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Review

Getting the mOST from OST: Role of organic solute transporter, OSTα-OSTβ, in bile acid and steroid metabolism

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ABSTRACT

The organic solute transporter (OST)(alpha)-OST(beta) is an unusual heteromeric carrier expressed in a variety of tissues including the small intestine, colon, liver, biliary tract, kidney, and adrenal gland. In polarized epithelial cells, OSTα-OSTβ protein is localized on the basolateral membrane and functions in the export or uptake of bile acids and steroids. This article reviews recent results including studies of knockout mouse models that provide new insights to the role of OSTα-OSTβ in the compartmentalization and metabolism of these important lipids.

1. Introduction

Many of the transporters important for maintenance of the enterohepatic circulation of bile acid have been identified over the past 2 decades. Notably absent from that list was the major transporter responsible for export of bile acids across the basolateral membrane of the enterocyte, cholangiocyte, and renal proximal tubule cell. Despite numerous attempts over the past 3 decades using protein purification [1], photoaffinity labeling [2], or candidate gene approaches [3,4], the identity of the basolateral membrane bile acid transporter remained an important missing link in our understanding of the enterohepatic circulation of bile acids. This mystery was recently solved with the identification and characterization of a novel organic solute transporter (OST), OSTα-OSTβ [5].

The previously identified solute carrier (SLC) and ATP-binding cassette (ABC) transporter family members important for maintaining the enterohepatic circulation of bile acids are thought to function as monomers or homo-multimers. In contrast, OST activity requires coexpression of multiple subunits. OST consists of a larger polytopic membrane protein (OSTα) and a smaller type 1 single-pass membrane protein (OSTβ), a paradigm more similar to the heteromeric amino acid transporters [6–8]. Since OSTα-OSTβ was first identified and cloned from the little skate in 2001 [5], much has been learned about the properties, regulation, and function of this novel transporter [9,10]. This review highlights our current understanding of the physiological roles of OSTα-OSTβ in bile acid and steroid transport and also identifies important questions that remain to be answered.

2. Introduction to the enterohepatic synthesis of bile acids and regulation of hepatic bile acid synthesis

This section briefly highlights the major transporters and mechanisms involved in the enterohepatic circulation of bile acids and regulation of their hepatic synthesis, subjects that have recently been reviewed in detail [11–15]. The tissue expression and function of OSTα-OSTβ and other major transporters involved in the metabolism and enterohepatic circulation of bile acids are summarized in Fig. 1. Bile acids are synthesized from cholesterol in the liver, conjugated (N-

Abbreviations: ABC, ATP-binding cassette; ASBT, apical sodium-dependent bile acid transporter; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone-3-sulfate; ER, endoplasmic reticulum; Endo H, endoglycosidase H; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FXR, farnesoid X receptor; GFP, green fluorescent protein; HEK, human embryonic kidney; MDCK, Madin–Darby canine kidney; MRP, multidrug resistance-associated protein; OST/Ost, organic solute transporter; PNGase, peptide:N-glycosidase F; SLC, Solute Carrier; YFP, yellow fluorescent protein

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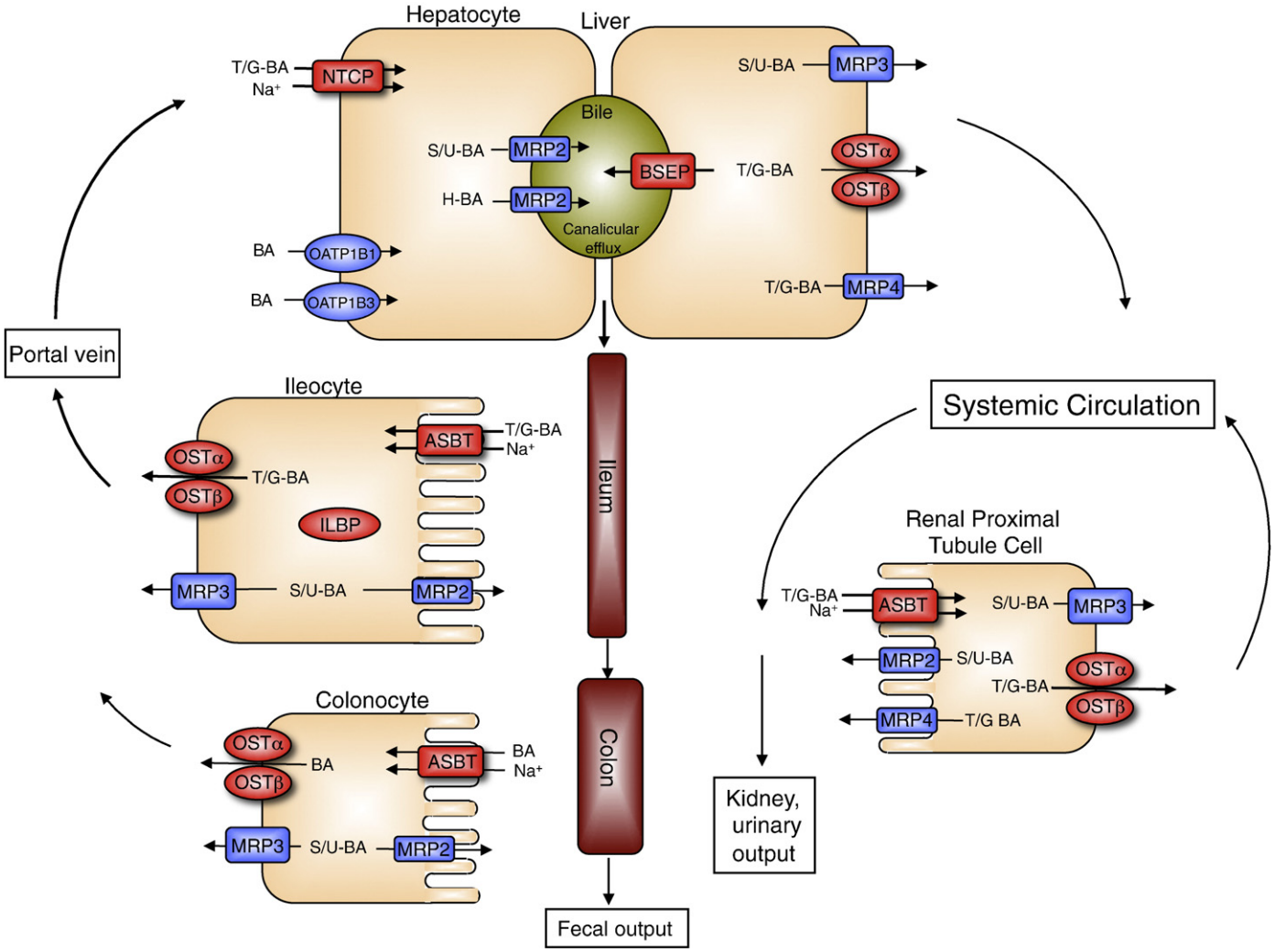

Fig. 1. Enterohepatic circulation of bile acids showing the individual transport proteins in hepatocytes, ileocytes (ileal enterocytes), and renal proximal tubule cells. Overall, this integrated transport system minimizes fecal and urinary bile acid loss and functions to largely restrict these potentially cytotoxic detergents to the intestinal and hepatobiliary compartments. BA, bile acids; T/G, taurine- or glycine-conjugated bile acids; sulfate or glucuronide (S/U)-conjugated bile acids; H, tetrahydroxylated bile acids.

acyl amidated) to taurine or glycine, secreted into bile, and stored in the gallbladder. After entering the small intestine, bile acids facilitate absorption of fat-soluble vitamins and cholesterol [16]. Most of the bile acids (>90%) are reabsorbed from the intestine and returned to the liver via the portal venous circulation. They are then taken up by the hepatocyte and resecreted across the canalicular membrane into bile [17]. Since these processes, i.e. intestinal absorption, return to the liver in the portal circulation, and hepatic extraction of bile acids, are so efficient, the majority of the bile acids secreted by the hepatocyte are derived from the recirculating bile acid pool with less than 10% from new *de novo* hepatic synthesis.

After their synthesis or reconjugation in the hepatocyte, taurine- and glycine-conjugated bile acids are secreted into bile by the canalicular membrane bile salt export pump (BSEP; gene symbol *ABCB11*). The small amount of bile acids that have been modified by the addition of sulfate or glucuronide is secreted into bile by the multidrug resistance-associated protein-2 (MRP2; gene symbol *ABCC2*) and possibly the breast cancer related protein (BCRP; gene symbol ABCG2). Bile acids can also be modified by additional hydroxylation and these species are secreted into bile by MRP2 and possibly P-glycoprotein (MDR1; gene symbol *ABCB1A*). The divalent or tetrahydroxylated bile acids are present in very small quantities under normal physiological conditions, but may accumulate in disease states such as cholestasis. After their secretion, bile acids are stored in the gallbladder and empty into the intestinal lumen in response to a meal. Bile acids are poorly absorbed in the proximal small intestine, but efficiently taken up by the apical sodium-dependent bile acid transporter (ASBT; gene symbol *SLC10A2*) in the ileum. After entering the ileal enterocyte, bile acids bind to the cytosolic ileal lipid binding protein (ILBP; gene symbol *FABP6*) and are efficiently exported across the basolateral membrane into the portal circulation by the more recently discovered heteromeric transporter OSTα-OSTβ. The multidrug resistance-associated protein-3 (MRP3; gene symbol *ABCC3*) is a minor contributor to basolateral membrane export of native bile acids from the enterocyte, but may have a more significant role in export of any modified (glucuronidated or sulfated) bile acids that may be formed. MRP2 may also serve to export modified bile acids, across the apical brush border membrane back into the intestinal lumen. The small fraction of bile acids that escape absorption in the small intestine spill into the colon, where they are extensively deconjugated and dehydroxylated by the endogenous bacterial flora. The unconjugated bile acids can be absorbed passively or actively and returned to the liver, where they are efficiently reconjugated and mix with newly synthesized bile acids to be resecreted into bile. This process of intestinal deconjugation and hepatic reconjugation is a normal part of bile acid metabolism. Colonocytes express very low levels of ASBT, but appreciable levels of MRP3 and OSTα-OSTβ. These carriers may contribute to the absorption of unconjugated bile acids from the