seven or nine (Geier et al. 2006; Hagenbuch and Dawson 2004), depending on the model. The most recent studies suggested that human ASBT is composed of seven transmembrane-spanning segments (Banerjee and Swaan 2006). In addition, the cytoplasmic tail of ASBT plays an important role in the sorting of ASBT in the apical membrane (Sun et al. 1998; Sun et al. 2003).

OSTα/β

The murine *Ostα* gene is located on chromosome 16B13 whereas murine *Ostβ* is mapped to chromosome 9C. The Ostα and Ostβ proteins are two distinct gene products with very different protein structures: Ostα is a 340 amino acid protein with seven transmembrane domains, whereas Ostβ is a 128-amino acid single transmembrane domain protein (Wang et al. 2001). Ostα and Ostβ need to be co-expressed to reach the membrane and function properly(Ballatori et al. 2005; Dawson et al. 2005).

5. Regulation of gene expression

Introduction to Nuclear Receptors

The expression of the bile acid transporter genes discussed in this paper is mainly regulated by the class II subfamily of the nuclear receptor (NR) superfamily. This superfamily comprises 48 ligand-regulatable transcription factors serving as intracellular receptors for endocrine hormones and endogenous and xenobiotic compounds (Karpen 2002) (Gronemeyer et al. 2004; Moore et al. 2006; Shulman and Mangelsdorf 2005; Zollner et al. 2006). The class II NR ligands are mostly endogenous lipophilic compounds such as cholesterol, lipids and bile acids and their metabolites, but also xenobiotic compounds such as rifampicin, St. John's Wort, spironolactone. To regulate target gene expression, a heterodimeric complex of class II NR members is formed with the common binding partner Retinoid X Receptor (RXR) in order to bind to response elements present in promoter regions of target genes. Among the twelve Class II NRs, 6 of these play major roles in regulating bile acid transport genes: Retinoic Acid Receptor (RARα), Farnesoid X Receptor (FXR), Pregnane X Receptor (PXR), Peroxisome Proliferator -Activated Receptor-alpha (PPARα), Constitutive Androstane Receptor (CAR), Liver X Receptor-alpha (LXRα), and their common partner, RXR. Non-Class II NRs also participate in bile acid transporter gene regulation, including Hepatocyte nuclear factor-4alpha (HNF4α, Short Heterodimeric Partner (SHP), and Liver Receptor Homologue-1 (LRH-1), as well as other liver enriched transcription factors such as HNF1-α/β and HNF3β A number of recent reviews provide greater details of the mechanisms by which NR family members

regulate and integrate gene expression and cell signaling. (Geier et al. 2007) (Alrefai and Gill 2007; Geier et al. 2006; Zollner et al. 2006).

NTCP

For NTCP, differential regulation between species exists with respect to the transcription factors that act on the NTCP promoter. Rat Ntcp expression is reduced by high concentrations of bile acids which is FXR mediated, however FXR does not act directly on the NTCP promoter but acts indirectly via activation of SHP, an inhibitory NR which in turn suppresses basal activation by RAR/RXR of rat Ntcp (Denson et al. 2001). During fasting NTCP is upregulated by HNF4α and PGC1α in rats (Dietrich et al. 2007), and this was suggested to provide a means of removing bile acids from the circulation to avoid signaling function in peripheral tissues.

In mice, Ntcp expression was decreased in mice fed a taurocholate containing diet (Sinal et al. 2000) (Wolters et al. 2002). Although no FXR/RXR binding site has been identified in the mouse Ntcp promoter, this does require FXR since this reduction was absent in *Fxr-/-* mice (Sinal et al. 2000); (Zollner et al. 2005). Basal Ntcp expression levels does not appear to be dependent on FXR since these were not changed in *Fxr-/-* mice (Sinal et al. 2000); (Zollner et al. 2005). Moreover basal Ntcp expression is not changed in *Shp-/-* mice (Kerr et al. 2002), and was still reduced when these mice were fed a CA diet (Wang et al. 2002). Therefore hepatic FXR and SHP do not seem to play an essential role in regulation of murine Ntcp by bile acids. Although not directly reported, it is quite possible that bile acids may primarily regulate murine hepatic Ntcp RNA expression via ileal FGF15, via hepatic activation of cell signaling expression (Inagaki et al. 2005). In addition, mouse Ntcp expression seems to be regulated mainly by HNF4α and HNF1α, although the relative contributions to overall Ntcp expression are not fully defined. Experimental data showing involvement of HNF4α and HNF1α in regulation of murine Ntcp expression include reduced Ntcp expression in both hepatocyte-specific *Hnf4α-/-* mice (Hayhurst et al. 2001) and in *Tcf1-/-* mice (the gene encoding the HNF1α protein) (Shih et al. 2001) and the presence of both HNF4α and HNF1α binding sites in the mouse Ntcp promoter (Jung et al. 2004). In addition HNF1α activity was reduced by bile acids via activation of FXR and induction of SHP, which in turn would interfere with HNF4α induced HNF1α activation subsequently reduced Ntcp expression (Jung et al. 2004; Jung and Kullak-Ublick 2003).

Two other liver enriched transcription factors have been reported to regulate NTCP expression. In rat, the homeobox gene Hex activated the NTCP promoter via an upstream response element (Denson et al. 2000), whereas HNF3β (or Foxa2) may act as a negative regulator of Ntcp, since overexpression of HNF3β in mice resulted in a decrease of Ntcp (Rausa et al. 2000). The binding site for HNF3β is conserved between rat, mouse and human NTCP (Jung et al. 2004; Shiao et al. 2000), but so far a physiological role has not been determined. Human NTCP is also regulated by members of the CCAAT/enhancer-binding protein (C/EBP) family of transcription factors (Jung et al. 2004; Shiao et al. 2000). In addition, the glucocorticoid receptor regulates the expression of human NTCP in a ligand dependent manner (Eloranta et al. 2006). This activation by GR was blocked by FXR induced expression of SHP, providing a negative feedback mechanism by bile acids on their uptake, but activation of NTCP by GR was increased in the presence of the coactivator PCG-1α (Eloranta et al. 2006).

A potential GR binding site was also identified in mouse Ntcp, (Cheng et al. 2007) and indeed, Dexamethasone induced Ntcp through activation of GR. Dexamethasone is also a ligand for PXR, and the effect of Dexamethasone on Ntcp is absent in *Pxr-/-* mice. However no PXR binding site in the mouse Ntcp promoter has been found. Moreover PCN showed no effect on Ntcp expression, suggesting PXR does not play a role in regulation of murine Ntcp expression. Estradiol reduced Ntcp RNA (Lee et al. 2000), which similar to regulation of Bsep by estradiol, was absent in *Erα-/-* mice (Yamamoto et al. 2006), indicating a role for ERα.

In HepG2 cells, NTCP expression was responsive to cholesterol treatment (Dias and Ribeiro 2007) however this could be either a direct or indirect effect since neither the transcription factors nor the mechanism involved were investigated, but may involve a role for Sterol regulatory element binding protein-2 (SREBP2), another cholesterol sensing transcription factor. Basal Ntcp gene expression is also influenced by gender: Ntcp protein and mRNA are expressed at higher levels in female murine and human liver tissue (Cheng et al. 2007). In contrast, in rats ntcp expression is higher in males (Simon et al. 2004). The difference in mice starts to become apparent 45 days after birth not due not to sex hormones, but rather to inhibitory effects of sex-specific growth hormone secretion patterns. The effect of growth hormone on Ntcp with respect to gender differential expression is mainly mediated by Stat5a and Stat5b (Clodfelter et al. 2006; Clodfelter et al. 2007). A potential Stat5b element in promoters of mouse and human NTCP has been identified (Cheng et al. 2007). In rat the Ntcp gene was upregulated by prolactin which was mediated by direct Stat5 binding to the Ntcp promoter (Ganguly et al. 1997). Finally, inflammation suppresses Ntcp expression rapidly and profoundly, mostly at the transcriptional level (Trauner et al. 1998; Zollner et al. 2006)

BSEP

The expression of the Bsep/BSEP gene is highly regulated by the heterodimer FXR/RXR in both human and rodents. Bile acids have been identified as ligands for FXR (Makishima et al. 1999) (Parks et al. 1999; Wang et al. 1999), resulting in a feedforward regulation of Bsep by the substrates it transports. By increasing Bsep RNA expression as a result of elevated levels of intracellular bile acids, increased efflux of bile acids from the hepatocytes results in a return to normal levels of intracellular bile acids. Physiological dependency on FXR for regulation of Bsep gene expression was confirmed in *Fxr-/-* mice which showed markedly reduced basal expression levels of Bsep (Sinal et al. 2000), along with a complete lack of induction by bile acids (Sinal et al. 2000; Wolters et al. 2002).

Recently hepatocyte-specific *Fxr-/-* mice and intestinal epithelial cell-specific *Fxr-/-* mice were created (Kim et al. 2007) and the contribution of FXR in these organs to Bsep expression was studied. Only the hepatocyte-specific absence of *Fxr* affected bile acid regulation of Bsep, whereas in the intestine-specific *Fxr-/-* mice the hepatic FXR-dependent regulation of Bsep was intact. Although Bsep expression is directly regulated by FXR in the hepatocytes, Bsep expression was decreased in livers of hepatocyte-specific *Lrh1-/-* mice (Mataki et al. 2007), although there may be other explanations, such as a reduction in the bile acid pool size. In addition Bsep expression was decreased in mice overexpressing human *SHP* specifically in the hepatocytes (Boulias et al. 2005), again probably indirectly due to decreased bile acid pool.

Hydrophobic bile acids are better ligands for FXR than hydrophilic bile acids with CDCA and CA being the most potent FXR agonists (Makishima et al. 1999; Parks et al. 1999; Wang et al. 1999). In contrast, *in vitro* studies showed the hydrophobic bile acid Litocholic acid antagonizes CDCA-induced Bsep expression as well as activation by the synthetic FXR ligand GW4064 (Yu et al. 2002). In addition, the synthetic RXRα ligand LG268 antagonized CDCA-induced FXR activity on the human BSEP promoter *in vitro* (Kassam et al. 2003). Other *in vitro* studies showed that the coactivators CARM1 and PRMT1 are required for full activation of FXR by bile acids to increase BSEP expression (Ananthanarayanan et al. 2004) (Rizzo et al. 2005), suggesting that there are multiple layers of complexity to the overall contributions of regulation of Bsep/BSEP RNA expression.

In addition to being regulated by bile acids, the FXR/RXR binding site identified in the rat minimal Bsep promoter is inhibited by rifampicin and estradiol and activated by tamoxifen, which are ligands for PXR and ER (Gerloff et al. 2002). Estradiol treatment of mice reduced Bsep RNA levels (Lee et al. 2000), which appears to be ERα dependent (Yamamoto et al. 2006). Although the mechanism is not fully known this could potential be explained by the

reduced bile acid synthesis due to reduced expression of Cyp7a1, Cyp7b1, Cyp8b1 in mice treated with ethinyl estradiol, EE2. Further upstream in the Bsep promoter several other potential sites were identified, such as NF-1 and an overlapping SP-1/ HNF3β binding sites so far not shown to be functional. In addition MyoD was suggested to potentially have a repressive effect on the rat Bsep promoter (Gerloff et al. 2002).

Early observations reported spironolactone to increase bile flow in rodents (Klaassen 1974; von Bergmann et al. 1974). Later spironolactone was identified as a ligand for PXR, the Glucocorticoid Receptor (GR) and for the Mineralocorticoid Receptor (MR). Recently spironolactone was shown to induce Bsep expression (Cheng et al. 2007) potentially explaining the increase bile flow induced by this compound. Basal Bsep expression levels were lower in *Pxr-/-* mice compared to wild-type mice and spironolactone induced Bsep expression was absent, indicating the involvement of Pxr. Potential PXR response elements in mouse and human bsep/BSEP promoters were identified, confirming potential direct regulation of Bsep/ BSEP expression by PXR. However, treatment of mice with the typical murine PXR ligand PCN did not affect Bsep expression. However another study did show that PXR was required for upregulation of mouse Bsep by PCN and RU486 (Teng and Piquette-Miller 2005). In addition potential GR elements were found in the murine Bsep promoter, but appear not to be functional since activation of GR with dexamethasone treatment did not affect Bsep expression (Cheng et al. 2007). Finally, there is substantial inflammation-mediated suppression of Bsep RNA, apparently via reduction in the amount and function relevant transcriptional regulators (Geier et al. 2006; Zollner et al. 2006) All together, ligand and NR regulation of Bsep gene expression is complex, and points to this gene as a critical component of the hepatocytes response to a variety of disease states and xenobiotics.

ASBT

Similar to Ntcp, differential regulation of Asbt exists between species. In rat Asbt expression in the ileum was not affected by reduced amounts of bile acids present in the intestinal lumen (Arrese et al. 1998). In mice, however, Asbt is under negative feedback regulation by bile salts concluded from experiments in mice with increased secretion of biliary bile acids as a result of overexpression of hepatic *Bsep* (Figge et al. 2004). Bile acid feeding decreased Asbt levels (Chen et al. 2003; Zollner et al. 2006), which was absent in *Fxr-/-* mice. In vitro studies confirmed that mouse but not rat Asbt is regulated by the FXR/SHP/LRH-1 pathway (Chen et al. 2003), however FXR appears not to be required for basal Asbt expression since *Fxr-/-* mice did not show a change in expression of Asbt (Sinal et al. 2000).

For human ASBT, a different mechanism of regulation by bile acids has been found, such that bile acids activate FXR, which in turn activates SHP but this represses RXR-RAR induced activation of Asbt (Neimark et al. 2004). In addition, the human Asbt gene was responsive to the RXR ligand, 9-cis retinoic acid. In rabbits bile acid mediated downregulation of Asbt was shown to be mediated by the FXR-SHP-FTF cascade (Li et al. 2005).

Besides regulation by bile acids through FXR, Asbt is regulated by multiple other transcription factors, including other nuclear receptors, one of which is the Glucocorticoid Receptor. Human intestinal ASBT expression was increased by GR and its synthetic ligand dexamethasone (Jung et al. 2004) and the human ASBT promoter contains 2 GR response elements (IR-3) which were induced by dexamethasone-activated GR (Jung et al. 2004). Similarly, an increase in Asbt in response to glucocortiocoids in rat and rabbit was shown (Nowicki et al. 1997), suggesting also in other species Asbt may be regulated by GR and its ligands.

Rat and human Asbt/ASBT are also regulated by vitamin D3 (Chen et al. 2006) via a Vitamin D Receptor (VDR) response element. Activation resulted in increased ileal bile acid transport in mice, indicating there might be a physiological role for VDR in intestinal bile acid uptake.

Interestingly the VDR is also activated by certain bile acids, such as lithocholic acid and its conjugated forms (Makishima et al. 2002) but its role in regulating Asbt gene expression is unknown. In addition a functional PPARα/RXR DR-1 binding site was identified in human ABST, resulting in increased promoter activity and upregulated ASBT expression in a cholangiocytes cell line (Jung et al. 2002).

In mice Asbt appears to be regulated by HNF1α as well, since the expression was reduced to absence in intestine and kidney of *Tcf (HNF1α)-/-* mice (Shih et al. 2001). In addition basal promoter activity of human ASBT was dependent on HNF1α (Jung et al. 2002). In human intestinal epithelial cells the addition of 25-OH-cholesterol repressed ASBT promoter activity, RNA expression levels and transport activity of ASBT protein (Alrefai et al. 2005). No direct regulation by the cholesterol sensor LXRα has been shown, but rather the downregulation of ASBT by cholesterol metabolites required both the presence of SREBP2, another transcription factor sensing cholesterol levels, and HNF1α, the latter directly interacting with the ASBT promoter, whereas SREBP2 did not (Thomas et al. 2006). The exact mechanism as to how SREBP2 and HNF1α mediate repression of the *ASBT* gene is not yet clear. SREBP2 did not bind directly to the ASBT promoter. In addition, the HNF1α promoter was insensitive to regulation by cholesterol, excluding the possibility of SREBP2 binding to HNF1α but suggesting a cooperative mechanism of potential SREBP2 and HNF1α interaction. The physiological relevance of cholesterol regulating ASBT levels and transport activity may be considered an adaptive response to systemic high cholesterol levels leading to the inhibition of intestinal bile acid absorption and resulting in the reduction in bile acids entering the liver. This in turn would relieve the suppression of bile acid synthesis by bile acids and increase in the metabolism of cholesterol into bile acids, resulting in reduction of high cholesterol levels.

Finally, the *Asbt/ASBT* gene in both rodents and human is downregulated by activation of AP-1, in particular by the component protein c-Fos, in response to inflammatory cytokines, such as IL-1β and TNFα in CaCo2 and IEC6 cells (Chen et al. 2001; Chen et al. 2002; Neimark et al. 2006). Another very recent study indicates that the human *ASBT* gene can be activated by bile acids on the AP-1 site, via the EGF-receptor and ERK1/2 activation (Duane et al. 2007).

Octα/β

Little is known of the regulation of expression of Ostα and Ostβ genes, due mainly to their recent discovery. In humans, OSTα/β have higher expression in liver compared to the intestine, whereas in mice, they are very low expressed in the liver with much higher expression levels in the intestine (Ballatori et al. 2005; Seward et al. 2003) (Boyer et al. 2006).

Both genes are regulated by bile acids via the FXR/RXR heterodimer, which is conserved in human (Landrier et al. 2006) and mouse (Frankenberg et al. 2006). Ostα and Ostβ were shown to be responsive to a CA containing diet but not to UDCA diet, with a complete lack of response in *Fxr-/-* mice, indicating that indeed FXR is required for this increase (Zollner et al. 2006) in both liver and intestine. OSTα/β expression was also increased ex vivo in human ileal biopsies exposed to CDCA (Landrier et al. 2006). Increased Ostα/β promoter activity induced by ligand activated FXR indicates a feedforward regulation exists by bile acids inducing their own clearance by upregulating Ostα/β expression, similar to Bsep. Reduced expression of Ostα/β was observed in the ileum of *Asbt-/-* mice, whereas the expression was increased in the cecum and proximal colon (Dawson et al. 2005). This could be explained by a reduction in ileal bile acid uptake in these *Asbt-/-* mice, resulting in decreased activation of FXR and as a consequence the increased concentration of bile acids in the colon and cecum may increase the activation of FXR and increasing the expression of Ostα/β. In addition LRH-1 binding sites in both mouse and human OSTα/β have been found (Frankenberg et al. 2006) indicating a more complex regulation in which bile acids can also indirectly inhibit Ostα/β via activation of FXR and SHP-mediated inhibition of LRH-1.

Another recent study identified an LXR activation site for mouse Ostα/β (Okuwaki et al. 2007), which overlapped with the FXR/RXR site. The activation of Ostα but not Ostβ by ligand activated LXR may be enhanced by HNF4α but no physiological relevant function has been associated with it yet. In addition to regulation by nuclear receptors, ileal Ostα/β expression was dependent on c-fos in a mouse model of indomethacin induced intestinal inflammation (Neimark et al. 2006).

6. Post-translational regulation

Besides regulation at the gene expression level which results in delayed effects, a more rapid regulation of transporter function can be obtained by actions on the protein itself. These post-translational modifications include phosphorylation/dephosphorylation of the transport proteins, increasing or decreasing the amount of protein on the membrane by insertion or retrieval of vesicles to or from the basolateral or apical membranes to submembrane, intracellular pools. Activation of several signaling pathways has been shown to be involved in bile acid uptake and bile formation. These signaling pathways include intracellular cAMP, cGMP, $Ca2^{+}$ increase, PKC activation, PI_3K and MAPK activation (Anwer 2004; Bouscarel et al. 1999)

NTCP

Initial studies showed that cAMP stimulates bile acid uptake in hepatocytes (Botham and Suckling 1986) (Grune et al. 1993). This was later shown to be due to effects on NTCP transport activity: increased cAMP resulted in a cAMP-dependent increase in vesicular trafficking of Ntcp from an intracellular pool to the basolateral membrane, resulting in an increased presence of NTCP (Dranoff et al. 1999; Mukhopadhayay et al. 1997). Trafficking of these NTCP containing vesicles was dependent on actin skeleton/microfilaments (Dranoff et al. 1999) (Webster and Anwer 1999). In addition PI_3K and PKCζ signaling are required for the vesicle transport of NTCP to and from the basolateral membrane (Webster and Anwer 1999; Webster et al. 2000).

NTCP is a serine/threonine phosphorylated protein and is de-phosphorylated in response to cAMP, which leads to increased retention of NTCP in the membrane (Mukhopadhyay et al. 1998; Mukhopadhyay et al. 1998). This dephosphorylation is mediated by protein phosphatase 2B (PP2B), which is a calcium/calmodulin-dependent serine and threonine protein phosphatase (Webster et al. 2002). PP2B requires calcium for its activity and an increase of intracellular Ca^{2+} levels was shown to be induced by cAMP (Webster et al. 2002). The effect of cAMP on increased Ntcp activity may be resulting from dephosphorylation of Ntcp at S226 (Anwer et al. 2005) leading to increased translocation of the protein to the membrane. Dephosphorylation retains Ntcp in the membrane and prevents its removal, resulting in higher levels on the membrane and increased bile acid uptake activity. The mechanism that seemed to emerge from this is the following: cAMP increases intracellular Ca^{2+}, activating PP2B, which in turn dephosphorylates NTCP, facilitating its translocation to the membrane. The latter is dependent upon PI_3K. In addition phosphorylation of 2 tyrosine residues on the cytoplasmic tail of rat NTCP appear to be involved in targeting to the basolateral membrane (Sun et al. 2001). Finally, Ntcp is degraded via the ubiqutination/proteasomal pathway (Kuhlkamp et al. 2005).

BSEP

Similar to Ntcp, Bsep is recruited to the apical membrane from intracellular sub-apical vesicles in response to several stimuli, including cAMP and PI_3K-dependent signaling, hypo-osmolarality induced cell swelling, and certain bile acids (Kipp et al. 2001; Misra et al. 1998; Schmitt et al. 2001; Suchy and Ananthanarayanan 2006). Newly synthesized Bsep directly targeted from Golgi to canalicular membranes via subcanalicular pools (Kipp and Arias

2000; Kipp et al. 2001). The insertion and retrieval of Bsep in and from the canalicular membrane appears to be dependent on the microtubule cytoskeleton (Boyer and Soroka 1995; Gatmaitan et al. 1997) as well as on PI_3K signaling (Misra et al. 1998) and on PI_3K generated lipid products, such as $PI_{3,4}P_2$ (Misra et al. 1999). In addition, radixin, a protein involved in cross-linking the plasma membrane and intracellular actin filaments is required for maintaining Bsep in the plasma membrane (Wang et al. 2006).

Cyclic AMP stimulates canalicular secretion of bile acids (Hayakawa et al. 1990) and induced a 3-fold increase of Bsep in the canalicular membrane, which was partially dependent on microtubules (Gatmaitan et al. 1997; Kipp et al. 2001). In addition, Bsep is recruited to the canalicular membrane in response to the bile acid taurocholate, which is dependent on microtubules (Gatmaitan et al. 1997), although others found this to be independent of cAMP (Misra et al. 1998; Misra et al. 2003).Cell swelling also stimulates biliary bile acid secretion and translocation of Bsep to the canalicular membrane (Schmitt et al. 2001) and also activates PI_3K (Krause et al. 1996) suggesting that PI_3K signaling is involved in cell swelling induced translocation of Bsep. Regulation of trafficking of rat Bsep to the canalicular membrane is regulated by PKC and p38 MAPK kinase signaling (Kubitz et al. 2004). Phosphorylation of murine Bsep was mediated by PKCα (Noe et al. 2001), and enhances its affinity for substrates, whereas phosphorylation of rat Bsep by PKC led to retrieval of Bsep from the membrane in HepG2 cells (Kubitz et al. 2004).

ASBT

Only a few studies have reported on posttranslational regulation of Asbt and almost all of these are in cholangiocytes. It is currently unknown if similar modifications occur in the intestinal epithelial cells. Similar to Ntcp and Bsep, Asbt seems to be residing in subapical vesicles, for a fast response to stimuli to go to the membrane. In rat cholangiocytes, secretin increased the activity of Asbt by shuttling the protein from subapical endosomes to apical membrane and thereby increasing the expression at the surface membrane (Alpini et al. 2005). Under basal conditions Asbt is ubiquitinated and degraded by the proteasome (Xia et al. 2004). In response to the cytokine Il-1β, Asbt is phosphorylated which resulted in increased proteasomal degradation.

OSTα/β

Data on posttranslational modifications of Ostα and Ostβ are beginning to emerge. Two recent studies reported on trafficking to of the Ostα and Ostβ to the membrane. For human OSTα and OSTβ, in vitro studies showed a protein-protein interaction needs to exist between the two partners before translocation to the membrane can occur (Ballatori et al. 2005; Sun et al. 2007), with an important role for the N-terminal part of hOSTα in this interaction (Sun et al. 2007). In mice (Dawson et al. 2005), co-expression of both Ostα and Ostβ was required for the synthesis of a mature glycosylated Ostα protein. In addition both Ostα and Ostβ were required to be expressed for their appearance at the membrane, whereas expression of either one of the proteins results in degradation (Li et al. 2007). This was further confirmed in *Ostα-/-* mice, where Ostβ RNA was expressed, but not the protein, indicating that Ostα is required for Ostβ protein stability (Li et al. 2007) and Ostβ was suggested to function as a chaperone and as a regulator of the transport activity of the dimer.

6. Regulation of transport activity

In addition to gene and protein regulation, a direct effect of compounds on the transport activity of the respective protein is an effective manner of influencing transport (Anwer 2004; Meier and Stieger 2002)

NTCP

Transport activity of Ntcp is sodium dependent, and acts via an electrogenic mechanism, with a 2:1 stoichiometry with Na^+. Certain drugs act as inhibitors of Ntcp transport, These are cyclosporine, R- and S-proranolol, BSP, furosemide, DIDS, 17-b-eostradiol-3-sulfate, tauro-lithocholate-3-sulfate (Hata et al. 2003; Kim et al. 1999; Kramer et al. 1999).

BSEP

Bsep protein transport activity is inhibited by glybenclamide and troglitazone by direct binding of these compounds to Bsep (Byrne et al. 2002; Funk et al. 2001) and cause drug induced cholestasis. In addition, Estradiol-17b-glucuronide, cyclosporine A, rifampicin and bosentan inhibit Bsep transporter function (Stieger et al. 2000) (Bohme et al. 1994) (Fattinger et al. 2001) Also internalization of membrane vesicles induced by taurolithocholate is involved in drug-induced cholestasis (Crocenzi et al. 2003; Crocenzi et al. 2003).

ASBT

Asbt transport function is inhibited by BSP, and cyclosporine (Baringhaus et al. 1999). Several chemical Asbt specific inhibitors have been developed: dimeric bile acid analogues, which bind to Asbt but cannot be transported (Kramer and Wess 1996; Wess et al. 1994) (Baringhaus et al. 1999). A different class of inhibitors consists of benzothiazepine derivatives, benzothiepine derivatives, and naphtol derivatives, (Kramer et al. 1999) (Tollefson et al. 2000) (Huang et al. 2005; Kurata et al. 2004; Root et al. 2002; West et al. 2002). Inhibition of Asbt by chemical inhibitors would be beneficial in reducing serum cholesterol due to increased bile acid synthesis as result of decreased absorption.

OSTα/β

For Ostα/β transport function in rodents no inhibitory compounds have been identified yet. However, skate Ostα/β mediated TCA transport is inhibited by hydrophobic sulfated bile acids (Wang et al. 2001) steroids such as estrone sulfate and spironolactone as well as by sulfobromophtalein and indomethacin.

8. Roles in diseases

Genetic defects, mutations and polymorphisms (see Table)

NTCP (SLC10A1)—No major diseases have been associated with defects in the NTCP gene, however several ethnicity dependent polymorphisms have been identified as well as marked inter-personal variations in human NTCP RNA expression levels (Ho et al. 2004) (Kullak-Ublick et al. 1997). These low frequency polymorphisms were associated with reduced membrane localization and with decreased to near absence of transport activity of bile acids and were suggested to potentially play role in development of hypercholanemia. Unfortunately it was not possible to relate these polymorphisms to clinical phenotypes, because of anonymity of the DNA samples. Moreover *Ntcp*-deficient mice have not been generated yet.

BSEP (ABCB11)—Mutations in the *BSEP* gene lead to the inherited cholestatic disorder Progressive Familial Intrahepatic Cholestasis type 2 or PFIC2 (Jansen et al. 1999; Oude Elferink et al. 2006; Strautnieks et al. 1998). This liver disease has is characterized by severe jaundice, hepatomegaly, failure to thrive and pruritus from infancy onset, whereas liver histology shows portal inflammation and giant-cell hepatitis (Bezerra and Balistreri 2000). In addition, high bile acids and aminotransferases are detected in serum, however a clinical hallmark of this disease presents with normal gamma glutamyl transpeptidase levels. The disease has a rapid progressive course and generally leads to cirrhosis and liver failure with a need for liver transplantation within the first decade of life. A number of different mutations

have been found in the *BSEP* gene. Some of these mutations have been functionally analyzed in vitro. Most of these showed reduced transport activity, as a result of in decreased protein expression, altered membrane targeting, increased degradation by the proteasome (Hayashi et al. 2005; Kagawa et al. 2007; Wang et al. 2002), whereas others were functional but were unstable due to defective glycosylation (Plass et al. 2004). In addition a milder form of PFIC2 exists, BRIC2 (van Mil et al. 2004) (Noe et al. 2005) (Lam et al. 2007) (Kagawa et al. 2007), in which recurrent episodes of cholestasis occur and is associated with gallstone formation (van Mil et al. 2004).

In contrast to the human disease, mice lacking the *Bsep* gene have only mild, nonprogressive, but persistent intrahepatic cholestasis (Wang et al. 2001). This could be explained by the fact that the bile acid pool in mice is much more hydrophilic compared to the human bile acid pool, and that the mouse liver has more active detoxifying pathways than human. Indeed, when *Bsep-/-* mice were fed a diet containing CA to increase the hydrophobicity of the murine bile salt pool, severe cholestasis was induced (Wang et al. 2003).

Although no human gene defects have been identified that are associated with increased Bsep activity, in mice overexpression of hepatic *Bsep* (Figge et al. 2004), resulted in reduced hepatic steatosis when placed on a high cholesterol, high fat and cholic acid containing diet (Figge et al. 2004).

A number of studies have identified polymorphisms and sequence variabilities in the human *ABCB11* gene (Pauli-Magnus et al. 2004) (Stieger et al. 2007). Interindividual variability for basal BSEP protein levels was identified in a study of 110 healthy liver tissue samples from an overall white population, but no correlation between expression level and cholestasis markers was found (Meier et al. 2006), however, a specific SNP (presence of C-allele at position 1457) in the *ABCB11* gene tended to be associated with low BSEP protein expression levels. 86 polymorphisms were found in a population of Caucasians, Koreans and African-Americans. The polymorphisms were found in exons, introns as well as in 5'flanking regions. Most variants were population specific, with the largest variation found in the African-American group, but no functionality of the protein was determined for any of the variants (Lang et al. 2006). In addition, 82 polymorphisms were identified in a Japanese population (Saito et al. 2002) but again this was not associated with functionality studies of the variants. Polymorphisms in BSEP have also been associated with intrahepatic cholestasis of pregnancy (Keitel et al. 2006; Pauli-Magnus et al. 2004) and drug-induced cholestasis (Lang et al. 2007).

ASBT (SLC10A2)—A mutation in Asbt was identified in and shown to be directly responsible for primary bile acid malabsorption (PBAM) (Oelkers et al. 1997), which is a disease associated with interrupted enterohepatic circulation, infantile diarrhea, fat malabsorption and reduced level of plasma cholesterol (Balistreri et al. 1983) (Heubi et al. 1982; Thaysen and Pedersen 1973). A point mutation in the human *ASBT* gene, resulting in lack of taurocholate transport was identified in a patient with Crohn's disease (Wong et al. 1995), although its relationship to Crohn's Disease is uncertain.

In addition several other mutations and polymorphisms have been identified in *ASBT/Asbt* which reduced bile acid transport activity (Geyer et al. 2006). Consistent with the human phenotype, mice lacking the *Asbt* gene show profound intestinal bile acid malabsorption and an increase in elimination fecal bile acid (Dawson et al. 2003) as well as a slight increase in plasma cholesterol levels, confirming that Asbt is the major mechanism of intestinal bile acid absorption.

OSTα/β—No diseases, mutations or polymorphisms have been reported for *Ostα/β;* however in mouse models of cholestasis changes in gene expression have been shown suggesting alterations in function. Recently *Ostα-/-* mice were generated but no phenotype was described other than lack of both Ostα and Ostβ proteins and growth retardation, but no explanation was provided (Li et al. 2007)..

Besides genetic defects the expression bile acid transporters have been shown to be changed in several other liver diseases, such as inflammation induced cholestasis, obstructive cholestasis, and cholestasis of pregnancy, mainly due to effects of these pathological states on the function of nuclear receptors regulating the expression of bile acid transporter genes (reviews by (Arrese 2006; Geier et al. 2006; Geier et al. 2007). This will be discussed more extensively in the chapter by Graham of this issue.

Summary

The genes responsible for bile acid transport have been only recently discovered, but their substrate specificities, and main mechanisms of functional regulation are beginning to be understood. Among the main points are the high functionality and regulatability of these genes, especially in response to cholestasis, the narrow substrate specificities, and the regulation at transcriptional and post-transcriptional levels. Moreover, human diseases result when the function of some of these genes, i.e. BSEP and ASBT is reduced, either by genetic mutations, or external regulation by inflammation or exogenous compounds. All together, we are currently at a point where we now have a broad view of the landscape of how bile acid transporters function in the cell (see Figure 1), and how this may be targeted for regulation in various disease states—both from a pathogenic view, as well as a therapeutic one.

Abbreviations used in this review

Asbt/Slc10a2	Apical sodium bile salt transporter
Bsep/Abcb11/Spgp	Bile salt export pump
BSP	bromosulphothalein
cAMP	cyclic Adenosine-monophosphate
CAR	Constitutive androstane receptor
ER	Estrogen receptor
FXR	Farnesoid X receptor
GCA	glycocholate
GR	Glucocorticoid receptor
HNF	Hepatocyte nuclear factor
LRH-1	Liver receptor homologue-1
LXR	Liver X receptor
NR	nuclear receptor
Ntcp/Slc10a1	Sodium taurocholate co-transporting polypeptide
mEH	microsomal epoxide hydrolase
OATP/SLCO	Organic anion transport polypeptide

Ostα/β	Organic solute transporter α and β
PI_3K	Phosphoinositol-3-kinase
PKC	Protein kinase C
PP2B	Protein phosphatase 2B
PPAR	Peroxisome proliferator-activated receptor
PGC1α	Peroxisome proliferator-activated receptor gamma coactivator 1 alpha
PXR	Pregnane X receptor
RAR	Retinoic acid receptor
RXR	Retinoid X receptor
SHP	Short heterodimeric partner
SREBP2	Sterol regulatory element binding protein-2
TCA	taurocholate
TCDCA	taurochenodeoxycholate
TDCA	taurodeoxycholate
UDCA	Ursodeoxycholic acid
VDR	Vitamin D receptor

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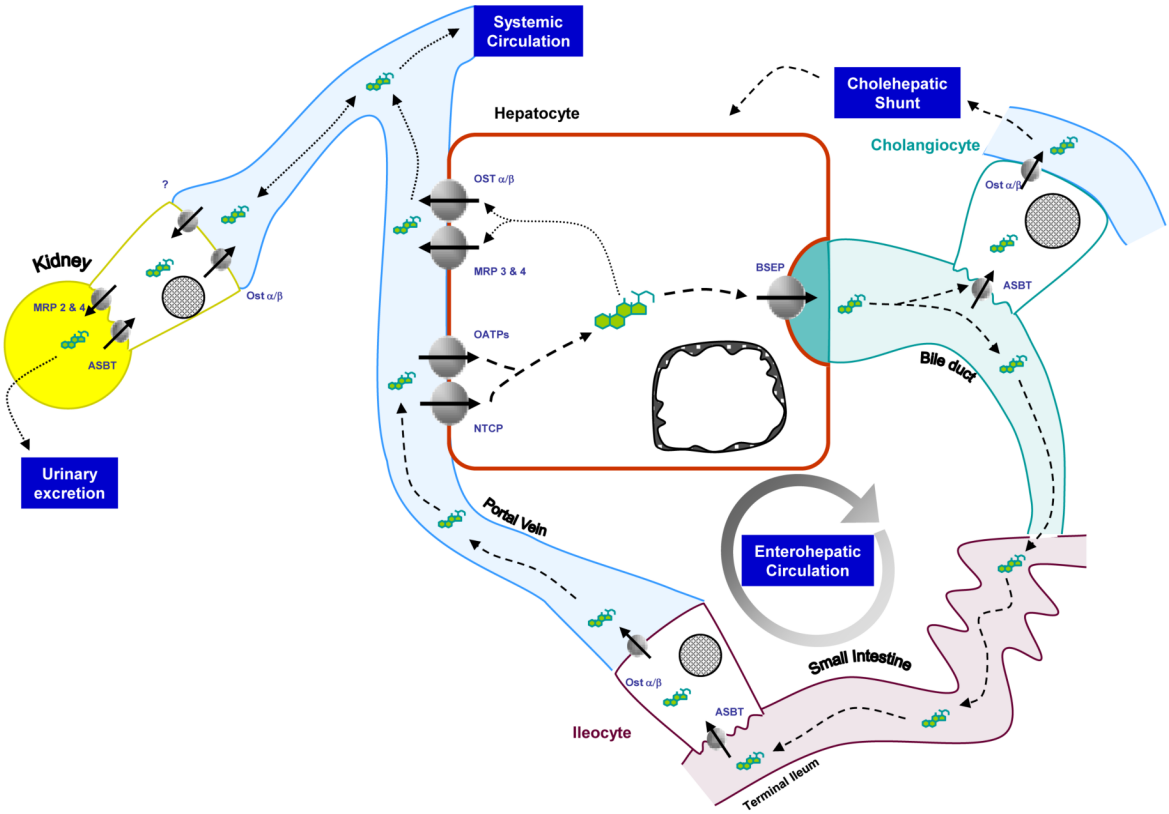

Figure 1. Roles for bile acid transporters in enterohepatic and systemic circulations

Bile acids are taken up from the intestinal lumen by the apical sodium bile acid transporter (Asbt) in the terminal ileum. After intracellular transport in the ileocyte mediated by Intracellular bile acid binding protein (Ibabp, not shown), bile acids are excreted by the heterodimeric transporter Ostα/β into the portal circulation. Upon reaching the liver sinusoids, the majority of conjugated bile acids are taken up by hepatocytes via sodium dependent and independent mechanisms, mediated by Ntcp and Oatps, respectively. Intracellular transport to the canalicular membrane is mediated by several possible transport proteins (see text), and subsequently excreted across the canalicular membrane into bile by the bile salt export pump (Bsep). After secretion into bile, the majority of bile acids travel the bile ducts to reach the intestinal lumen. A small proportion of bile acids can be taken up by cholangiocytes lining the bile ducts via Asbt and secreted across the basolateral membrane back into circulation, destined for either reuptake by the liver, (cholehepatic shunting), or or systemic circulation. Under conditions of cholestasis, alternative routes for elimination are used exporting bile acids across the sinusoidal membrane into the systemic circulation via Mrp3, Mrp4 and Ostα/β, ultimately destined for urinary excretion via the kidney. For more information about Mrp and Oatp proteins, see accompanying reviews in this Issue. The various components of the enterohepatic and cholehepatic shunts are connected with dashed lines, while those routes for systemic circulation or urinary excretion are denoted by dotted lines.

Table

Transporter	Tissue/Cell type	Cellular location	Major role	Regulation in human disease	Human SNPs, polymorphisms & mutations
Bsep	Hepatocyte	Canalicular membrane	ATP-dependent bile acid efflux	Suppressed in sepsis and cholestasis	Strautnieks et al. 1998 Jansen et al. 1999 Saito et al 2002 Wang et al 2002 Pauli-Magnus et al 2004 Plass et al 2004 Van Mil et al 2004 Hayashi et al 2005 Noe et al 2005 Lang et al 2006 Meier et al 2006 Kagawa et al 2007 Lam et al 2007 Lang et al 2007 Stieger et al 2007
Ntcp	Hepatocyte	Sinusoidal membrane	Na^+ dependent bile acid uptake	Suppressed in sepsis & cholestasis	Ho et al 2004 Geyer et al 2007
Asbt	Enterocyte, cholangiocyte, kidney	Apical membrane	Na^+ dependent bile acid uptake	Unknown	Oelkers et al 1997 Geyer et al 2007
Ostα/β	Hepatocyte, enterocyte, cholangiocyte, kidney	Sinusoidal membrane	bile acid efflux by facilitated diffusion	Upregulated in liver in late stage PBC	None described