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REVIEW

New insights in bilirubin metabolism and their clinical implications

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Abstract

Bilirubin, a major end product of heme breakdown, is an important constituent of bile, responsible for its characteristic colour. Over recent decades, our understanding of bilirubin metabolism has expanded along with the processes of elimination of other endogenous and exogenous anionic substrates, mediated by the action of multiple transport systems at the sinusoidal and canalicular membrane of hepatocytes. Several inherited disorders characterised by impaired bilirubin conjugation (Crigler-Najjar syndrome type Ⅰ and type Ⅱ, Gilbert syndrome) or transport (Dubin-Johnson and Rotor syndrome) result in various degrees of hyperbilirubinemia of either the predominantly unconjugated or predominantly conjugated type. Moreover, disrupted regulation of hepatobiliary transport systems can explain jaundice in many acquired liver disorders. In this review, we discuss the recent data on liver bilirubin handling based on the discovery of the molecular basis of Rotor syndrome. The data show that a substantial fraction of bilirubin conjugates is primarily secreted by MRP3 at the sinusoidal membrane into the blood, from where they are subsequently reuptaken by sinusoidal membrane-bound organic anion transporting polypeptides OATP1B1 and OATP1B3. OATP1B proteins are also responsible for liver clearance of bilirubin conjugated in splanchnic organs, such as the intestine and kidney, and for a number of endogenous compounds, xenobiotics and drugs. Absence of one or both OATP1B proteins thus may have serious impact on toxicity of commonly used drugs cleared by this system such as statins, sartans, methotrexate or rifampicin. The liver-blood cycling of conjugated bilirubin is impaired in cholestatic and parenchymal liver diseases and this impairment most likely contributes to jaundice accompanying these disorders.

Key words: Hyperbilirubinemia; Hereditary jaundice; UGT1A1; ABCC2; Organic anion transporting polypeptide 1B1; Organic anion transporting polypeptide 1B3

Core tip: Experiments with *Oatp1a/1b*-null mice and *Oatp1a/1b*; *Abcc3* combination knockout mice plainly demonstrated that even under physiologic conditions a substantial portion of bilirubin glucuronides is not excreted directly into bile but is transported back to the blood by Abcc3. *Oatp1a/1b* activity accentuated in downstream (centrizonal) hepatocytes allows efficient reuptake of bilirubin conjugates, with a subsequent possibility being safely eliminated by excretion into bile. This and molecular findings in Rotor syndrome suggest that human transporters MRP3 and OATP1Bs form a sinusoidal liver-to-blood cycle which mediates shifting (hopping) of bilirubin and other substrates from periportal to centrizonal hepatocytes (References 18, 19, 22, 125).

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INTRODUCTION

Bilirubin is the end product of heme breakdown. About 80% of bilirubin originates from degradation of erythrocyte haemoglobin in the reticuloendothelial system; the remaining 20% comes from inefficient erythropoiesis in bone marrow and degradation of other heme proteins[1-4]. Water insoluble, unconjugated bilirubin (UCB) bound to albumin is transported to the liver where it is removed from the plasma. The exact mechanism of UCB uptake is unknown; however, passive transmembrane diffusion seems to be combined with active transport mediated by several sinusoidal transporters (see below). Within the cytoplasm of hepatocytes, bilirubin is bound to ligandin and transported to endoplasmic reticulum where conjugation with glucuronic acid takes place. Conjugation is catalysed by the enzyme uridine diphosphate glycosyltransferase 1A1 (UGT1A1; EC2.4.1.17), a member of an enzyme family in the endoplasmic reticulum and nuclear envelope of hepatocytes[5-8]. In addition to the liver, UGT activity has also been detected in the small intestine and kidney[9,10]. *UGT1A1* gene (ID: 54658) is a part of a complex locus encoding 13 UDP-glucuronosyltransferases[11]. The locus contains a series of thirteen unique alternate promoters and first exons, followed by four common exons No. 2-5. Theoretically, each of the unique first exons is spliced to the first of the four shared exons. The unique first exons encode different substrate binding domains whereas the other functional domains encoded by the shared exons 2-5 are the same[11-15]. In reality, only 9 of the 13 predicted *UGT1A*s are active genes encoding functional enzymes; four are nonfunctional pseudogenes.

The excretion of conjugated bilirubin into bile is mediated by an ATP-dependent transporter identified as the multidrug resistance-associated protein MRP2/cMOAT and, to a lesser extent, also by ATP-binding cassette (ABC) efflux transporter ABCG2. MRP2 is encoded by *ABCC2* and expressed under physiologic conditions at the apical (canalicular) membrane of hepatocytes and, to a much lesser extent, in the kidney, duodenum, ileum, brain and placenta[16]. Since the MRP2 mediated export represents an important step in detoxification of many endogenous and exogenous substrates, the absence of functionally active MRP2 prevents the secretion of these conjugates into bile. Absence of MRP2 mediated transport is followed by upregulation of the basolateral MRP2 homologues at the sinusoidal membrane of hepatocytes and conjugated bilirubin flow is redirected into sinusoidal blood[17]. Aside from MRP2 mediated transport of conjugated bilirubin into bile, recent studies have shown that a significant fraction of the bilirubin conjugated in the liver is, under physiologic conditions, secreted into sinusoidal blood and subsequently reuptaken by hepatocytes for final biliary excretion[18,19]. The process is mediated by sinusoidal transporters MRP3 and organic anion-transporting polypeptides OATP1B1 and OATP1B3. OATP1B transporters facilitate sodium-independent uptake of numerous endogenous and exogenous substrates[20,21]. Since expression of OATP1Bs is higher in centrilobular hepatocytes, the MRP3-OATP1B1/3 loop is likely responsible for shifting (hopping) of conjugated bilirubin and other substrates from the periportal to the centrilobular zone of the liver lobule (Figure 1). Such intralobular substrate transfer may protect periportal hepatocytes against elevated concentrations of various xenobiotics[22]. In addition, the OATP1B proteins mediate hepatic clearance of bilirubin conjugated in splanchnic organs and may represent an important alternative pathway in enterohepatic circulation[18].

OATP1Bs may also contribute to liver uptake of UCB since complete absence of both OATP1Bs in Rotor syndrome (RS, see below) is associated with elevated levels of UCB and single nucleotide polymorphisms in genes encoding OATP1B proteins have been shown to influence serum bilirubin level[23,24]. Furthermore, results of functional studies demonstrate that OATP1B3, but not OATP1B1, may play an important role in the carrier-mediated uptake of foetal UCB by the placental trophoblast and contribute to elimination of UCB across the placental barrier[25,26].

Mild or moderately elevated serum bilirubin seems to be beneficial: Bilirubin is known as a strong antioxidant[27,28] and the protective effects of bilirubin on atherogenesis and cancerogenesis have been demonstrated in both *in vitro* and *in vivo* studies[29-33]. On the other hand, patients with profound unconjugated hyperbilirubinemia are at risk for bilirubin encephalopathy (kernicterus)[34,35]. The toxic effects of bilirubin are explained by inhibition of DNA synthesis[36]. Bilirubin may also uncouple oxidative phosphorylation and inhibit adenosine triphosphatase (ATPase) activity of brain mitochondria[37,38]. Bilirubin mediated inhibition of various enzyme systems, RNA synthesis and protein synthesis in the brain and liver, and/or alteration of carbohydrate metabolism in the brain can also contribute to its toxicity[39-43]. The accumulation of bilirubin in plasma and tissues results in characteristic yellow discoloration of tissues known as icterus or jaundice.

Inherited disorders of bilirubin excretory pathway played the key role in understanding the individual steps of the bilirubin excretory pathway. Disrupted regulation of hepatobiliary transport systems explained jaundice in many acquired liver disorders[44-48]. Additional information was obtained from a number of animal models of hereditary jaundice. These include the Gunn rat and *Ugt1*(-/-) mouse mimicking the Crigler-Najjar syndrome type I [49-51], the Bolivian population of squirrel monkeys mimicking Gilbert syndrome (GS)[52,53] and mutant TR or GY (Groningen yellow) rats with organic anion excretion defect (TR -/-), Eizai hyperbilirubinuria rats (EHBR), mutant Corriedale sheep, and *Mrp2*(-/-) mice, all modelling the Dubin-Johnson syndrome (DJS)[54-58].

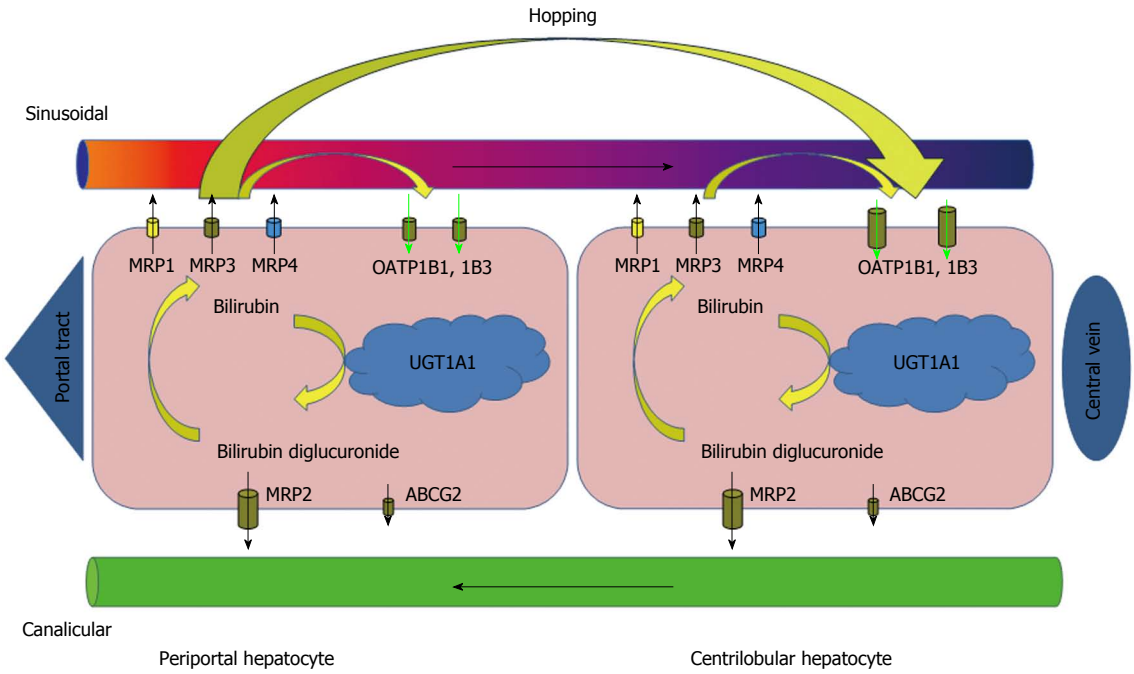

Figure 1 Liver cycle of conjugated bilirubin. Bilirubin conjugated in endoplasmic reticulum of hepatocytes is secreted into the bile. This process is mediated by MRP2/ABCC2 with possible minor contribution of other transporters (ABCG2) at the canalicular membrane of hepatocytes. In addition, even under physiologic conditions, a fraction of bilirubin conjugates is secreted by MRP3 across the sinusoidal membrane into the blood, from where they can be subsequently reuptaken by sinusoidal membrane-bound OATP1B1 and OATP1B3 transporters. The highest overall expression of OATP1Bs has been demonstrated at the centrilobular hepatocytes. The process of substrate shifting (hopping) from periportal to centrizonal hepatocytes may act as a protection of the periportal hepatocytes against elevated concentrations of various xenobiotics. MRP: Multidrug resistance-associated protein; OATP: Organic anion transporting polypeptide; UGT: Uridine diphosphate glucuronosyltransferase; ABC: ATP-binding cassette.

HEREDITARY PREDOMINANTLY UNCONJUGATED HYPERBILIRUBINEMIA

Conjugation of bilirubin in endoplasmic reticulum is catalysed by the enzyme UGT1A1. Mutations in *UGT1A1* can lead to decreased expression or partial or even complete inactivation of the enzyme[59]. By contrast, expression of *UGT1A1* can be increased by phenobarbital (PB) administration. PB response activity is delineated to a 290-bp distal enhancer module sequence (-3483/-3194) glucuronosyltransferase phenobarbital response enhancing motif (gtBPREM) of the human *UGT1A1*[59,60]. gtBPREM is activated by the nuclear orphan receptor, human constitutive active receptor (hCAR). CAR is a cytoplasmic receptor which, after treatment with activators such as PB, translocates into the nucleus, forms a heterodimer with the retinoid X receptor and activates the PB response enhancer element.

Three types of inherited, predominantly unconjugated hyperbilirubinemia with different levels of UGT1A1 activity are recognised: Crigler-Najjar syndrome type I (CN1), type II (CN2) and GS.

CN1 (MIM#218800), the most deleterious form, described in 1952 by Crigler and Najjar[61], is characterised by complete or almost complete absence of UGT1A1 enzyme activity with severe jaundice[62]. Icterus occurring shortly after birth is complicated by bilirubin encephalopathy (kernicterus). Until the introduction of phototherapy and plasmapheresis, kernicterus was fatal in almost all cases during the first two years of life or caused serious brain damage with permanent neurologic sequelae. Intermittent phototherapy is lifelong and it results in a thorough elimination of water-soluble photoisomers of unconjugated bilirubin *via* bile. The effectiveness of phototherapy may decrease gradually with age and patients are at higher risk of sudden brain damage[63].

Although new treatment modalities such as hepatocyte or hepatic progenitor cell transplantation have already been used to treat CN1 patients, liver transplantation is still considered to be the only definitive treatment for CN1[63-67]. Gene therapy seems to be a promising therapeutic possibility for the patients with CN1 in the near future[68,69].

CN2 (Arias syndrome, MIM #606785), described by Arias in 1962[70], is characterised by reduced UGT1A1 enzyme activity with a moderate degree of nonhemolytic jaundice. Bilirubin levels do not exceed 350 μmol/L and CN2 is only rarely complicated by kernicterus[71]. Virtually all the mutations responsible for the syndrome are autosomal recessive, as in CN1, but several observations have also suggested the possibility of autosomal dominant pattern of inheritance[72-74].

An important clinical difference between CN type I and type II is the response to PB treatment, with no effect in type I (complete loss of the UGT1A1 enzyme activity) and a decrease of serum bilirubin levels by more than 30% in CN type II (some residual UGT1A1 activity is preserved). Moreover, bilirubin glucuronides are present in bile in CN2. However, the method of choice for the diagnosis of CN syndrome is mutation analysis of

UGT1A1[75].

GS (MIM #143500), described in 1901 by Gilbert and Lereboulet[76], is characterised by fluctuating mild, unconjugated nonhemolytic hyperbilirubinemia < 85 μmol/L without overt haemolysis, usually diagnosed around puberty, and aggravated by intercurrent illness, stress, fasting or after administration of certain drugs[77,78]. Physical examination and the results of routine laboratory tests are normal apart from elevated serum bilirubin and jaundice. The clinical diagnosis of GS can be established if patients have a mild, predominantly unconjugated hyperbilirubinemia and normal activity of liver enzymes. The reduced caloric intake test and phenobarbital stimulation test have low diagnostic specificity in GS subjects[79]. Histological findings in GS are mild, with a slight centrilobular accumulation of pigment with lipofuscin-like properties[80]. Ultrastructurally, hepatocytes reveal hypertrophy of smooth endoplasmic reticulum[81,82]. Since the morphological picture of GS is completely non-specific and the disorder is benign, liver biopsy is not indicated.

GS is characterised by reduced levels of UGT1A1 activity to about 25%-30% caused by homozygous, compound heterozygous, or heterozygous mutations in the *UGT1A1* with autosomal recessive transmission[80].

GS is the most frequent hereditary jaundice affecting nearly 5%-10% of the Caucasian population[83]. The genetic basis of GS was first disclosed in 1995[84] as presence of the allele *UGT1A1*28*, characterised by insertion of TA in the TATAA box (A[TA]7TAA) in the proximal promoter of *UGT1A1*. *UGT1A1*28* has been identified as the most frequent mutation in Caucasian GS subjects[85]. The insertion is responsible for reduction of transcription of *UGT1A1* to 20% from normal and for a decrease of hepatic glucuronidation activity by 80% in a homozygous state[86]. In Caucasians and African Americans, the frequency of *UGT1A1*28* allele is about 35%-40%, but it is much lower in Asians, including Koreans (13%), Chinese (16%), and Japanese (11%)[87-89]. Moreover, in the majority of Caucasian GS subjects, expression of UGT1A1 is further decreased by the presence of the second mutation T>G in gtPBREM[59,60]. In addition to the mutations in the promoter, GS may be caused by mutations in structural regions of the *UGT1A1*. In Asians, other variants, such as *UGT1A1*6* characterised by a missense mutation involving G to A substitution at nucleotide 211 (c.211G>A) in exon 1 (also known as p.G71R), *UGT1A1*7* (p.Y486D), *UGT1A1*27* (p.P229Q), and *UGT1A1*62* (p.F83L) have been detected[60,87-90].

In addition to biochemical defect leading to reduced glucuronidation, other factors, such as impaired hepatic (re)uptake of bilirubin (see Rotor syndrome below for the possible mechanism) or an increased load of bilirubin, seem to be necessary for clinical manifestation of GS[86,91,92].

GS is benign and GS carriers present with no liver disease. However, the mutations in the *UGT1A1* identical to those recognised in GS subjects may contribute to the development of prolonged neonatal hyperbilirubinemia in breast-fed infants[93,94].

Moreover, since the process of glucuronidation is an important step in elimination of numerous endogenous and exogenous substrates, GS subjects may be more susceptible to the adverse effects of some drugs metabolised by UGT1A1, such as indinavir, atazanavir[95-99] or irinotecan[100-102].

HEREDITARY PREDOMINANTLY CONJUGATED HYPERBILIRUBINEMIA

Two types of hereditary conjugated jaundice are known as Dubin-Johnson and Rotor syndrome. Both are characterised by the presence of mixed, predominantly conjugated hyperbilirubinemia, with conjugated bilirubin more than 50% of total bilirubin.

DJS (MIM # 237500), a benign autosomal recessive disorder described in 1954 by Dubin *et al*[103] and Sprinz *et al*[104], is characterised by fluctuating mild, predominantly conjugated hyperbilirubinemia, with typical manifestation in adolescence or young adulthood. Most patients are asymptomatic except of occasional slight abdominal pain and fatigue. Urine excretion of total coproporphyrin in 24 h is normal, but 80% are represented by coproporphyrin I. Biliary excretion of anionic dyes including bromosulfophthalein (BSP), indocyanine green and cholescintigraphy radiotracers is delayed with absent or delayed filling of the gallbladder[105]. BSP clearance in DJS subjects is normal at 45 min with the second peak at 90 min[106]. Liver histology in DJS shows an accumulation of distinctive melanin-like lysosomal pigment in an otherwise normal liver that gives the organ a characteristic dark pink or even black colour. The pigment is positive in PAS and Masson-Fontana reaction with marked autofluorescence. In contrast to melanin, DJS pigment does not reduce neutral silver ammonium solution[103,107]. The amount of pigment may vary and possible transient loss may occur in coincidence with other liver diseases[108,109]. The molecular mechanism in DJS is absence or deficiency of human canalicular multispecific organic anion transporter MRP2/cMOAT caused by homozygous or compound heterozygous mutation in *ABCC2* (gene ID: 1244) on chromosome 10q24[110-114]. The *ABCC2* mutation alters not only MRP2-mediated transport of conjugated bilirubin but also transport of many anionic substrates as well as a wide range of drugs, such as chemotherapeutics, uricosurics, antibiotics, leukotrienes, glutathione, toxins and heavy metals. Absence of MRP2/cMOAT may result in impaired elimination and in subsequent renal toxicity of the substrates mentioned above[115-120].

A rare type of hereditary mixed hyperbilirubinemia caused by the simultaneous presence of mutations characteristic for DJS and GS has been classified as dual hereditary jaundice[121]. Serum direct bilirubin concentrations in dual hereditary jaundice reach only 20%-50% of total bilirubin.

RS (MIM #237450), described in 1948 by Rotor *et al*[122],

is characterised by mild, predominantly conjugated hyperbilirubinemia with delayed excretion of anionic dyes without re-increase of their concentration. Total urinary coproporphyrin excretion is significantly increased and the proportion of coproporphyrin I in urine is approximately 65% of the total in homozygotes and 43% in heterozygotes[123,124]. By histopathological examination, the liver tissue does not display any marked architectural or cytomorphological abnormalities and pigment is not present.

The presence of homozygous mutations in both *SLCO1B1* and *SLCO1B3* neighbouring genes located on chromosome 12 with complete and simultaneous deficiency of proteins OATP1B1 and OATP1B3 has recently been identified as the molecular mechanism of the syndrome[125]. The complete absence of both transporters OATP1B1 and OATP1B3 has been confirmed by immunohistochemistry in all studied Rotor subjects. Interestingly, the presence of a single functional allele of either *SLCO1B1* or *SLCO1B3* prevented the jaundice.

RS does not require any therapy but, with regard to the impact of OATP1B transporters on pharmacokinetics of a broad spectrum of commonly used drugs such as penicillins, statins, sartans, rifampicin, methotrexate and many others, it is assumed that RS subjects and also those with the deleterious mutations in either of the *SLCO1B* genes, even without full clinical expression of the syndrome, may be at increased risk for drug toxicity[125-129].

BILIRUBIN HANDLING PROTEINS IN CHOLESTASIS

Animal models of obstructive and intrahepatic cholestasis help us to discover and understand the main principles of acquired defects in hepatobiliary transport of bile salts and other organic anions. Up and down regulation of these mechanisms can explain impaired liver uptake and excretion of the biliary constituents resulting in the cholestasis and icterus which accompanies many common acquired liver disorders[48,130,131]. A general pattern of response to cholestatic liver injury is initiated by downregulation of the basolateral membrane bound transporters NTCP and OATP1B1. The expression of several canalicular export pumps is relatively unaffected [bile salt export pump (BSEP), multidrug resistance protein 2 (MDR2)] or even upregulated (MDR1). Decreased expression of MRP2 in sepsis or in obstructive cholestasis is followed by upregulation of several MRP homologues at basolateral membrane of hepatocytes that may extrude bile salts back to the sinusoidal blood and systemic circulation. Most of these changes are believed to help prevent an accumulation of potentially toxic bile components and other substrates in the liver.

Similar patterns of expression of the bilirubin and bile salts handling proteins and mRNA are observed in cholestatic liver diseases in humans. At the stage Ⅰ and Ⅱ of primary biliary cirrhosis (PBC), expression and localisation of OATP1B1, OATP1B3, NTCP, MRP2, MRP3 and MDR3 are unchanged. At stage Ⅲ, immunostaining intensities of the sinusoidal uptake transporters and their mRNA levels decrease. Irregular MRP2 immunostaining suggests redistribution of MRP2 into intracellular structures in the advanced stages of PBC; however, at stage Ⅲ and Ⅳ, basolateral uptake transporters NTCP and OATP1B1 are downregulated. Expression of the canalicular export pumps for bile salts (BSEP) and bilirubin (MRP2) remains unchanged and the canalicular P-glycoproteins MDR1 and MDR3 and the basolateral efflux pump MRP3 are upregulated[132-135].

At the early-stages of cholestasis in extrahepatic biliary atresia, BSEP, MDR3, MRP2, NTCP/SLC10A1, SLCO1A2 and nuclear receptor farnesoid X receptor are downregulated. At the late-stages of cholestasis, farnesoid X receptor and BSEP levels returns to normal, MDR3 and MDR1 are upregulated and MRP2 is downregulated[136].

In primary sclerosing cholangitis, the level of OATP1B1 mRNA in liver tissue has been demonstrated to represent 49% of controls and the level of MRP2 mRNA dropped to 27% of controls[137].

CONCLUSION AND PERSPECTIVES

Over the last decades, molecular basis of hyperbilirubinemia syndromes has been elucidated and mutations affecting the basolateral and apical membrane transporters responsible for accumulation of either conjugated or unconjugated bilirubin have been identified.

Except for GS, the majority of inherited hyperbilirubinemia syndromes are rare autosomal recessive disorders with a low prevalence in the general population and, apart from CN syndrome type I and some cases of CN type Ⅱ in neonatal period, mostly not requiring further therapy. Nonetheless, the enzyme and transport systems involved in bilirubin metabolism may play an important role in the elimination and disposition processes of many other endogenous and exogenous substrates including hormones, drugs, toxins and heavy metals[102,138]. Dysfunction or absence of these systems, including selected ABC transporters and OATPs, may alter pharmacokinetics and pharmacodynamics of many biologically active agents, affect penetration of the substrates into various tissues and lead to their intracellular accumulation with a subsequent increase of organ toxicity[126,127,128]. In addition, the absence of the functional transport proteins involved in hepatobiliary and enterohepatic circulation may involve drug disposition, drug-drug or drug-food interactions and result in decreased effectiveness or even resistance to a diverse spectrum of chemotherapeutic agents and xenobiotics[139-141]. Individuals with mutations in the responsible gene or genes with the fully expressed phenotype of the corresponding hyperbilirubinemia syndrome, as well as subjects carrying mutations without clinical manifestation of hyperbilirubinemia under normal conditions, may be more susceptible to the adverse effects of some drugs and metabolites[142,143].

Clarifying the molecular genetic basis of hereditary hyperbilirubinemia syndromes together with the discoveries of the major systems essential for the metabolism and transport of bilirubin and other endogenous and exogenous substrates represent a substantial contribution to the current knowledge of the heme degradation pathway. Further investigation of how bilirubin transport proteins and their variations affect pharmacokinetics of drugs may be of significant clinical importance.

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