# Chapter 2
# Hepatobiliary Transport of Bile Acids

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**Abstract** Bile acids are the major driving force of bile excretion from hepatocytes; they are synthesized from cholesterol via at least 17 enzymatic reactions. They play a critical role in cholesterol disposal and the absorption of fat and fat-soluble vitamins. The concentration of intracellular bile acid is tightly regulated by modulating expression of bile acid transporters via nuclear receptors. This article provides a comprehensive overview of the characteristics and regulatory networks of hepatobiliary bile acid transporters.

**Keywords** Bile acid • Transporter • Cholestasis

## 2.1 Introduction

Bile acids are the major driving force of bile excretion from hepatocytes; they are synthesized from cholesterol via at least 17 enzymatic reactions. They play a critical role in cholesterol disposal and the absorption of fat and fat-soluble vitamins. After excretion from hepatocytes into the bile canaliculus, most bile acids (~95%) are reabsorbed in the terminal ileum and return to the liver via the portal vein (enterohepatic circulation). Influx and efflux of bile acids in organs is mediated by organ-specific transporters (Fig. 2.1). In hepatocytes, bile acids are absorbed from the sinusoid by the $Na^+$-taurocholate cotransporting polypeptide (NTCP, SLC10A1) and secreted into the bile canaliculus by the bile salt export pump (BSEP, ABCB11). Other bile components are secreted by their corresponding transporters: phospholipids by multidrug resistance protein 3 (MDR3, ABCB4), organic anions by multidrug resistance-associated protein 2 (MRP2, ABCC2), and cholesterol by ABCG5/G8. In the terminal ileum, bile acids are absorbed from the intestinal lumen by the apical sodium-dependent bile acid transporter (ASBT, SLC10A2) and excreted into the portal vein by the organic solute transporters (OSTα/OSTβ, SLC51A/SLC51B) that facilitate bidirectional diffusion.

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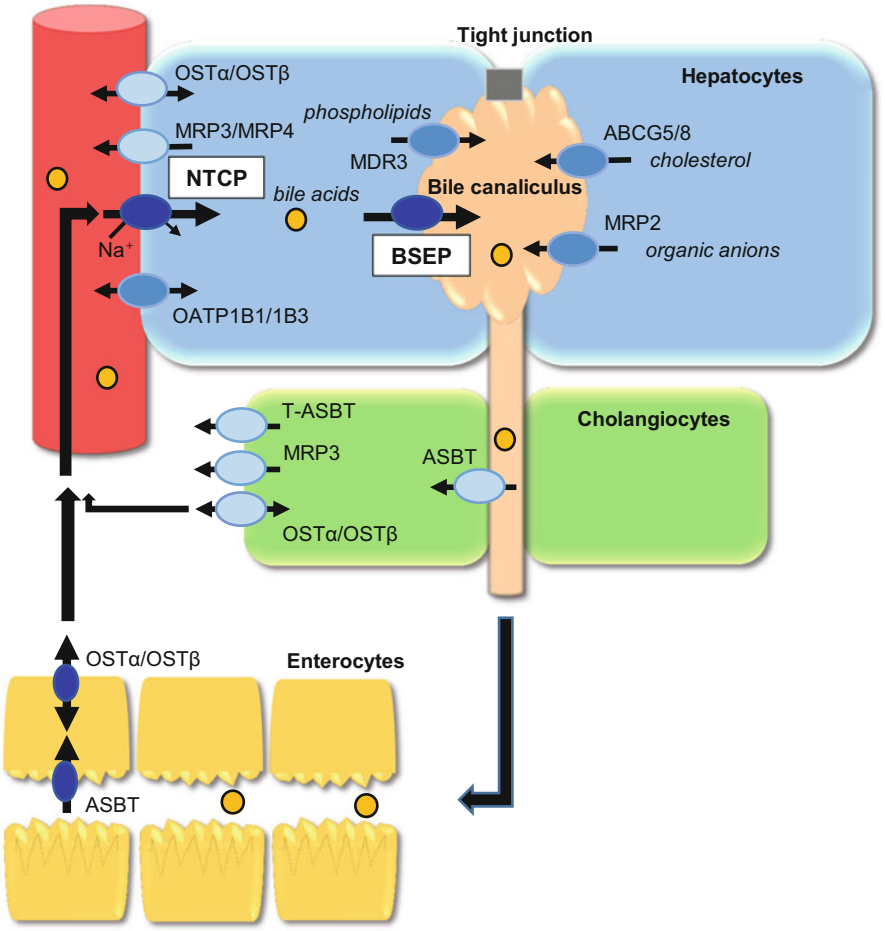


**Fig. 2.1** Bile acid transporters. In hepatocytes, bile acids are absorbed from the sinusoid by NTCP, and in part by OATPs, and are secreted into the bile canaliculus by BSEP. In the terminal ileum, they are absorbed from the intestinal lumen by ASBT and excreted into the portal vein by OSTα/OSTβ to return to the liver (enterohepatic circulation). Other components of bile are secreted into the bile canaliculus by MDR3 (phospholipids), MRP2 (organic anions), and ABCG5/G8 (cholesterol). OSTα/OSTβ, MRP3, and MRP4 are involved in retrograde bile acid elimination from the basolateral membrane to the sinusoid in cholestasis. In cholangiocytes, bile acids are absorbed by ASBT and secreted into the peribiliary plexus by OSTα/OSTβ, MRP3, and a truncated ASBT (t-ASBT) (cholehepatic shunting)

Bile acids are detergents and toxic to cells at high concentrations; therefore, their cellular concentration must be tightly regulated by refined feedback systems. Bile acids, now known as a signaling molecule, activate a nuclear receptor, farnesoid X receptor (FXR, NR1H4), and the G protein-coupled bile acid receptor, TGR5, thereby triggering a number of physiological reactions (see [Chap. 4] "Nuclear Receptor

Regulation"). In hepatocytes, bile acids bind to FXR, which represses NTCP and prevents further bile acid uptake, downregulates cholesterol 7α-hydroxylase (CYP7A1) to inhibit further bile acid synthesis, and activates BSEP to induce bile acid secretion into the bile canaliculus. All of these events ultimately result in a reduction in the concentration of intracellular bile acids. This article provides a comprehensive overview of the characteristics and regulatory networks of hepatobiliary bile acid transporters.

## 2.2 BSEP

### *2.2.1 Characteristics*

The human *BSEP* gene is located on chromosome 2 (2q24) and is translated into a protein comprising 1,321 amino acids, with a molecular mass of ~160 kDa [1]. BSEP belongs to the ABC subfamily B, harboring 12 potential transmembrane segments and two sets of Walker A and B motifs that bind to ATP [2–4]. BSEP is exclusively expressed in hepatocytes, where it resides along the canalicular membranes and exports bile acids into the bile canaliculus in an ATP-dependent fashion. The rat Bsep receives *N*-linked glycosylation at four asparagine residues in the first extracellular loop [5], sites that are also present in human BSEP. These glycans are required for correct trafficking to the canalicular membrane; loss of two or more glycans results in rapid degradation at the proteasome [5]. The intracellular distribution of Bsep was analyzed using pulse-chase studies in rats [6, 7]. Newly synthesized Bsep traffics directly from the Golgi to the canalicular membrane through a post-Golgi endosomal fraction. This is in contrast to other canalicular proteins, such as dipeptidyl peptidase IV and the canalicular cell adhesion molecule (cCAM105), which reach the basolateral membrane before arriving at the canalicular membrane (transcytosis) [6]. Bsep cycles between intracellular pools and the canalicular membrane, and taurocholic acid (TCA) and cAMP increase the amount of Bsep in the canalicular membrane [7]. Studies using WIFB9 cells, a stable hybrid of rat hepatoma and human fibroblasts with sealed bile canaliculi, revealed that Bsep constitutively cycles between the canalicular membrane and Rab11a-positive recycling endosomes [8]. HS-1-associated protein X-1 (HAX-1) [9] and non-muscle myosin II regulatory light chain 2a (MLC2a) [10] were identified as binding partners in a yeast two-hybrid screen. HAX-1 participates in clathrin-mediated endocytosis through interactions with cortactin [9]. MLC2a is involved in trafficking of newly synthesized Bsep to the canalicular membrane [10]. The AP2 adaptor complex is involved in clathrin-dependent endocytosis through interactions with a tyrosine motif at the carboxyl terminus of BSEP [11, 12].

$p38^{MAPK}$ is involved in BSEP trafficking from the Golgi to the canalicular membrane, and tauroursodeoxycholic acid (TUDCA)-induced choleretic action is

dependent on $p38^{MAPK}$ activation [13]. Short-chain ubiquitination is associated with BSEP degradation and is modulated by 4-phenylbutyrate (4PBA) [14].

Human BSEP transports glycine and taurine conjugates of the two primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA), with high affinity and selectivity [2, 15–17].

### 2.2.2 Gene Regulation

*BSEP* expression is tightly regulated by the nuclear receptor, FXR. When bile acids bind to FXR, FXR forms a heterodimer with retinoid X receptor (RXR) [18] and induces *BSEP* upregulation via binding to the FXR-responsive element (FXRE) in the promoter region [19, 20]. Besides endogenous FXR agonists, such as CDCA, deoxycholic acid (DCA), and CA [18], more potent synthetic FXR agonists such as 6α-ethyl-CDCA (obeticholic acid, INT-747) [21], 6α-ethyl-3α,7α,23-trihydroxy-24-nor-5β-cholan-23-sulfate (INT-767) [22], and GW4064 [23] upregulate *BSEP* expression in various cell lines and animal models. As for obeticholic acid, clinical trials for primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and nonalcoholic steatohepatitis (NASH) are ongoing. Ursodeoxycholic acid (UDCA), which is often used to treat cholestasis, is not an FXR ligand. Notably, muricholic acid, one of the major bile acid species present in rodents but not in humans, is antagonistic to FXR [24]. In $Fxr^{-/-}$ mice, *Bsep* expression levels are markedly reduced at baseline and are not induced further by bile acid feeding [25], suggesting a critical role for FXR in the regulation of *BSEP* expression. Furthermore, a recent report documented four patients from two families with a homozygous loss of FXR exhibiting severe neonatal cholestasis [26].

Besides FXR, several other transcriptional factors regulate *BSEP* gene expression. Liver receptor homolog 1 (LRH-1, NR5A2), a transcriptional regulator for the biosynthesis and transport of cholesterol and bile acids, activates the BSEP promoter [27], and *Bsep* expression is reduced in LRH-1 knockout mice [28].

Nuclear factor erythroid 2-related factor 2 (Nrf2) is another transcriptional regulator for BSEP [29]. Nrf2 maintains redox homeostasis by regulating many phase I and II drug-metabolizing and detoxification enzymes. Nrf2 upregulates *BSEP* by binding to musculoaponeurotic fibrosarcoma recognition element (MARE) 1 in the BSEP promoter. Upregulation of *Bsep* expression by alpha-naphthyl isothiocyanate (ANIT) is abrogated in Nrf2-null mice [30].

Recently, Song et al. reported that 17β-estradiol (E2) repressed *BSEP* expression through direct interaction with estrogen receptor α (ERα) and FXR in the late stage of pregnancy [31], implicating a mechanistic role for the E2/ERα/FXR pathway in intrahepatic cholestasis of pregnancy (ICP).

### 2.2.3 BSEP-Associated Diseases

There are two types of hereditary intrahepatic cholestatic disease: progressive familial intrahepatic cholestasis (PFIC) and benign recurrent intrahepatic cholestasis (BRIC). PFIC patients progress to liver failure and require liver transplantation in childhood, whereas BRIC patients display intermittent and usually non-progressive jaundice (reviewed in [32]). PFIC1 and BRIC1 are caused by mutations in the *FIC1* (*ATB8B1*) gene, which encodes a P-type ATPase functioning as a flippase for phosphatidylserine, whereas PFIC3 is caused by mutations in the *MDR3* gene. PFIC2 and BRIC2 are caused by mutations in *BSEP*, and more than 150 genetic abnormalities, including missense, nonsense, deletions, insertions, and splice-site mutations, have been identified [3, 33–36]. Some missense mutations and single nucleotide polymorphisms (SNPs) can cause aberrant pre-mRNA splicing, resulting in impaired BSEP function [35]. PFIC2 is characterized by absent or much reduced canalicular BSEP expression [34, 37] as well as a markedly diminished concentration of biliary bile acid [37].

To elucidate the effects of these mutations and SNPs on BSEP function, a number of studies have been performed using cell lines expressing a mutated form of BSEP [38–42]. The BSEP protein harboring a disease-associated missense mutation is unstable and is degraded in the proteasome [41, 42]. TCA transport activity of BSEP was analyzed in BSEP-expressing MDCKII cells. The activity of PFIC2 mutants (D482G, E297G, K461E, G982R, R1153C, R1268Q, and 3767–3768insC) was 0–30% that of wild type, and BRIC2 mutants (A570T and R1050C) exhibited 50–60% wild-type activity [42]. The reduced activity corresponded to the stability of synthesized BSEP protein. Thus, the difference in the severity of the clinical phenotype between PFIC2 and BRIC2 may be explained by the differences in transport activity of BSEP harboring corresponding mutations [41, 42]. Several patients who had clinical and histopathological characteristics of BRIC progressed to PFIC [33, 43], suggesting a possible phenotypic progression between BRIC2 and PFIC2. Furthermore, the E297G mutation, which is responsible for PFIC2, is also found in BRIC2 patients [33]. Therefore, although the BSEP genotype appears to play an important role in determining clinical severity, other precipitating factors, including viral infection and pregnancy, may also participate [33].

Impaired BSEP function as a cause of cholestasis has been suggested for other congenital diseases. Although the exact molecular mechanism underlying cholestasis in PFIC1 is not fully understood, FIC1 deficiency may lead to a loss of asymmetric phospholipid distribution in the canalicular membrane, decreasing membrane stability, thereby disturbing the function of transporters including BSEP [44, 45]. Microvillus inclusion disease (MVID), a hereditary disorder manifesting intractable diarrhea associated with mutations in the *MYO5B* gene, occasionally accompanies PFIC-like cholestasis. Reduced BSEP expression in the canalicular membrane due to disturbed MYO5B/RAB11A apical recycling endosome pathway has been proposed as a molecular mechanism for cholestasis in this disease [46].

An association between BSEP SNP and acquired intrahepatic cholestasis has been reported. The C-allele frequency of *BSEP* c.1331T>C (p. V444A) (rs2287622) SNP was higher among patients with ICP (67% in patients versus 54% in controls, $P < 0.001$) [47]. In a recent comprehensive study, two intronic SNPs (rs7577650 and rs3815676) were identified as significant risk alleles associated with ICP. The V444A SNP remained associated with the disease, but the association was driven by rs7577650 [48], suggesting that the V444A SNP is not causative. The effect of an amino acid substitution at position 444 on BSEP function is controversial. Western blot analysis on normal liver tissues from patients undergoing liver resection revealed that canalicular BSEP expression was slightly, but not significantly, reduced in individuals carrying the 444A polymorphism [49]. In another study that utilized a bank of human liver samples, *BSEP* mRNA, but not protein, expression was significantly attenuated in individuals with the 444A polymorphism [50]. The bile acid transport activity of 444A BSEP was not reduced when expressed in Sf9 [51] and HeLa [50] cells and was slightly reduced by up to 20% in MDCKII cells [52].

Impaired BSEP function is also involved in drug-induced liver injury; its severity is associated with dual inhibition of BSEP and mitochondrial function [53]. The association of BSEP V444A SNP in drug-induced cholestasis has been reported in European populations (76% in patients versus 57% in controls) [51]. However, this association was not reproducible among Japanese patients with drug-induced cholestasis (66% in patients versus 78% in controls) [52]. Further investigation is necessary to identify underlying causative risk alleles in the different populations.

### *2.2.4 Choleretic Agents*

Given that bile acids are the major driving force for bile excretion, drugs that upregulate or activate BSEP are good candidates to treat intrahepatic cholestasis. UDCA is one of the drugs most commonly used for hepatobiliary diseases including PBC, PSC, cholestasis, and cholelithiasis. UDCA exerts a choleretic effect by targeting BSEP to the canalicular membrane [13, 54–56] via activation of $p38^{MAPK}$ and a $Ca^{2+}$-independent protein kinase C (PKC) isoform [13, 55]. In fact, UDCA administration induced remission at least transiently in children with PFIC2 by retargeting BSEP to the canalicular membrane [57].

4PBA enhanced the cell surface expression and transport capacity of wild-type BSEP and BSEP carrying a PFIC2 mutation (E297G and D482G) in MDCKII cells [58]. Administration of 4PBA also induced canalicular Bsep expression, accompanied by an increase in biliary excretion of TCA in rats [58]. These effects may be achieved by decreasing short-chain ubiquitination-mediated Bsep degradation [14]

and by reducing AP2 adaptor complex-mediated clathrin-dependent endocytosis [11]. In the clinical setting, 4PBA therapy improved liver function tests, liver histology, and itching in patients with PFIC2 [59, 60] and BRIC2 [61].

### *2.2.5 Antibody-Induced BSEP Deficiency*

Orthotopic liver transplantation usually yields a good outcome in PFIC2 patients. However, since the first case was documented by Keitel et al. [62], several cases have been reported of PFIC2 children with recurring progressive intrahepatic cholestasis in the presence of an autoantibody against BSEP after liver transplantation [63–66]. Generation of a polyclonal antibody to target the first extracellular loop of BSEP may therefore be responsible for inhibiting BSEP function [66].

## 2.3 NTCP

### *2.3.1 Characteristics*

NTCP is a glycoprotein of approximately 38 kDa, consisting of 349 amino acids [67, 68]. NTCP is localized to the sinusoidal membrane of hepatocytes and functions as an electrogenic sodium-solute cotransporter [69]. Major substrates of NTCP include glycine- and taurine-conjugated bile acids, but unconjugated and sulfated bile acids can still be transported to some extent [70–72].

Other sinusoidal transporters, including organic anion transporting polypeptides (OATP) 1B1 (SLCO1B1) and OATP1B3 (SLCO1B3), are able to transport conjugated bile acids in a sodium-independent manner, as well as unconjugated species [73]. The significance of NTCP in hepatic bile acid uptake is unknown due to a lack of NTCP-null patients. Recently a case of NTCP deficiency was documented [74], a 5-year-old girl manifesting conjugated hypercholanemia without any sign of liver injury. Sequencing of the *NTCP* gene revealed a single homozygous nonsynonymous point mutation (c.755G>A, p. R252H). The R252H mutation resulted in a marked reduction in TCA uptake, along with a lack of plasma membrane expression when it was expressed in HEK293T cells. This indicates that NTCP is the major transporter for hepatocellular uptake of conjugated bile acids. However, serum bile acid concentrations were unexpectedly normal in the majority of *Slc10a1*$^{-/-}$ mice [75], suggesting differences in NTCP contribution among species.

### 2.3.2 Transcriptional Regulation

*NCTP* regulation is important for suppressing further influx of potentially toxic bile acids into hepatocytes and is repressed in patients with inflammation-induced cholestasis [76] and advanced PBC [77], as well as in several cholestatic animal models [78–80]. Although its transcriptional regulation is mediated by bile acids, hormones such as estrogen and prolactin, and pro-inflammatory cytokines may also be involved, depending on the species (reviewed in [81]). Bile acids repress *NTCP* transcription through FXR activation, which in turn induces small heterodimer partner (SHP). SHP inhibits *NTCP* upregulation by competing with coactivators for binding to hepatocyte nuclear factor 4 alpha (HNF-4α) and RXRα [80] and by suppressing retinoic acid receptor alpha (RARα) in rats [82] and glucocorticoid receptor (GR) and peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) in humans [83]. However, an additional SHP-independent pathway probably exists, since *Ntcp* repression was not completely abolished in $Shp^{-/-}$ mice fed with CA [84].

NTCP expression is also regulated posttranslationally. Insertion of NTCP into the plasma membrane by cAMP is mediated by the phosphoinositide-3-kinase signaling pathway [85, 86] and protein phosphatase 2B (PP2B)-induced dephosphorylation of NTCP [87]. In contrast, taurochenodeoxycholic acid (TCDCA) decreases sinusoidal NTCP expression by inducing NTCP endocytosis in a PKC- and PP2B-dependent manner [88].

### 2.3.3 NTCP as a Receptor for Hepatitis B and D Virus (HBV and HDV)

NTCP is attracting much attention as a functional receptor for HBV and HDV [89]. The large surface protein pre-S1 domain of HBV is a key determinant for receptor binding. In vitro studies demonstrated that myrcludex B, a myristoylated lipopeptide derived from the pre-S1 domain, blocked bile acid uptake by NTCP [90], while taurine or glycine conjugates of CA and UDCA inhibited HBV infection [13]. CYP7A1, the rate-limiting enzyme that synthesizes bile acids from cholesterol, was induced in human liver chimeric mice that were infected with HBV or were given myrcludex B and in liver biopsy samples from HBV-infected patients [91]. This may be a compensatory response against reduced bile acid uptake by HBV binding to NTCP. Interestingly, the NTCP variant p. S267F (c.800C>T, s2296651), which exhibits reduced bile acid transport capacity and has only been observed among Asians [92], is protective against HBV chronic infection [93] as well as progression to cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis B [94].

## 2.4 Other Basolateral Bile Acid Transporters

Retrograde bile acid elimination from the basolateral membrane of hepatocytes to the sinusoid represents a rescue mechanism for avoiding intracellular bile acid overload. The relevant transporters include OSTα/OSTβ, MRP3 (ABCC3) and MRP4 (ABCC4).

OSTα comprises 340 amino acids, forms a heterodimer with OSTβ comprising 128 amino acids, and is expressed at the basolateral membrane of ileal enterocytes, hepatocytes, and cholangiocytes. Co-expression is necessary for stable expression of OSTα and OSTβ and their delivery to the plasma membrane [95, 96]. In enterocytes, OSTα/OSTβ is responsible for excreting bile acids into the portal circulation to achieve enterohepatic circulation under physiological conditions. In hepatocytes, this transporter is upregulated to transport excess bile acids back to the sinusoidal compartment in cholestasis. Hepatic OSTα/OSTβ expression was increased in patients with advanced PBC [97]. Upregulation was also observed in mice following common bile duct ligation (CBDL) [97], ANIT treatment [98], and CA feeding [99], which was dependent on FXR [100, 101].

Mrp3 and Mrp4 were upregulated in CBDL mice independently of FXR [102]. *Mrp3*$^{-/-}$ mice had normal bile acid transport function [103], whereas *Mrp4*$^{-/-}$ mice exhibited an impaired cytoprotective response to CBDL-induced cholestasis [104]. MRP4, but not MRP3, was upregulated in patients with PFIC2 and PFIC3 [105], suggesting that MRP4 plays an important role in the compensatory reaction to cholestatic liver injury. Regulatory nuclear receptors include constitutive androstane receptor (CAR), pregnane X receptor (PXR) and vitamin D receptor (VDR) for MRP3, and CAR and peroxisome proliferator-activated receptors α (PPARα) for MRP4 (reviewed in [81]).

## 2.5 Bile Acid Transporters in Cholangiocytes

Cholangiocytes play an important role in bile formation by secreting bicarbonate and water and possess transport systems for the influx and efflux of bile acids. Unconjugated bile acids possibly enter cholangiocytes via passive diffusion, whereas conjugated bile acids are absorbed by ASBT [106], which is also expressed in the terminal ileum to absorb bile acids from the intestinal lumen. Bile acid secretion from the basolateral membrane into the peribiliary plexus is mediated by OSTα/OSTβ, MRP3, and a truncated ASBT (t-ASBT) [106–110]. These transport systems may play a limited role under normal physiological conditions; however, "cholehepatic shunting" [111], which bypasses enterohepatic circulation along with bile duct proliferation, may help to reduce bile acid overload in cholestasis due to bile duct obstruction.

## 2.6 Conclusions

In this review, the characteristics and regulatory systems of hepatobiliary bile acid transporters are presented. Bile acids are among the most essential molecules to organisms. The majority of bile acids are recycled through the enterohepatic circulation, and their cellular concentration is tightly regulated by refined feedback mechanisms. Impaired function of bile acid transporters causes various types of liver injury and may be responsible for other diseases for which their causality is not yet known. Nuclear receptors regulating bile acid transporters are attractive therapeutic targets, and clinical trials for obeticholic acid are ongoing. Further understanding of bile acid transporters will likely lead to new therapeutic options for intractable liver diseases.

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